Supplementary material

A. Samples

The EADB studies (EADI, Bonn, DemGene, GR@ACE/DEGESCO, EADB-core and GERAD) are described in more details in (Bellenguez et al., 2022).

European Alzheimer's Disease Initiative (EADI) Consortium

EADI is composed of several case-control studies and one population-based cohort, the 3C study (Lambert et al., 2009). Case-control studies are comprised of AD cases and cognitively normal controls across France. 3C Study is a population-based, prospective study of the relationship between vascular factors and dementia carried out in three French cities: Bordeaux, Montpellier, and Dijon. The AD status was then defined based on 12, 14-15 and 17-18 years follow-up for Dijon, Montpellier, and Bordeaux participants, respectively. The AD cases from 3C were included as cases in the EADI discovery dataset and the other individuals were retained as controls. All AD cases from EADI were clinically diagnosed of probable AD by neurologists according to the DSM-III-R and NINCDS-ADRDA criteria. Samples that passed DNA quality control were genotyped with Illumina Human 610-Quad BeadChips.

Genetic and Environmental Risk in AD (GERAD) Consortium/Defining Genetic, Polygenic, and Environmental Risk for Alzheimer's Disease (PERADES) Consortium

The GERAD/PERADES sample comprises 3,177 Alzheimer's disease cases and 7,277 controls with available age and sex data (Harold et al., 2009). Cases and elderly screened controls were recruited by several institutions in the United Kingdom and in the United States of America. 6129 population controls were drawn from large existing cohorts with available GWAS data, including the 1958 British Birth Cohort (1958BC) (http://www.b58cgene.sgul.ac.uk), the KORA F4 Study and the Heinz Nixdorf Recall Study. All Alzheimer's disease cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) Alzheimer's disease. All elderly controls were screened for dementia using the MMSE or ADAS-cog, and determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. Genotypes from all cases and 4,617 controls were previously included in the AD GWAS by Harold and colleagues. Genotypes for the remaining 2,660 population controls were obtained from WTCCC2.

The Norwegian DemGene Network

This is a Norwegian network of clinical sites collecting cases from memory clinics based on a standardized examination of cognitive, functional, and behavioral measures and data on the progression of most patients. The Norwegian DemGene Network includes 2,224 cases and 3,089 healthy controls from different studies described elsewhere (Jansen et al., 2019). The cases were diagnosed according to recommendations from the NIA–AA, the NINCDS–ADRDA criteria, or the ICD-10 research criteria. The controls were screened with a standardized interview and cognitive tests. Additional controls from blood donors of the Oslo University

Hospital, Ulleval Hospital, were included (n=4992, age between 18-65 years, 48% female). They were thoroughly screened for diseases and medication, and provided blood for DNA analysis, in line with approval from the Regional Committee for Medical and Health Research Ethics. Individuals from the DemGene study and blood donors were genotyped using either the Human Omni Express-24 v1.1 chip (Illumina Inc., San Diego, CA) or the DeCodeGenetics_V1_20012591_A1 chip at deCODE Genetics (Reykjavik, Iceland).

Bonn studies

DietBB: The DietBB sample included in this GWAS is a subsample extracted from the German study on aging, cognition and dementia (AgeCoDe) (Jessen et al., 2014; Luck et al., 2007) cohort, a general practice (GP) registry-based longitudinal study in elderly individuals. The DietBB samples has genome-wide genotype data which was included in this study. Participants were recruited in six German cities (Bonn, Dusseldorf, Hamburg, Leipzig, Mannheim, and Munich) with a total of 138 GPs connected to the study sites. The inclusion criteria for this study were an age of 75 years and older, absence of dementia according to GP judgment, and at least one contact with the GP within the past 12 months. Dementia was diagnosed according to the criteria set of DSM-IV in a consensus conference with the interviewer and an experienced geriatrician or geriatric psychiatrist. The etiological diagnosis of dementia in AD was established according to the NINCDS-ADRDA criteria for probable AD. Mixed dementia and dementia in AD were combined. If the information provided was sufficient to judge etiology, dementia diagnosis in subjects who were not interviewed personally was based on the Global Deterioration Scale 32 (score ≥4 points). Cohort participants were included if they were dementia-free at baseline. This criterion led to the selection of 320 participants. In 120 of these participants, dementia of the AD-type occurred at any follow up. The additional 200, free of dementia until last follow up of AgeCoDe, are included as controls.

Bonn OMNI cohort: the Bonn OMNI cohort consists of AD patients and controls derived from a larger German GWAS cohort which was recruited from the following sources: (i) the German Dementia Competence Network (DCN); (ii) AgeCoDe (described above); (iii) the interdisciplinary Memory Clinic at the University Hospital of Bonn; and (iv) Heinz Nixdorf Recall (HNR) study cohort, for the controls.

The DCN: The DCN cohort includes 1,095 patients with mild cognitive impairment (MCI) and 648 cases with mild Alzheimer's disease (AD) clinical dementia syndrome that were recruited from 14 university hospital memory clinics across Germany between 2003 and 2005 (Kornhuber et al., 2009). The diagnosis of mild dementia was set according to ICD-10 criteria. These changes must have persisted for at least 3 months. The etiological diagnosis of AD was assigned according to NINCDS-ADRDA criteria.

Memory clinic Bonn: The interdisciplinary Memory Clinic of the Department of Psychiatry and

Department of Neurology at the University Hospital in Bonn provided further patients. Diagnoses were assigned according the NINCDS/ADRDA criteria and on the basis of clinical history, physical examination, neuropsychological testing (using the CERAD neuropsychological battery, including the MMSE), laboratory assessments, and brain imaging.

Control samples: The control samples were obtained from the population-based study, HNR study cohort (Schmermund et al., 2002; Stang et al., 2005). This sample was previously used for replication in Lambert et al. Briefly, 4814 participants aged 45 to 75 years were enrolled between 2000 and 2003. Cognitive performance of participants was evaluated at follow up 5 years and 10 years after baseline. Controls sample was selected if participant did not present cognitive impairment as reported at the last available evaluation.

GR@ACE/DEGESCO

The GR@ACE study (Moreno-Grau et al., 2019, de Rojas et al., 2021) recruited Alzheimer's disease (AD) patients from Fundació ACE, Institut Català de Neurociències Aplicades (Catalonia, Spain), and control individuals from three centers: Fundació ACE (Barcelona, Spain), Valme University Hospital (Seville, Spain), and the Spanish National DNA Bank–Carlos III (University of Salamanca, Spain) (http://www.bancoadn.org). Additional cases and controls were obtained from dementia cohorts included in the Dementia Genetics Spanish Consortium (DEGESCO) (Ruiz et al., 2014). At all sites, AD diagnosis was established by a multidisciplinary working group—including neurologists, neuropsychologists, and social workers—according to the DSM-IV criteria for dementia and the National Institute on Aging and Alzheimer's Association's (NIA–AA) 2011 guidelines for diagnosing AD. In our study, we considered as AD cases any individuals with dementia diagnosed with probable or possible AD at any point in their clinical course. Genotyping was conducted using the Axiom 815K Spanish biobank array (Thermo Fisher) at the Spanish National Centre for Genotyping (CeGEN, Santiago de Compostela, Spain). The genotyping array not only is an adaptation of the Axiom biobank genotyping array but also contains rare population-specific variations observed in the Spanish population.

The European Alzheimer's Disease DNA Biobank dataset (EADB)

This consortium groups together 20,464 Alzheimer's disease (AD) cases and 22,244 controls after quality controls from 16 European countries (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland, The Netherlands and the UK). These samples were genotyped using the ILLUMINA GSA array in three independent centers (France, Germany and the Netherlands) leading to define three nodes: EADB-France, EADB-Germany and EADB-Netherlands.

EADB-France

In the France node, samples were collected from nine countries (39 centers/studies), and after quality controls (QCs), we obtained 13,867 AD cases and 15,310 controls. All these samples were genotyped at the Centre National de Recherche en Génomique Humaine (CNRGH, Evry, France).

Belgium: The participants were part of a large prospective cohort (De Roeck et al., 2018) of Belgian AD patients and healthy elderly control individuals. The patients were ascertained at the memory clinic of Middelheim and Hoge Beuken (Hospital Network Antwerp, Belgium) and at the memory clinic of the University Hospitals of Leuven, Belgium. The control individuals were the partners of the patients or volunteers from the Belgian community. The study protocols were approved by the ethics committees of the Antwerp University Hospital and the participating neurological centers at the different hospitals of the BELNEU consortium and by the University of Antwerp.

Czech Republic: The Czech Brain Aging Study (CBAS) (Sheardova et al., 2019) is a longitudinal memory- clinic–based study recruiting subjects at risk of dementia (subjects referred for cognitive complaints-SCD, MCI). The CBAS+ study is a cross-sectional study of patients in the early stages of dementia. All subjects signed informed consent and both studies were approved by the local ethics committee.

Denmark: The Copenhagen General Population Study (CGPS) is a prospective study

of the Danish general population initiated in 2003 and still recruiting. Individuals were selected randomly based on the national Danish Civil Registration System to reflect the adult Danish population aged 20-100. Data were obtained from a self-administered questionnaire reviewed together with an investigator at the day of attendance, a physical examination, and from blood samples including DNA extraction.

Finland: The ADGEN cohort (Steinberg et al., 2015): a clinic-based collection of AD patients from Eastern and Northern Finland examined in the Department of Neurology in Kuopio University Hospital and the Department of Neurology in Oulu University Hospital. All the patients were diagnosed with probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS–ADRDA). The study was approved by the ethics committee of Kuopio University Hospital, Finland (420/2016). The FINGER study (Ngandu et al., 2015): a Finnish multidomain lifestyle RCT enrolling 1,260 older adults with an increased risk of dementia from the general population. The intensive lifestyle intervention lasted for two years, and follow-up extends currently up to seven years. The FINGER study was approved by the coordinating ethics committee of the Hospital District of Helsinki and Uusimaa (94/13/03/00/2009 and HUS/1204/2017), and all the participants gave written informed consent.

France: The BALTAZAR multicenter (23 memory centers) prospective study (Hanon et

al., 2018): 1,040 participants from September 2010 to April 2015. They were classified as AD cases (n = 501) according to DSM IV-TR and NINCDS–ADRDA criteria as well as amnestic mild cognitive impairment (MCI) cases (a MCI, n = 417) and non-amnestic MCI cases (na MCI, n = 122) according to Petersen's criteria. A comprehensive battery of cognitive tests was performed, including MMSE, verbal fluency, and FCSRT. All the participants or their legal guardians gave written informed consent. The study was approved by the Paris ethics committee (CPP Ile de France IV Saint Louis Hospital). MEMENTO: a clinic-based study (Dufouil et al., 2017) aimed at better understanding the natural history of AD, dementia, and related diseases. Between 2011 and 2014, 2,323 individuals presenting either recently diagnosed MCI or isolated cognitive complaints were enrolled in 26 memory centers in France. This study was performed in accordance with the guidelines of the Declaration of Helsinki. The MEMENTO study protocol has been approved by the local ethics committee (Comité de Protection des Personnes Sud-Ouest et Outre Mer III; approval number 2010-A01394-35). All the participants provided written informed consent. The CNRMAJ-Rouen study (Nicolas et al., 2016): early onset AD patients (n = 870). The patients or their legal guardians provided written informed consent. This study was approved by the ethics committee of CPP Ile de France II.

Italy: The AD cases and controls were collated through Italy in different centers: Brescia, Cagliari, Florence, Milan, Rome, Pertugia, San Giovani Rotondo and Torino. AD cases were diagnosed according to DSM III-R,IV and NINCDS–ADRDA criteria. Controls were defined a minima as subjects without DMS-III-R dementia criteria and with integrity of their cognitive functions (MMS>25).

Spain: The Dementia Genetic Spanish Consortium (DEGESCO) is a national consortium comprising 23 research centers and hospitals across the country, that holds the institutional coverage of The Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED). Created in 2013, DEGESCO's objective is the promotion and conduction of genetic studies aimed at understanding the genetic architecture of neurodegenerative dementias in the Spanish population and participates in coordinated actions in national and international frameworks. All DNA samples are in compliance with the Law of Biomedical Research (Law 14/2007) and the Royal Decree on Biobanks (RD 1716/2011). Patients included in the present study met clinical criteria for probable or possible disease established by the National Institute of Neurological and Communication Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA). Cognitively healthy controls were unrelated individuals who had a documented MMSE in the normal range. Contributing centers in the France node genotyping were Centro de Biología Molecular Severo Ochoa (CSIC-UAM (Madrid), the Institute Biodonostia, University of Basque Contry (EHU-UPV, San Sebastián), Institut de Biomedicina de Valencia CSIC (València), and Sant Pau Biomedical Research Institute (Barcelona).

Sweden: Upsala. The Swedish AD patients were ascertained at the Memory Disorder Unit at Uppsala University Hospital. For all patients, the diagnosis was established according

to the National Institute on Neurological Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) guidelines. (G. McKhann et al., 1984). Healthy control subjects were recruited from the same geographic region following advertisements in local newspapers and displayed no signs of dementia upon Mini Mental State Examination (MMSE). Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) data was collected. The original SNAC-K population consisted of 4590 living and eligible persons who lived on the island of Kungsholmen in Central Stockholm, belonged to pre-specified age strata, and were randomly selected to take part in the study. Between 2001 and 2004, 3363 persons participated in the baseline assessment. They belonged to the age cohorts 60, 66,72, 78, 81, 84, 87, 90, 93, and 96 years and 99 years and older. The examination consists of three parts: a nurse interview, a medical examination, and a neuropsychological testing session. Altogether, the examination takes about six hours. The participants are re-examined each time they reach the next age cohort. All parts of the SNAC-K project have been approved by the ethical committee at Karolinska Institutet or the regional ethical review board. Informed consent was collected from all the participants or, if the person was severely cognitively impaired, from their next of kin.

The UK: MRC. The sample set comprises individuals with AD and healthy controls recruited across the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK; Institute of Psychiatry, London, UK; University of Cambridge, Cambridge, UK. The collection of the samples was through multiple channels, including specialist NHS services and clinics, research registers and Join Dementia Research (JDR) platform. The participants were assessed at home or in research clinics along with an informant, usually a spouse, family member or close friend, who provided information about and on behalf of the individual with dementia. Established measures were used to ascertain the disease severity: Bristol activities of daily living (BADL), Clinical Dementia Rating scale (CDR), Neuropsychiatric Inventory (NPI) and Global Deterioration Scale (GlDS). Individuals with dementia completed the Addenbrooke's Cognitive Examination (ACE-r), Geriatric Depression Scale (GeDS) and National Adult Reading Test (NART) too. Control participants were recruited from GP surgeries and by means of self-referral (including existing studies and Joint Dementia Research platform). For all other recruitment, 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 Mini Mental State Examination (MMSE) or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. Control samples were chosen to match case samples for age, gender, ethnicity and country of origin. Informed consent was obtained for all study participants, and the relevant independent ethical committees approved study protocols. SOTON, University of Southampton, Southampton, UK. 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. Nottingham and

Manchester, University of Nottingham, Nottingham, UK and Manchester Brain Bank. 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. KCL, London Neurodegenerative Diseases Brain Bank. 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. PRION, 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. CFAS Wales, The Cognitive Function and Ageing Study Wales (CFAS-Wales) is a longitudinal population-based study of people aged 65 years and over in rural and urban areas of Wales that aims to investigate physical and cognitive health in older age and examine the interactions between health, social networks, activity, and participation. Individuals aged 65 years and over were randomly sampled from general medical practice lists between 2011 and 2013, stratified by age to ensure equal numbers in two age groups, 65-74 years and 75 and over. The baseline sample included 3593 older people and included those living in care homes as well as those living at home. Those who provided written consent to join the study were interviewed in their own homes by trained interviewers and could choose to have the interview conducted through the medium of either English or Welsh. Participants were followed up 2 years later. 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 CAMCOG, and were determined to be free from dementia. UCL-DRC. the UCL Alzheimer's disease cohort of the Dementia Research Centre (UCL - EOAD DRC) included patients seen at the Cognitive Disorders Clinics at The National Hospital for Neurology and Neurosurgery (Queen Square), or affiliated hospitals. Individuals were assessed clinically and diagnosed as having probable Alzheimer's disease based on contemporary clinical criteria in use at the time, including imaging and neuropsychological testing where appropriate.

EADB-Germany

In the German node, samples were collected from seven countries (11 centers/studies) and after QCs, we obtained 4,159 AD cases and 4,545 controls. All these samples were genotyped at Life&brain (Bonn, Germany).

Germany: DELCODE (the multicenter DZNE-Longitudinal Cognitive Impairment and Dementia Study). This is an observational longitudinal memory clinic-based multicenter study in Germany comprising 400 subjects with Subjective cognitive decline (SCD), 200 mild cognitive impairment (MCI) patients, 100 AD dementia patients, 200 control subjects without subjective or objective cognitive decline, and 100 first-degree relatives of patients with a documented diagnosis of AD dementia. All patient groups (SCD, MCI, AD) are referrals,

including self-referrals, to the participating memory centers. The control group and the relatives of AD dementia patients are recruited by standardized public advertisement. Ten university-based memory centers are participating, all being collaborators of local DZNE sites. All patient groups (SCD, MCI, AD) were assessed clinically at the respective memory centers before entering DELCODE. The assessments include medical history, psychiatric and neurological examination, neuropsychological testing, blood laboratory work-up, cerebrospinal fluid (CSF) biomarkers, and routine MRI, all according to the local standards. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery was applied at all memory centers to measure cognitive function. German age, sex, and education-adjusted norms of the CERAD neuropsychological battery are available online (www.memoryclinic.ch). Detail description is of recruitment protocol is reported elsewhere. The VOGEL study: The VOGEL study is a prospective, observational, long-term follow-up study with three time points of investigation within 6–8 years. This cohort includes dementia and healthy subjects. Residents of the city of Würzburg born between 1936 and 1941 were recruited. Every participant underwent physical, psychiatric, and laboratory examinations and performed intense neuropsychological testing as well as VSEP and NIRS according to the published procedures. A total of 604 subjects were included. The Heidelberg/Mannheim memory clinic sample: This cohort includes 61 subjects from whom 40 MCI patients were recruited and assessed between 2012 and 2016. Some of those patients converted to dementia by AD or other dementias. The PAGES study: This study includes 301 subjects. AD patients were recruited at the memory clinic of the Department of Psychiatry, University of Munich, Germany. Participants in whom dementia associated with AD was diagnosed fulfilled the criteria for probable AD according to the NINCDS–ADRDA. The control group included participants who were randomly selected from the general population of Munich. Controls who had central nervous system diseases or psychotic disorders or who had first-degree relatives with psychotic disorders were excluded. The Technische Universität München study: This cohort includes 359 healthy, AD, and other dementias patients recruited from the Centre for Cognitive Disorders. All the participants provided written informed consent. A biobank was submitted to the ethics committee of the Technical University of Munich, School of Medicine (Munich, Germany), which raised no objections and approved the biobank (reference number 347-14). The Göttingen Universität study: This study includes 111 in- and outpatients with a healthy or AD dementia status from the Department of Psychiatry of the University of Göttingen. The study's ethical statement was provided locally at the Göttingen University Medical Centre. The German Dementia Competence Network (DCN) cohort: Individuals from the DCN cohort were recruited from university hospital memory clinics across Germany between 2003 and 2005 (Kornhuber et al., 2009). The study was approved by the respective ethics committees, and written informed consent was obtained from all the participants prior to inclusion. The German Study on Aging, Cognition, and Dementia (AgeCoDe): The AgeCoDe study is a general practice (GP) registry-based longitudinal study in elderly individuals that recruited patients aged 75 years and above in six German cities from 2003 to 2004 (Luck et al., 2007). The study was approved by the respective

ethics committees, and written informed consent was obtained from all the participants prior to inclusion.

Greece: the HELIAD study, comprising 49 AD cases and 1,150 controls. HELIAD is a population-based, multidisciplinary, collaborative study designed to estimate, in the Greek population over the age of 64 years, the prevalence and incidence of MCI, AD, other forms of dementia, and other neuropsychiatric conditions of aging and to investigate associations between nutrition and cognitive dysfunction or age-related neuropsychiatric diseases. The participants were selected through random sampling from the records of two Greek municipalities, Larissa and Marousi. All the participants signed informed consent in Greek. Portugal: the Lisbon study from Portugal, totaling 78 AD cases and 74 controls. This cohort was recruited in 2008–2009 to investigate the connections between oxidative stress and lipid dyshomeostasis in AD. The project includes 190 subjects and was approved by the local ethics committee, and all the participants provided written informed consent. This study includes healthy and dementia-by-AD subjects.

Spain: Those samples are part of DEGESCO. DEGESCO Centers from whom DNA samples were genotyped in the German node (1,778 cases and 470 controls) were the Alzheimer Research Center and Memory Clinic, Fundació ACE, Institut Català de Neurociències Aplicades (Barcelona), the Neurology Service at University Hospital Marqués de Valdecilla (Santander), the Alzheimer's disease and other cognitive disorders, Neurology Department, at Hospital Clínic, IDIBAPS (Barcelona), the Neurological Tissue Bank - Biobank, Hospital Clinic-FRCB-IDIBAPS (Barcelona), the Molecular Genetics Laboratory, at the Hospital Universitario Central de Asturias (Oviedo), and Fundació Docència i Recerca Mútua de Terrassa and Movement Disorders Unit, Department of Neurology, University Hospital Mútua de Terrassa (Barcelona).

Switzerland: Two datasets from Switzerland and Austria were combined, totaling 182 AD cases and 388 controls. The Lausanne study: This study includes 137 community-dwelling participants aged 55+ years with cognitive impairment (memory clinic patients with MCI, dementia) or normal cognition (recruited by advertisement, word of mouth). The study's ethical statement was provided locally at the Department of Psychiatry, Geneva University Centre, Switzerland. The VITA study: This is a longitudinal study of 606 individuals (Vienna, Austria) who were 75 years old in 2000, followed up every 30–90 months. This cohort includes dementia and healthy subjects. All the participants gave written informed consent. The study conformed to the latest version of the Declaration of Helsinki and was approved by the ethics committee of the City of Vienna, Austria.

EADB-Netherlands

In the Dutch node, samples were collected from six organizations in the Netherlands and after QCs, we obtained 2,438 AD cases and 2,389 controls. All these samples were genotyped at

the Erasmus Medical University (Rotterdam, The Netherlands). The Medical Ethics Committee (METC) of the local institutes approved the studies. All the participants and/or their legal guardians gave written informed consent for participation in the clinical and genetic studies. Samples from the following institutes were included. 1) Erasmus Medical Center: most individuals were selected from population studies from the epidemiology department and accounted for most of the controls, while a smaller subset of samples originated from the neurology department, where AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD (G. M. McKhann et al., 2011). 2) The Amsterdam Dementia Cohort (ADC) (Van Der Flier & Scheltens, 2018): This cohort comprises patients who visit the memory clinic of the VU University Medical Centre, the Netherlands. The diagnosis of probable AD is based on the clinical criteria formulated by the NINCDS–ADRDA and based on the NIA–AA. Diagnosis of MCI was made according to Petersen and NIA-AA. Controls presented with subjective cognitive decline at the memory clinic, but performed within normal limits on all clinical investigations. 3) The 100-Plus study: This study includes Dutch-speaking individuals who (i) can provide official evidence for being aged 100 years or older, (ii) self-report to be cognitively healthy, which is confirmed by a proxy, (iii) consent to the donation of a blood sample, (iv) consent to (at least) two home visits from a researcher, and (v) consent to undergo an interview and neuropsychological test battery (Holstege et al., 2018). 4) Parelsnoer Institute: a collaboration between 8 Dutch University Medical Centers in which clinical data and biomaterials from patients suffering from chronic diseases (so called "Pearls") are collected according to harmonized protocols. The Pearl Neurodegenerative Diseases (Aalten et al., 2014) includes individuals diagnosed with dementia, mild cognitive impairment, and controls with subjective memory complaints. 5) The Netherlands Brain Bank: a non-profit organization that collects human brain tissue of donors with a variety of neurological and psychiatric disorders, but also of non-diseased donors. A clinical diagnosis of AD is based on the clinical criteria of probable AD (Dubois et al., 2007; G. M. McKhann et al., 2011). The selected AD patients for this study all received a definitive diagnosis which was based on autopsy. 6) Maastricht University Medical Center: a subset of individuals that were referred to the memory clinic for cognitive complaints were included if they participated in the BioBank-Alzheimer Centrum Limburg (BB-ACL). Diagnosis of MCI was made according to the criteria of Petersen, and diagnosis of AD-type dementia was made according to the criteria of the DSM-4, and the NINCDS-ADRDA (G. M. McKhann et al., 2011). The Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting VUmc fonds. The clinical database structure was developed with funding from Stichting Dioraphte. Genotyping of the Dutch case-control samples was performed in the context of EADB (European Alzheimer DNA biobank) funded by the JPco-fuND FP-829-029 (ZonMW projectnumber 733051061).

Alzheimer's Disease Genetics Consortium (ADGC)

The ADGC dataset comprises subjects from 35 datasets including two waves of the Adult Changes in Thought (ACT) cohort study [ACT1/ACT2]; ten waves of cases and cognitively normal controls from the National Institute on Aging (NIA) Alzheimer Disease Centers (ADCs); the Alzheimer Disease Neuroimaging Initiative (ADNI); the Biomarkers of Cognitive Decline Among Normal Individuals (BIOCARD) Cohort; two waves of the Religious Orders Study/Memory and Aging Project (ROSMAP1-2) and the Chicago Health and Aging Project (CHAP) cohort studies at Rush University; the Einstein Aging Study (EAS); the Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer's Disease (GenADA) Study by GlaxoSmithKline; Mayo Clinic Jacksonville (MAYO) and Rochester (RMAYO) case-control datasets; the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study; the NIA Late-Onset Alzheimer's Disease (LOAD) Family Study (NIA-LOAD); the Netherlands Brain Bank (NBB) case-control dataset; the Oregon Health and Science University (OHSU) case-control dataset; the Pfizer case-control dataset; the Texas Alzheimer's Research and Care Consortium (TARCC) dataset; the Translational Genomics Research Institute series 2 (TGEN2) dataset; the University of Miami (UM)/ Case Western Reserve University (CWRU)/ Mt. Sinai School of Medicine (MSSM) and UM/CWRU/TARCC wave 2 datasets [UM/CWRU/MSSM and UM/CWRU/TARCC2]; the Universitatsklinikum Saarlandes (UKS) case-control dataset; the University of Pittsburgh (UPITT) case-control dataset; Washington University (WASHU) wave 1 and 2 case-control datasets [WASHU1/WASHU2]; and the Washington Heights-Inwood Community Aging Project (WHICAP) study datasets.

Descriptions of the ACT1, ADC waves 1-7, ADNI, BIOCARD, CHAP, EAS, GenADA, MAYO, MIRAGE, NBB, NIA-LOAD, OHSU, PFIZER, RMAYO, ROSMAP1, ROSMAP2, TARCC, TGEN2, UKS, UM/CWRU/MSSM, UM/CWRU/TARCC2, UPITT, WASHU1, WASHU2, and WHICAP cohorts have been provided in previous ADGC and IGAP studies (G Jun et al., 2016; Gyungah Jun et al., 2010; Kunkle et al., 2019; Lambert et al., 2013; Naj et al., 2011; Sims et al., 2017). Here we update descriptions of these studies, where applicable, and provide descriptions for ACT2, ADC wave 8-10. All analyses were restricted to individuals of European ancestry. All subjects were recruited under protocols approved by the appropriate Institutional Review Boards (IRBs). BIOCARD, CHAP, EAS, NBB, RMAYO, ROSMAP2, WASHU2 and WHICAP were not included in the XWAS because they had less than 50 samples in at least one subgroup defined by sex and AD-status.

ACT1/ACT2: The ACT cohort is an urban and suburban elderly population from a stable HMO that includes 2,581 cognitively intact subjects age ≥ 65 who were enrolled between 1994 and 1998 (Kukull et al., 2002; Larson et al., 2006). An additional 811 subjects were enrolled in 2000-2002 using the same methods except oversampling clinics with more minorities. More recently, a Continuous Enrollment strategy was initiated in which new subjects are contacted, screened, and enrolled to keep 2,000 active at-risk person-years accruing in each calendar year. This resulted in an enrollment of 4,146 participants as of May 2009. All clinical data are

reviewed at a consensus conference. Dementia onset is assigned half-way between the prior biennial and the exam that diagnosed dementia. A waiver of consent was obtained from the IRB to enroll deceased ACT participants. In total, ACT contributed data on 553 individuals with probable or possible Alzheimer's disease (70 with autopsy-confirmation) and on 1,579 cognitively normal elders (CNEs, 155 with autopsy-confirmation) who were included in the analyses, with 2,103 cases/1,571 CNEs in the first wave (ACT1) and 29 cases/8 CNEs in the second wave (ACT2).

NIA ADC Samples (ADC1-10): The NIA ADC cohort included subjects ascertained and evaluated by the clinical and neuropathology cores of the 32 NIA-funded ADCs. Data collection is coordinated by the National Alzheimer's Coordinating Center (NACC). NACC coordinates collection of phenotype data from the 32 ADCs, cleans all data, coordinates implementation of definitions of Alzheimer's disease cases and controls, and coordinates collection of samples. The complete ADC cohort consists of 3,311 autopsy-confirmed and 2,889 clinically-confirmed Alzheimer's disease cases, and 247 cognitively normal elders (CNEs) with complete neuropathology data who were older than 60 years at age of death, and 3,687 living CNEs evaluated using the Uniform dataset (UDS) protocol (Beekly et al., 2007; Morris et al., 2006) who were documented to not have mild cognitive impairment (MCI) and were between 60 and 100 years of age at assessment. Based on the data collected by NACC, the ADGC Neuropathology Core Leaders Subcommittee derived inclusion and exclusion criteria for Alzheimer's disease and control samples. All autopsied subjects were age ≥ 60 years at death. Based on the data collected by NACC, the ADGC Neuropathology Core Leaders Subcommittee derived inclusion and exclusion criteria for Alzheimer's disease and control samples. All autopsied subjects were age ≥ 60 years at death. Alzheimer's disease cases were demented according to NINCDS-ADRDA/DSMIV-V criteria or Clinical Dementia Rating (CDR) ≥ 137 (G. McKhann et al., 1984; G. M. McKhann et al., 2011). Neuropathologic stratification of cases followed NIA/Reagan criteria explicitly or used a similar approach when NIA/Reagan criteria were coded as not done, missing, or unknown. Cases were intermediate or high likelihood by NIA/Reagan criteria with moderate to frequent amyloid plaques (Mirra et al., 1993) and neurofibrillary tangle (NFT) Braak stage of III-VI (Braak & Braak, 1991; Nagy et al., 1998). Persons with Down's syndrome, non-Alzheimer's disease tauopathies and synucleinopathies were excluded. All autopsied controls had a clinical evaluation within two years of death. Controls did not meet NINCDS-ADRDA/DSMIV-V criteria for dementia, did not have a diagnosis of mild cognitive impairment (MCI), and had a CDR of 0, if performed. Controls did not meet or were low-likelihood Alzheimer's disease by NIA/Reagan criteria, had sparse or no amyloid plaques, and a Braak NFT stage of 0 – II. ADCs sent frozen tissue from autopsied subjects and DNA samples from some autopsied subjects and from living subjects to the ADCs to the National Cell Repository for Alzheimer's Disease (NCRAD). DNA was prepared by NCRAD for genotyping and sent to the genotyping site at Children's Hospital of Philadelphia. ADC samples were genotyped and analyzed in separate batches (waves 1-10). The ADC data used in the analyses (ADC1-10) consist of 6,292 cases and 4,980 CNEs in total.

ADNI: ADNI is a longitudinal, multi-site observational study including Alzheimer's disease, mild cognitive impairment (MCI), and elderly individuals with normal cognition assessing clinical and cognitive measures, MRI and PET scans (FDG and 11C PIB) and blood and CNS biomarkers. For this study, ADNI contributed data on 268 Alzheimer's disease cases with MRI confirmation of Alzheimer's disease diagnosis and 173 healthy controls with Alzheimer's disease-free status confirmed as of most recent follow-up. Alzheimer's disease subjects were between the ages of 55–90, had an MMSE score of 20–26 inclusive, met NINCDS-ADRDA criteria for probable Alzheimer's disease (G. McKhann et al., 1984; G. M. McKhann et al., 2011), and had an MRI consistent with the diagnosis of Alzheimer's disease. Control subjects had MMSE scores between 28 and 30 and a Clinical Dementia Rating of 0 without symptoms of depression, MCI or other dementia and no current use of psychoactive medications. According to the ADNI protocol, subjects were ascertained at regular intervals over 3 years, but for the purpose of our analysis we only used the final ascertainment status to classify case-control status. Additional details of the study design are available elsewhere (Gyungah Jun et al., 2010; Petersen et al., 2010).

GenADA: GenADA study data analyzed included 666 Alzheimer's disease cases and 712 CNEs ascertained from nine memory referral clinics in Canada between 2002 and 2005. Patients and CNEs were of non-Hispanic White (NHW) ancestry from Northern Europe. All patients with Alzheimer's disease satisfied NINCDS-ADRDA and DSM-IV criteria for probable Alzheimer's disease with Global Deterioration Scale scores of 3-7 (G. McKhann et al., 1984; G. M. McKhann et al., 2011). CNEs had MMSE test scores higher than 25 (mean 29.2 ± 1.1), a Mattis Dementia Rating Scale score of ≥ 136, a Clock Test without error, and no impairments on seven instrumental activities of daily living questions from the Duke Older American Resources and Services Procedures test. Data were collected under an academic-industrial grant from Glaxo-Smith-Kline, Canada by Principal Investigator P. St George-Hyslop. Detailed characteristics of this cohort have been described previously (Li et al., 2008).

MAYO/RMAYO: All 671 cases and 1,279 controls consisted of NHW subjects from the United States ascertained at the Mayo Clinic. All subjects were diagnosed by a neurologist at the Mayo Clinic in Jacksonville, Florida or Rochester, Minnesota. The neurologist confirmed a Clinical Dementia Rating score of 0 for all controls; cases had diagnoses of possible or probable Alzheimer's disease made according to NINCDS-ADRDA criteria (G. McKhann et al., 1984; G. M. McKhann et al., 2011). Autopsy-confirmed samples (221 cases, 216 CNEs) came from the brain bank at the Mayo Clinic in Jacksonville, FL and were evaluated by a single neuropathologist. In clinically-identified cases, the diagnosis of definite Alzheimer's disease was made according to NINCDS-ADRDA criteria. All Alzheimer's disease brains analyzed in the study had a Braak score of 4.0 or greater. Brains employed as controls had a Braak score of 2.5 or lower but often had brain pathology unrelated to Alzheimer's disease and pathological diagnoses that included vascular dementia, frontotemporal dementia, dementia with Lewy bodies, multi-system atrophy, amyotrophic lateral sclerosis, and progressive supranuclear palsy.

MIRAGE: The MIRAGE study is a family-based genetic epidemiology study of Alzheimer's disease that enrolled Alzheimer's disease cases and unaffected sibling controls at 17 clinical centers in the United States, Canada, Germany, and Greece (details elsewhere (Green et al., 2002)), and contributed 1,229 subjects (491 Alzheimer's disease cases and 738 CNEs), a subset of the cases and controls that were incorporated into our prior studies (Gyungah Jun et al., 2010; Naj et al., 2011) which met more stringent QC criteria for this study. Briefly, families were ascertained through a proband meeting the NINCDS-ADRDA criteria for definite or probable Alzheimer's disease (G. McKhann et al., 1984; G. M. McKhann et al., 2011). Unaffected sibling controls were verified as cognitively healthy based on a Modified Telephone Interview of Cognitive Status score ≥ 86 (Roccaforte et al., 1992).

UM/CWRU/TARCC2: The UM/CWRU/TARCC2 sample included 256 cases and 189 controls from the University of Miami, Case Western Reserve University, and the Texas Alzheimer's Research Care Consortium (wave 2). All Alzheimer's disease cases had onset of disease symptoms after age 65 years and met NINCDS-ADRDA criteria for probable or possible Alzheimer's disease (G. McKhann et al., 1984; G. M. McKhann et al., 2011). Controls were adjudicated to have MMSE scores greater than 28 and no clinically identified signs of cognitive impairment. Additional details of subject recruitment at these sites are described in the UM/CWRU/MSSM (formerly UM/VU/MSSM) and TARCC cohort descriptions in this supplement and elsewhere (G Jun et al., 2016; Naj et al., 2011; Sims et al., 2017).

NIA-LOAD: The NIA LOAD Family Study (Lee et al., 2008) recruited families with two or more affected siblings with LOAD and unrelated, CNEs similar in age and ethnic background. A total of 1,819 cases and 1,969 CNEs from 1,802 families were recruited through the NIA LOAD study, NCRAD, and the University of Kentucky, with 1,798 cases and 1,568 CNEs included for analysis. One case per family was selected after determining the individual with the strictest diagnosis (definite > probable > possible LOAD). If there were multiple individuals with the strictest diagnosis, then the individual with the earliest age of onset was selected. The controls included only those samples that were neurologically evaluated to be normal and were not related to a study participant.

OHSU: The OHSU dataset includes 132 autopsy-confirmed Alzheimer's disease cases and 153 deceased controls that were evaluated for dementia within 12 months prior to death (age at death > 65 years), which are a subset of the 193 cases and 451 controls examined in our previous study (Gyungah Jun et al., 2010) meeting more stringent QC criteria in this study. Subjects were recruited from aging research cohorts at 10 NIA-funded ADC and did not overlap other samples assembled by the ADGC. A more extensive description of control samples can be found elsewhere (Kramer et al., 2011).

Pfizer: The Pfizer sample collection comprises Alzheimer's disease cases taken from the Lipitor's Effect in Alzheimer's Disease (LEADe) trial, including subjects who converted to Alzheimer's disease after ascertainment as MCI, as well as 216 probable Alzheimer's disease

subjects enrolled by PrecisionMed for a case-control study and 149 subjects from a Phase II trial (#A3041005) of CP-457920 (a selective α5 GABAA receptor inverse agonist) in Alzheimer's disease. Samples were collected from multiple clinical sites, and with appropriate IRB/ethics committee approvals at each individual site, with written and informed consent given by subjects for use in follow-up studies. All subjects were diagnosed with probable or possible Alzheimer's disease if they met NINCDS-ADRDA and/or DSM-IV criteria, and had Mini-Mental Status Exam (MMSE) scores < 25 at baseline (G. McKhann et al., 1984; G. M. McKhann et al., 2011). The control group included subjects from two studies: 1) the PrecisionMed case-control study (#A9010012), which recruited elderly subjects free of neurological or psychiatric conditions, and 2) 999-GEN-0583-001, which obtained a reference population of cognitively, neurologically, and psychiatrically normal subjects. Controls have no neuropsychiatric conditions or diseases and had MMSE>27 at the time of enrollment. For Alzheimer's disease analysis, all cases with age-at-onset (AAO) less than 65 years were removed to exclude early-onset Alzheimer's disease subjects. All controls were re-matched with remaining cases according to gender, age (all controls are older than cases), and ethnicity (only individuals with NHW background were analyzed). The final Pfizer Alzheimer's disease case-control GWAS dataset included 696 cases and 762 controls. Cases from the PrecisionMed/ A3041005 and LEADe studies and age-matched controls were genotyped using the Illumina HumanHap550 array. *APOE* genotypes were determined from genotypes for rs429358 and rs7412 obtained using Taqman assays.

TARCC: The TARCC is a collaborative Alzheimer's research effort directed and funded by the Texas Council on Alzheimer's Disease and Related Disorders (the Council), as part of the Darrell K Royal Texas Alzheimer's Initiative. Composed of Baylor College of Medicine (BCM), Texas Tech University Health Sciences Center (TTUHSC), University of North Texas Health Science Center (UNTHSC), the UT Southwestern Medical Center at Dallas (UTSW), University of Texas Health Science Center at San Antonio (UTHSCSA), Texas A&M Health Science Center (TAMHSC), and the University of Texas at Austin (UTA), this consortium was created to establish a comprehensive research cohort of well characterized subjects to address better diagnosis, treatment, and ultimately prevention of Alzheimer's disease (Hall et al., 2013). The resulting prospective cohort, the Texas Harris Alzheimer's Research Study, contains clinical, neuropsychiatric, genetic, and blood biomarker data on more than 3,000 participants diagnosed with Alzheimer's disease, mild cognitive impairment (MCI), and cognitively normal individuals. Longitudinal data/sample collection and follow-up on participants occurs on an annual basis. Two waves of case-control data from TARCC were examined as part of genetic analyses in the ADGC. Data from the TARCC included 323 cases and 181 controls in the first wave (included in the TARCC1 cohort), with 84 cases and 115 controls in the second wave (included in the UM/CWRU/TARCC2 cohort). All TARCC subjects were greater than 65 years of age at disease onset (cases) or at last disease-free exam (non-cases).

TGEN2: Among the TGEN2 data analyzed were 668 clinically- and neuropathologically-characterized brain donors, and 365 CNEs without dementia or significant Alzheimer's disease

pathology. Of these cases and CNEs, 667 were genotyped as a part of the TGEN1 series (Reiman et al., 2007). Samples were obtained from twenty-one different National Institute on Aging-supported Alzheimer's disease Center brain banks and from the Miami Brain Bank as previously described (Caselli et al., 2007; Petyuk et al., 2018; Reiman et al., 2007; Webster et al., 2009). Additional individual samples from other brain banks in the United States, United Kingdom, and the Netherlands were also obtained in the same manner. The criteria for inclusion were as follows: self-defined ethnicity of European descent, neuropathologically confirmed Alzheimer's disease or neuropathology present at levels consistent with status as a control, and age of death greater than 65. Autopsy diagnosis was performed by board-certified neuropathologists and was based on the presence or absence of the characterization of probable or possible Alzheimer's disease. Where possible, Braak staging and/or CERAD classification were employed. Samples derived from subjects with a clinical history of stroke, cerebrovascular disease, comorbidity with any other known neurological disease, or with the neuropathological finding of Lewy bodies were excluded.

UKS: The UKS cohort is a thoroughly diagnosed case-control cohort from Universitätsklinikum des Saarlandes, consisting of individuals clinically diagnosed with sporadic Alzheimer's disease (N = 596; mean age onset, 72.2 ± 6.6 years) and cognitively healthy, age-, gender-, and ethnicity-matched population-based controls (N = 170; 64.1 ± 3.0 years).

UM/CWRU/MSSM: The UM/CWRU/MSSM dataset (formerly UM/VU/MSSM (Beecham et al., 2009; Edwards et al., 2010; Naj et al., 2010; Scott et al., 2001)) contains 1,177 cases and 1,126 CNEs ascertained at the University of Miami, Case Western Reserve University and Mt. Sinai School of Medicine, including 409 autopsy-confirmed cases and 136 controls, primarily from the Mt. Sinai School of Medicine (Haroutunian et al., 1998). An additional 16 cases were included and 34 controls excluded from the data analyzed in the Jun et al. 2010 study (Gyungah Jun et al., 2010). Each affected individual met NINCDS-ADRDA criteria for probably or definite Alzheimer's disease (G. McKhann et al., 1984; G. M. McKhann et al., 2011) with age at onset greater than 60 years as determined from specific probe questions within the clinical history provided by a reliable family informant or from documentation of significant cognitive impairment in the medical record. Cognitively healthy controls were unrelated individuals from the same catchment areas and frequency matched by age and gender, and had a documented MMSE or 3MS score in the normal range. Cases and controls had similar demographics: both had similar ages-at-onset/ages-at-exam of 71.1 (±17.4 SD) for cases and 73.5 (±10.6 SD) for controls, and cases and controls were 64.5% and 61.3% female, respectively.

UPITT: The University of Pittsburgh dataset contains 1,255 NHW Alzheimer's disease cases (of which 277 were autopsy-confirmed) recruited by the University of Pittsburgh Alzheimer's Disease Research Center, and 829 NHW, CNEs ages 60 and older (2 were autopsy-confirmed). All Alzheimer's disease cases met NINCDS-ADRDA criteria for probable or definite Alzheimer's

disease (G. McKhann et al., 1984; G. M. McKhann et al., 2011). Additional details of the cohort used for GWAS have been previously published (Kamboh et al., 2012).

WASHU: An NHW LOAD case-control dataset consisting of 377 cases and 281 healthy elderly controls was used in analyses for this study. This dataset was split between two analysis datasets (WASHU1 and WASHU2). Participants were recruited as part of a longitudinal study of healthy aging and dementia. Diagnosis of dementia etiology was made in accordance with standard criteria and methods (Morris et al., 2006). Severity of dementia was assessed using the Clinical Dementia Rating scale (Hughes et al., 1982).

CHARGE

CHS

The Cardiovascular Health Study (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 (Fried et al., 1991). 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 available using the Illumina 370CNV BeadChip system (for European ancestry participants, in 2007) or the Illumina HumanOmni1-Quad_v1 BeadChip system (for African-American participants, in 2010). 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.

FHS

The Framingham Heart Study (FHS), started in 1948, is a three-generation community-based prospective cohort study. The FHS includes the Original cohort followed since 1948, the Offspring and their spouses followed since 1971, and the third generation enrolled in 2002. In this study, we included only original and offspring cohorts. The original cohort consisted of 5,209 adult men and women from Framingham, Massachusetts. Survivors undergo biennial examinations. The Offspring cohort is examined approximately once every 4 years. DNA extraction and genotyping were performed in the 1990s and we limited genetic analyses to high-quality samples. Prevalent study analyses included 1,787 participants aged 65 or older at DNA draw, excluding those with dementia other than AD. For incident analyses, 1,904 genotyped persons were included. The Institutional Review Board of the Boston Medical

Campus approved the study. The Original cohort has been evaluated biennially since 1948, screened for dementia and AD in 1974-76, and under surveillance for incident cases since then. Offspring are examined every 4 years and screened for dementia using neuropsychological tests and brain MRI. Participants with baseline age <65 at DNA draw were excluded. Participants receive questionnaires, physical exams, and lab tests at clinic exams. Dementia screening and follow-up methods involve standardized neuropsychological tests, MMSE administration, and further testing for abnormalities. Neurological and neuropsychological examinations are conducted for suspected cognitive impairment, with a panel reviewing medical records for dementia determination based on DSM-IV and NINCDS-ADRDA criteria.

RS

This study included samples from the Rotterdam study (RS). RS is a prospective population-based study designed to investigate the etiology of age-related disorders. At the baseline examination in 1990-93, study recruited 7983 subjects ≥ 55 years of age from the Ommoord district of Rotterdam (RS-I). At the baseline entry and after every 3 to 4 years, all the study participants were extensively interviewed and physically examined at the dedicated research center. During 2000 to 2001, the baseline cohort (RS-I) was expanded by adding 3011 subjects ≥55 years of age, who were not yet part of RS-I (RS-II). Second expansion of RS was performed by recruiting 3932 persons having ≥45 years of age during 2006-2008 (RS-III). The study has been approved by the Medical Ethical Committee of Erasmus Medical Center and by the Ministry of Health, Welfare and Sport of the Netherlands. Written Informed consents were also obtained from each study participant to participate and to collect information from their treating physicians.

Blood was drawn for genotyping from participants of RS cohort during their first visit and DNA genotyping was performed at the internal genotyping facility of Erasmus Medical Center, Rotterdam. All samples were genotyped with the 550K, 550K duo, or 610K Illumina arrays.

UK Biobank (UKB)

We used the data August 2023 release of the UKB (application number 61054).

UKB-diagnosed: AD cases were extracted from UK Biobank self-report, ICD10 code G30 for diagnoses, primary care and cause of death. Our analysis included 3,865 diagnosed cases and 427,835 controls.

UKB-proxy: Participants were asked to report their parent dementia status and proxy AD/dementia cases included i) all female participants who reported at least one parent affected with dementia and ii) all male participants who reported an affected mother, in both cases either at baseline or follow up. Individuals who did not report dementia i) in both parents for females and ii) in mother only for males, were used as controls in the proxy

AD/dementia analysis. Our analysis included 55,868 proxy cases of dementia and 235,171 proxy-controls.

FinnGen

Patients and control subjects in FinnGen provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, separate research cohorts, collected prior the Finnish Biobank Act came into effect (in September 2013) and start of FinnGen (August 2017), were collected based on study-specific consents and later transferred to the Finnish biobanks after approval by Fimea (Finnish Medicines Agency), the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Fimea. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) statement number for the FinnGen study is Nr HUS/990/2017.

The FinnGen study is approved by Finnish Institute for Health and Welfare (permit numbers: THL/2031/6.02.00/2017, THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019, THL/1721/5.05.00/2019 and THL/1524/5.05.00/2020), Digital and population data service agency (permit numbers: VRK43431/2017-3, VRK/6909/2018-3, VRK/4415/2019-3), the Social Insurance Institution (permit numbers: KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, KELA 134/522/2019, KELA 138/522/2019, KELA 2/522/2020, KELA 16/522/2020), Findata permit numbers THL/2364/14.02/2020, THL/4055/14.06.00/2020,,THL/3433/14.06.00/2020, THL/4432/14.06/2020, THL/5189/14.06/2020, THL/5894/14.06.00/2020, THL/6619/14.06.00/2020, THL/209/14.06.00/2021, THL/688/14.06.00/2021, THL/1284/14.06.00/2021, THL/1965/14.06.00/2021, THL/5546/14.02.00/2020, THL/2658/14.06.00/2021, THL/4235/14.06.00/2021 and Statistics Finland (permit numbers: TK-53-1041-17 and TK/143/07.03.00/2020 (earlier TK-53-90-20) TK/1735/07.03.00/2021).

The Biobank Access Decisions for FinnGen samples and data utilized in FinnGen Data Freeze 8 include: THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, BB2020_1, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017, Auria Biobank AB17-5154 and amendment #1 (August 17 2020), AB20-5926 and amendment #1 (April 23 2020), Biobank Borealis of Northern Finland_2017_1013, Biobank of Eastern Finland 1186/2018 and amendment 22 § /2020, Finnish Clinical Biobank Tampere MH0004 and amendments (21.02.2020 & 06.10.2020), Central Finland Biobank 1-2017, and Terveystalo Biobank STB 2018001.

FinnGen research project is a public-private partnership combining genotype data from Finnish biobanks and digital health record data from Finnish health registries (Kurki et al., 2022). FinnGen utilizes biobank samples that consist of 1) prospective samples (‘new

samples') and 2) legacy samples.

'New samples' can be collected from voluntary individuals thought Hospital biobank, Terveystalo Biobank or Blood Service Biobank. Legacy samples are older sample cohorts that have been collected for a specific research project before the Finnish Biobank Act came into effect (September 2013) and have then been transferred to a biobank according to the Finnish Biobank Act 13 §. The 'new samples' were genotyped with FinnGen ThermoFisher Axiom custom array at the ThermoFisher genotyping service in San Diego, CA, US. The 'legacy samples' were genotyped over the years using various generations of Illumina and Affymetrix GWAS arrays.

We used the AD cases from the FinnGen Data Freeze 8 using G6_ALZHEIMER where cases are defined by having ICD-10 code G10 or ICD-9 code 3310 in either hospital discharge records or as the cause of death. In total, the G6_ALZHEIMER has 7,759 cases and 334,740 controls with high-quality genotypes and genotype-verified sex.

The following exclusions were applied: 1) all controls under the age of 30 at the common end date of follow-up for Data Freeze 8, Dec 31, 2019, and 2) all controls diagnosed with other dementias, *i.e.* whose inpatient or specialist outpatient HILMO registry data had any of the following ICD codes for hospital diagnosis or operation by the end of follow-up on the HILMO registry, Mar 24, 2021: ICD10 F01, F010-F013, F018, F019, F02, F020-F024, F028, F03, G310, G318; ICD9 290, 2901-4, 2908-9, 2941A, 3311A, 3312X, 3317, 3319X, 4378A, 4378X; ICD8 29009, 29011, 29018-9, 29209. After exclusions, there were 7,759 cases and 313,216 controls.

B. Quality control

1. EADB studies quality control

We applied the same X-chromosome quality control (QC) protocol to all EADB studies: EADB-core, EADI, GR@ACE/DEGESCO, GERAD, Bonn and DemGene.

All variants or samples failing the (Bellenguez et al., 2022) QC were excluded from the X-chromosome analysis. This QC consisted of assessment of chip's variants, variant intensity QC and autosomal sample QC (exclusion of individuals with high heterozygosity or missingness on the autosomes, of individuals with discordant genetic and clinical sex, of population outliers and of related individuals).

An additional sample and variant QC specific to the X-chromosome and adapted from the (Bellenguez et al., 2022) protocol was then performed. For the X-chromosome variant QC, only samples failing the heterozygosity, missingness or sex-check QC from the autosomal sample QC were removed. From this point, we replaced missing self-reported sex by genetic sex.

a. X-chromosome QC Protocol

The X-chromosome QC was applied to both PAR (pseudo autosomal region) and non-PAR regions (positions in assembly GRCh38: PAR1 = 10,001 – 2,781,478; PAR2 = 155,701,384 – 156,030,895; non-PAR = 2,781,479 – 155,701,383).

All the analyses of the X-chromosome QC were performed using PLINK (v1.9) (Purcell et al., 2007).

Sample Quality Control specific to the X-chromosome

Pre-quality control. All variants failing those pre-QC criteria were excluded from all the sample QC steps:

- PAR variants showing departure from the Hardy-Weinberg equilibrium (HWE) in controls (P-value < $1x10^{-15}$);
- non-PAR variants showing departure from the HWE (P-value < $1x10^{-15}$) in female controls (or in female cases and controls if the number of controls was too low);
- variants showing a high missingness overall (> 0.025).

Sample QC. Were excluded:

- samples showing high missingness on X-chromosome (missingness > 0.02 in EADB-core and > 0.05 in all other studies) (including both PAR and non-PAR variants);
- male samples showing heterozygosity higher than 1% in non-PAR variants;
- samples for which genetic sex could not be determined.

Variant Quality Control of the X-chromosome

For the variant QC, the initial set of X-chromosome variants was used (re-integrating the variants failing the pre-QC of the sample QC). All samples failing the autosomal sample QC, or the sample QC specific to X-chromosome were removed for the variant QC of the X-chromosome.

1) Steps specific to the X-chromosome

non-PAR region. Were excluded variants:

- with missingness >0.05 in either males or females;
- with heterozygosity >0.01 in males;
- failing the HWE test (P-value < $5x10^{-8}$) in female controls (or in female cases and controls if the number of controls was too low).

2) Steps identical to autosomal variant QC

For the following steps, the same exclusion criteria as for the autosomes in (Bellenguez et al.,

2022) protocol were applied to the X-chromosome variants.

PAR regions. Were excluded variants:

- showing a high missingness (> 0.05);
- failing the HWE tests (P-value < $5x10^{-8}$) in controls.

PAR and non-PAR regions. Were excluded variants:

- showing a differential missingness between cases and controls (Fisher's exact test P-value < $5x10^{-8}$) (if the samples are split in batches, the test was performed globally as well as for all the batches including both cases and controls and a variant was excluded if it failed in at least one test).
- failing the frequency checks. Population outliers were excluded for this step.
    - A frequency test comparing the allelic frequency in the study with the one in the reference panels (1) Genome Aggregation Database (Karczewski et al., 2020) (gnomAD) (Finnish and non-Finnish allele counts and frequencies were included) and (2) Haplotype Reference Consortium (McCarthy et al., 2016) (HRC) was performed. If the variant was not present in either panel, its allelic frequency was compared with the one in TopMED. The χ^2 test threshold used was adapted to each study's sample size (see below).
    - If the study includes several sample batches, GWAS were performed between controls across batches using SNPTEST "newml" (Marchini et al., 2007) to assess the genotype frequency differences between the batches. The controls from a batch were compared to the ones from each of the other batches; we thus carried out as many GWAS as there are pairs of batches. For each GWAS, the batches were converted into a binary variable and used as the analysis phenotype. Males' genotypes were coded 0/2 and females' genotypes were coded 0/1/2. We selected the batches with more than 400 controls. The related samples were also excluded for this step.
- failing ambiguous variants check. All ambiguous variants (A/T or C/G) with MAF > 0.4 were removed.
- failing duplicated variants check. For duplicated variants of the chip, only the copy with the minimum missingness was kept if both copies pass previous variant QC.

Clinical data QC and definition of covariates

For the association analyses, we additionally excluded controls with age below 30 and individuals with known pathogenic mutations.

The following covariates were included in some analyses:

- Principal components. The principal components used as adjustment in the analysis were computed using the flashPCA2 software, as reported previously (Abraham et al.,

2017);

- Sex. Sex was defined as the self-reported sex, or, when missing, as the genetically determined sex. Samples with discordant sex between self-reported and genetically determined sex were excluded;
- Age. Age of AD cases was defined as the age at onset, if available. Otherwise, we used, by order of priority, the baseline age, the age at last exam and the age at death. For controls, age was defined as the age at last exam, and if not available the age at death and the baseline age, by order of priority;
- *APOE ε*4 and *ε*2. The number of *APOE ε*4 and *ε*2 alleles were coded 0, 1 or 2. *APOE ε*4 and *ε*2 were determined from the genotyped *APOE* status specified in the clinical file of the study. If unavailable in the clinical file of the study, *APOE ε4* and *ε*2 were defined using the imputed data; rs429358 and rs7412, the two *APOE* variants, had a good imputation quality ($r^2 > 0.8$) in all studies. For a given individual, genotypes of the two *APOE* variants were only considered if their probability was higher than 0.8. This means that *APOE* status could be missing even after imputation. For samples with both genotyped and imputed *APOE* status available, the *APOE s*tatus was set to missing if the genotyped and imputed statuses were different.
- Other study-specific variables, when necessary, such as the genotyping centre for EADB-core and the genotyping chip for Bonn (Supplementary Table S4).

b. X-chromosome QC specific thresholds per study

All the EADB studies X-chromosome sample and variant QC followed the described pipeline with the same metrics and thresholds, except when specified otherwise.

European Alzheimer's Disease Initiative (EADI) Consortium

For the frequency tests (1) only allele counts and frequencies from non-Finnish samples were extracted from the gnomAD reference panel and (2) the χ^2 threshold used was set to 1,500.

After autosomal QC and exclusion of individuals with known pathogenic mutations, the EADI study was made up of 2,400 AD cases and 6,338 controls. After X-chromosome QC, the EADI study included 2,377 AD cases and 6,207 controls for 12,194 X-chromosome variants (including 20 from PAR1).

Genetic and Environmental Risk in AD (GERAD)

For the frequency tests, the χ^2 threshold used was set to 500. All 10,641 variants passing QC were liftover from Assembly GrCh37 to GrCh38. 3,168 cases, 7,267 controls and 10,624 variants were used for imputation.

The Norwegian DemGene Network

The X-chromosome QC and imputation of the samples genotyped by DECODE and omni chips were performed separately.

DECODE chip: For all Hardy-Weinberg equilibrium tests, both female cases and controls were included, instead of only female controls as the number of controls was too low. For the frequency tests, the χ^2 threshold used was set to 250. A total of 1 case and 1,892 variants (25 in PAR) were excluded in the X-chromosome QC. After autosomal QC, exclusion of individuals with known pathogenic mutations and X-chromosome QC, the DemGene DECODE chip batch included 299 cases, 11 controls and 15,685 variants (489 in PAR).

Omni chip: The DemGene omni chip batch is split in 14 sub-batches. The differential missingness between cases and controls test for variants was performed globally as well as for the 4 batches including both cases and controls with enough sample sizes and a variant was excluded if it failed in at least one test. For the frequency tests, the χ^2 threshold used was set to 1,500. A GWAS across controls was also performed between the 4 batches with more than 400 controls (using the same pipeline and thresholds described above). 13 controls, 6 cases and 933 variants (20 in PAR) were excluded with the X-chromosome QC. After autosomal QC, exclusion of individuals with known pathogenic mutations and X-chromosome QC, DemGene omni chip included 1,392 cases, 7,301 controls and 16,530 variants (362 in PAR).

Bonn studies

The X-chromosome QC and imputation of the samples genotyped by dietBB and omni chips were performed separately.

DietBB chip: For the frequency tests (1) only allele counts and frequencies from non-Finnish samples were extracted from the gnomAD reference panel and (2) the χ^2 threshold used was set to 250. 908 (29 in PAR) variants were excluded with the X-chromosome QC. No additional samples were excluded. After autosomal QC, exclusion of individuals with known pathogenic mutations and X-chromosome QC, Bonn dietBB chip batch included 139 cases, 177 controls and 21,627 variants (487 in PAR).

Omni chip: For the frequency tests (1) only allele counts and frequencies from non-Finnish samples were extracted from the gnomAD reference panel and (2) the χ^2 threshold used was set to 500. 3 cases and 982 (59 in PAR) variants were excluded with the X-chromosome QC. After autosomal QC, exclusion of individuals with known pathogenic mutations and X-chromosome QC, Bonn omni chip batch included 496 cases, 1030 controls and 23,680 variants (791 in PAR).

GR@ACE

For the frequency tests, the χ^2 threshold used was set to 1000. 146 cases, 20 controls and 304 (7 in PAR) variants were excluded with the X-chromosome QC. After autosomal QC, exclusion of individuals with known pathogenic mutations and X-chromosome QC, GR@ACE included 6,375 cases, 6,474 controls and 15,128 variants (54 in PAR).

The European Alzheimer's Disease DNA Biobank dataset (EADB-core)

The sample missingness threshold was set to 0.02 for EADB-core to remove less variants. For the frequency tests, the χ^2 threshold used was set to 1000. A GWAS across controls was performed between the three genotyping centers of EADB-core. 172 cases, 201 controls and 1,095 (7 in PAR) variants were excluded with the X-chromosome QC. After autosomal QC, exclusion of individuals with known pathogenic mutations and X-chromosome QC, EADB-core included 19,977 cases, 21,525 controls and 16,943 variants (507 in PAR).

2. ADGC Quality control

For the X-chromosome QC, the same sample and variant QC used for the autosomes was applied, but additionally including the following steps:

- Samples showing high missingness on the X-chromosome, male samples showing high level of heterozygosity and samples for which genetic gender cannot be determined were excluded.
- X-chromosome non-PAR variants showing high missingness in either males or females or showing high heterozygosity in males were excluded.

3. CHARGE Quality Control

CHS

Participant-level exclusions: 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. Beyond laboratory genotyping failures, participants were excluded if they had a call rate<=95% or if their genotype was discordant with known sex or prior genotyping (to identify possible sample swaps). All non-European ancestry participants were excluded from the analysis. After quality control, genotyping was successful for 3,268 European ancestry participants.

SNP exclusions: In CHS, the following exclusions were applied to identify a final set of 306,655

autosomal SNPs: call rate < 97%, HWE P < 10^{-5}, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap. A similar X-chromosome QC than for the EADB studies was applied to CHS.

FHS

The same sample QC as autosomes were performed, with additional exclusions based on the following criteria:

- males with high level of heterozygosity;
- individuals for which genetic gender could not be determined;
- individuals with high missingness on the X-chromosome.

In the non-PAR region, were excluded variants:

- with high level of heterozygosity in males (> 1%);
- with high missingness in females or in males (>2% in females or males);
- with low MAF in females or in males (<1% in females or males):
- showing departure from HWE in female controls (p < 1e-6);
- showing differential missingness between males and females (p<1e-7).

In the PAR regions, the same exclusion criteria as for autosomes were used. Were excluded variants:

- with high missingness overall;
- with low MAF;
- showing departure from HWE.

RS

Genotyping quality control criteria include call rate < 95%, Hardy-Weinberg equilibrium *P* < 1.0×10^{-6} and MAF < 1%. Moreover, study samples with excess autosomal heterozygosity, call rate < 97.5%, ethnic outliers and duplicate or family relationships were excluded during quality control analysis.

A similar X-chromosome QC than for the EADB studies was applied to RS.

4. UKB Quality Control

The quality control of the UKB, including additional X-chromosome specific steps, is described in (Bycroft et al. 2018). The QC includes first a marker-based QC testing for batch, plates, and sex effect (genotype frequency differences), departure from HWE within each batch (only females included in the non-PAR region of the X chromosome) and discordance across control replicates. The genotype calls of the variants failing at least one test were set to missing. The p-value threshold used for the marker-based QC was set to 10^{-12}. For the non-PAR region of the X chromosome all marker-based QC tests were performed separately using males-only

(haploid), females-only (diploid), and both combined, but then used the smallest of the three p-values.

Then, a sample QC was performed, removing samples with poor quality genotype calls, related individuals, population outliers, PC-adjusted heterozygosity above the mean (0.1903) and high missingness in the autosomes (0.05).

For our analysis, all related individuals up to third degree relatives were excluded, as well as all individuals of non-European ancestry. For UKB-diagnosed related individuals, controls were excluded over AD cases, while for UKB-proxy, controls were excluded over proxy-AD cases.

For UKB-proxy, participants were asked to report their parent dementia status and those who answered "Do not know" or "Prefer not to answer" were excluded from analyses. AD-diagnosed individuals among proxy-controls were excluded. All proxy controls whose parents age/age at death is missing or < 60 were removed.

An additional sex-chromosome QC step was applied: samples showing a putative sex chromosome aneuploidy were removed. After sample QC, markers that failed quality control in more than one batch, had a greater than 5% overall missing rate, and had a MAF of less than 0.0001 were removed.

5. FinnGen Quality control

The genotype data processing from Data Freeze 7 onward was used (described in detail in: https://finngen.gitbook.io/finngen-handbook/finngen-data-specifics/red-library-data-individual-level-data/genotype-data/description-of-how-the-data-is-processed-in-refinery). Individuals with ambiguous sex, high genotype missingness (>5%), excess heterozygosity (+-3SD) and non-Finnish ancestry were excluded, and variants with high missingness (>2%), low HWE P-value (<1e-6) and low minor allele count (MAC<3) were excluded. No additional X-chromosome QC was performed in FinnGen, but a QC after imputation specific to the X-chromosome was performed (described below).

The covariates used in GWAS included the sex, age, defined as the age of first Alzheimer's diagnosis for cases and as the age at the common end date of follow-up for Data Freeze 8, Dec 31, 2019, for controls, population structure (the first 10 principal components), the main genotyping batches, and the *APOE* risk genotypes.

C. Imputation

1. TOPMed imputation for EADB studies

All samples and variants passing the X-chromosome QC were used as the input of the imputation process. Related samples and population outliers were not excluded for the imputation. All remaining heterozygous non-PAR variants in males were set as missing. Males were set as haploid in the non-PAR region (using +fixploidy bcftools (Danecek et al., 2021) plugin).

The imputation was performed on the Michigan Imputation Server (MIS) where the TOPMed Freeze5 reference panel was granted to the EADB consortium. The server version used was the 1.2.4 with Eagle v2.4 as the phasing software and Minimac4 v4-1.0.2 as the imputation software.

2. TOPMed imputation for ADGC studies

The same pre-imputation protocol as for the EADB studies was followed. Samples were imputed with the TOPMed Freeze 8 reference panel.

3. Other imputations

a. 1000 Genomes imputation for CHARGE

For CHS, after merging the genotypes from the two chips, a set of 10,377 X chromosome SNPs were used for imputation (updated to hg19 positions). MaCH was used to pre-phase the genotypes. The phased genotypes were imputed into a reference panel of 1,092 individuals of multiple ethnicities from the Phase1 version3 haplotypes of 1000 Genomes project using minimac (release stamp 2012-11-16). SNPs were excluded from analysis for variance of the allele dosage ≤0.01.

For FHS, heterozygous SNPs from the non-PAR region in males were set at missing and hemizygous males are treated as homozygous. Imputation was performed using 1000G data (Phase 1 v3, March 2012, MACGT1, ALL panel) as reference panel. MaCH was used to pre-phase the genotypes and IMPUTE2 and Minimac for the imputation.

A similar imputation protocol was followed for RS. The PAR regions were excluded for males. Imputation was performed using 1000G data (Phase 1 v3, March 2012, MACGT1, ALL panel) as reference panel. MaCH was used to pre-phase the genotypes and IMPUTE2 and Minimac for the imputation.

b. UKB

UKB dataset was phased with SHAPEIT3 and imputed with a new version of the IMPUTE2

program referred to as IMPUTE4 (Bycroft et al., 2018). The imputation panel used is a combination of HRC, UK10K and 1000 Genomes. All samples and variants passing the UKB autosomes and X-chromosome QC were used as the input of the imputation process: related individuals and population outliers were not excluded. As described in the IMPUTE2 X-chromosome imputation pipeline, males were set to haploid in the non-PAR region prior to imputation.

A recent report found significant differences of frequency between males and females in UKB imputed data (Chen et al 2024). To check this observation, we tested the difference of frequency between males and females in the non-PAR region in our UKB imputed data, considering the frequencies computed by SAIGE on the dosages. We performed a X^2 test of difference of frequency between males in females using a 2x2 allele count contingency table for each variant in UKB imputed data and found that 736 out of 2,497,933 non-PAR variants have a significant difference of frequency between males and females ($p<5x10^{-8}$); 693 of them are low-frequency variants (MAF<5%). Thus, we found no major differences of frequency between males and females in the UKB imputed data used in this analysis for most variants.

c. FinnGen

The genotype data were imputed with a Finnish population specific reference panel, Sisu (V4), described in https://finngen.gitbook.io/finngen-handbook/finngen-data-specifics/red-library-data-individual-level-data/genotype-data/imputation-panel. Genotype imputation process is described in https://dx.doi.org/10.17504/protocols.io.xbgfijw. In the pipeline used by FinnGen R8 for the X-chromosome imputation, males were set as diploid for both the phasing and imputation. Thus, we included an additional QC after imputation for FinnGen.

Prior to analyses, all genotypes with all genotype probabilities lower than 0.9 were set to missing.

Variant pre-QC. Were excluded in the pre-QC:

- variants showing departure from the HWE in female controls (p-value < $1x10^{-15}$);
- variants showing high missingness globally (> 0.025);
- variants in the X-transposed region (in Xq21.3, from position 89Mb to 93.5Mb in assembly 38).

All variants failing pre-QC were excluded to all the following sample QC steps.

Sample QC. Were excluded:

- samples showing missingness rate > 0.05 on the X-chromosome;
- male samples showing high level of heterozygosity (more than 1%).

Variant QC. For the variant QC, the initial set of X-chromosome variants was used (re-integrating the variants failing the pre-QC of the sample QC). All samples failing the general

sample QC, or the X-chromosome specific sample QC were removed for the X-chromosome variant QC. Were excluded:

- variants showing high missingness in either males or females (>0.05);
- variants showing high heterozygosity in males (> 0.01);
- variants failing the HWE test (P-value < $5x10^{-8}$) in female controls;
- variants in the X-transposed region (in Xq21.3, from position 89Mb to 93.5Mb in assembly 38).

D. XWAS association tests

1. EADB studies

For each EADB study (all case-control), we performed a logistic regression of AD status in males and females combined with an additive genetic model and a robust variance estimation with the snpStats (v 3.4) package in R (snpStats, 2023).

The robust variance approach (or Huber-White Sandwich estimator) allows to account for heterogeneity of variance within a regression model. Let us consider a regression model y = Xβ + ε, where y is an nx1 vector representing the dependent variable and X is an nxk matrix of covariates. If the regression errors εi (i in [1:n]) are independent, but have distinct variances, the robust variance can be estimated as (White 1980):

$$\hat{V} = (X^T X)^{-1} \sum_{i=1}^{n} (\hat{\varepsilon}_i^2 x_i^T x_i)(X^T X)^{-1}$$

, where $\hat{\varepsilon}_i = y_i - x_i \hat{\beta}_i$.

We also performed sex stratified logistic regressions of the AD status on the genetic variants with an additive genetic model using SNPTEST (v 2.5.6) “newml” method (Marchini et al., 2007). Each stratified model included only samples from one of the subsets defined by sex (female-only or male-only). Additionally, a logistic regression of the AD status on the genetic variants was performed using SNPTEST “newml” method using a general genetic model and including only females. GP (genotype probabilities) were used for all models in snpStats and SNPTEST and males were coded as female homozygous (equivalent to genotype (G) = {0, 2} for males and G = {0, 1, 2} for females).

All analyses were adjusted on principal components and other study-specific variables, when necessary (Supplementary Table S4).

As sensitivity analyses, we also performed the sex-stratified additive and general genetic models adjusted on i) age and ii) age, *APOEε4* and *APOEε2* statuses.

2. ADGC studies

The same protocol was followed for ADGC studies association tests.

3. CHARGE studies

The same protocol was followed for CHARGE studies association tests.

4. UKB

UKB with diagnosed cases:
We performed a sex-combined regression of the AD status on the genetic variants with an additive genetic model and adjusted on sex using a logistic mixed model as implemented in SAIGE (v1.0.9) with G = {0, 2} for males and G = {0, 1, 2} for females. We also ran sex-stratified regression with an additive genetic model. Dosages were used for all models. Analyses were adjusted on principal components and genotyping center. We also performed the sex-stratified models adjusted on i) age and ii) age, *APOE*ε4 and *APOE*ε2 statuses.
The genetic relatedness, used in the first step of the SAIGE analysis, was constructed from autosomal variants:

- that were genotyped;
- with MAF ≥1%;
- with HWE P >= 1×10^{-15};
- with missingness < 0.01;
- not involved in inter-chromosomal LD (the list of those variants is available in the Supplementary Table 19 of REGENIE paper (Mbatchou et al., 2021));
- not in the *APOE* region (40 to 50 Mb on chr 19 in GrCh37 and GrCh38);
- not in regions of high LD;
- remaining after LD pruning using a r^2 threshold of 0.9 with a window size of 1,000 markers and a step size of 100 markers.

We set the option « impute_method » to « best guessed » in step 2.

UKB with proxy cases:
The association test on proxy status in UKB was performed separately for males and females using the SAIGE protocol described above, and a correction factor was applied to the association statistics.
Let us consider a variant with two alleles. We note f_x and f_{xx} the allelic frequency in males and females, respectively. Males X-chromosome is only transmitted by the mother. Thus, at the n^{th} generation, we have the following frequency in males: $f_x(n) = f_{xx}(n-1)$. Females receive their X-chromosome from both parents. The allelic frequency in females at the n^{th} generation is: $f_{xx}(n) = (f_{xx}(n-1) + f_x(n-1)) / 2$. If we compare allelic frequencies in males and females at the n^{th} generation, we have:
$f_x(n) - f_{xx}(n) = - ½ (f_x(n-1) - f_{xx}(n-1)) = (- ½)^n (f_x(0) - f_{xx}(0))$, and thus $\lim(f_x(n) - f_{xx}(n))_{n->+inf} = 0$,

which means that, at equilibrium (e): $f_x(e) = f_{xx}(e)$.
Thus, the frequency of the X-chromosome variants remains constant across generations and is the same in males and females. Then, the proxy-GWAS approach developed for the autosomes can also be applied to the XWAS. For females, both mother and father dementia statuses are considered, and a female is a proxy case if either the father or the mother is affected. Thus, the frequency in female AD-proxy is the same as in autosomes:
$f_p = (f_A + f_C)/2$, where f_p, f_A and f_C are the allele frequency in proxy cases, AD-cases and controls, respectively. For the males, only the status of the mother is considered, which means that the frequency of the males AD-proxy is: $f_p = f_A$
We thus performed a sex stratified regression of the AD-proxy status and included a correction factor of two on the β and its corresponding standard error only for the female model.
However, as we did not consider the sex of the parent with this method, we did not use the sex-stratified models in either the sex-stratified analysis, or the e-XCI approach.

5. FinnGen

The association analyses were performed in the FinnGen sandbox using a standard FinnGen-implemented WDL pipeline for REGENIE (v2.2.4) with a minor modification to enable the use of a plink file set as input (https://finngen.gitbook.io/documentation/v/r8/methods/phewas/logistic-regression).

We performed two sex-combined mixed logistic regression of the AD status on the genetic variants with an additive genetic model and adjusted on sex with REGENIE (v2.2.4) (default settings), one with r-XCI genotype coding (genotype (G) = {0, 2} for males and G = {0, 1, 2} for females) and one with e-XCI coding (G = {0, 1} for males and G = {0, 1, 2} for females). We also ran sex-stratified regression with an additive genetic model. Best guessed genotypes were used for all models. Analyses were adjusted on principal components and genotyping center. We also performed the sex-stratified models adjusted on i) age and ii) age, *APOEε4* and *APOEε2* statuses.

The genetic relatedness, used in the first step of the REGENIE analysis, was constructed only with autosomal markers. We thus used the same variants selected for the autosome analysis in the original FinnGen Data Freeze 8 genetic relationship matrix (GRM) file. In the GRM file were included variants 1) imputed with an INFO score > 0.95 in all batches and 2) with > 97 % non-missing genotypes and 3) MAF > 1 %. The remaining variants were LD pruned with a 1Mb window and a r^2 threshold of 0.1. The original FinnGen Data Freeze 8 GRM file was additionally modified to remove all variants present in the original GRM within ±1MB (43 variants) of the variant chr19_44870482_A_G (rs4081918) (the closest variant to the Alzheimer's risk variants in the *APOE* locus).

6. Meta-analysis

The models used in the three approaches can be written as in Supplementary Table S5.

A r-XCI meta-analysis adjusted on sex (sensitivity analysis) was obtained from the meta-analysis of i) the sex-stratified models of case-control studies and the UKB and ii) the sex-combined model adjusted on sex for Finngen. For this meta-analysis, we included the sex-stratified models only adjusted on PCs (Supplementary Table S6).

FinnGen was excluded from the e-XCI meta-analyses adjusted on i) age and ii) age and *APOE,* and from the r-XCI meta-analyses adjusted on i) sex and age and ii) sex, age and *APOE.* Indeed, only the sex-stratified results were available for these models, which cannot be meta-analysed together because FinnGen samples are related.

Inflation of the test statistics was computed using only independent common variants, defined as variants 1) with MAF > 0.01 and 2) selected with the PLINK pruning procedure among EADB-core variants, by keeping only one variant from each pair of variants with r^2>0.2 and within 500 kb from each other. LD was computed in female samples only.

For results display, all r-XCI and s-XCI approaches OR and confidence intervals were rescaled to the real XCI coding (equivalent to G = {0, 1} for males and G = {0, 0.5, 1}).

7. Sex-stratified analysis

The differences of effect between males and females were obtained using the sex-stratified meta-analyses; we computed the interaction p-value with a Wald test using the effect size (β_i) and corresponding standard error (se_i) of the interaction between two groups:

$\beta_i = \beta_F - \beta_M$; se_i = square root($se_M^2 + se_F^2$), where β_F and β_M are the effect sizes of the female-only and male-only (reference) models, respectively, and se_M and se_F are their standard errors.

E. Supplementary analyses

1. Cognitive decline analysis

We used the following linear mixed model:

$$NormMMSE_{ij} = \beta_0 + \beta_{Time}Time_{ij} + \beta_{Age}(Age)_{ij} + \beta_{Age*Time}(Age*Time)_{ij} + \beta_{PCs}(PCs)_{ij} + \beta_{PCs*Time}(PCs*Time)_{ij} + \beta_{DS}(DS)_{ij} + \beta_{DS*Time}(DS*Time)_{ij} + b_{i0} + b_{iTime}Time + \varepsilon_{ij}$$

Where DS is the variant probability, ij is the j^{th} follow-up of the i^{th} individual, β_X is the fixed effect of a term X, b_{iX} is the random effect of the i^{th} individual for a term X, with $b_{iX} \sim N(\mu, \sigma|X)$, and ε is an unknown vector of random errors with $\varepsilon \sim N(\mu, \sigma)$.

We used the following sex-combined quadratic mixed model:

$NormMMSE_{ij} = \beta_0 + \beta_{Time}Time_{ij} + \beta_{Sex}(Sex)_{ij} + \beta_{Sex*Time}(Sex*Time)_{ij} + \beta_{Sex*Time2}(Sex*Time^2)_{ij} + \beta_{Age}(Age)_{ij} + \beta_{Age*Time}(Age*Time)_{ij} + \beta_{Age*Time2}(Age*Time^2)_{ij} + + \beta_{PCs}(PCs)_{ij} + \beta_{PCs*Time}(PCs*Time)_{ij} + \beta_{PCs*Time2}(PCs*Time^2)_{ij} + \beta_{DS}(DS)_{ij} + \beta_{DS*Time}(DS*Time)_{ij} + \beta_{DS*Time2}(DS*Time^2)_{ij} + b_{i0} + b_{iTime}Time + b_{iTime2}Time^2 + \varepsilon_{ij}$

All models were computed using the 'lmer' function from the 'lme4' R package (Bates et al., 2015).

We used the 'rma.uni' function from the 'metafor' R package (Viechtbauer, 2010) for the linear model's results meta-analysis and the 'mvtmeta_fe' function from the 'mvtmeta' R package (Gasparrini et al., 2012) for the quadratic model's results meta-analysis.

2. Gene-based analysis

Gene–based analyses were performed using MAGMA v1.08 (de Leeuw et al., 2015). The analysis was corrected for the number of variants in each gene, LD between variants and LD between genes. LD was computed from the EADB-core TOPMed imputed dataset using only genotypes with high imputation quality (at least one GP ≥ 0.9 in EADB-core). Each variant with a high imputation quality was assigned to its closest gene, using a window of 35 kb upstream and 10 kb downstream. We used q-values to account for multiple testing (804 genes were considered in the analysis). However, we did not identify any X chromosome gene significantly associated with AD risk at the X chromosome level, whatever the approach, with the gene-based analysis.

3. *TMEM187-G6PD/IKBKG* locus in EADB-core

We performed the r-XCI approach analysis for the three rare variants associated at the X-chromosome-wide significance threshold with AD-risk in the *TMEM187-G6PD/IKBKG* locus stratified per country in the EADB-core study. To account for the rarity of the variants, the association tests were performed using Firth's penalized logistic regression with the logistf() function from the logistf R package (v1.26). Each model was adjusted for sex, genotyping center and 10 PCs of the corresponding country. The analyses were only performed in German, Spanish, French, British, Greek, Italian, Dutch and Swedish samples, which included at least one carrier of the three rare variants each. For each country, we filtered out variants with at least one missing datum (on effect, standard error, or p-value) or an absolute effect size greater than 5. The results were then combined across studies in a fixed effect meta-analysis with an inverse-variance weighted approach with METAL (Willer at al., 2010).

4. Comparison of the results with Belloy et al 2024 study

The loci identified in the Belloy et al., 2024 study and in our study do not overlap (Supplementary Table S15). Even if two signals are located in the *NLGN4X* region, they are

different: the two index variants (rs150798997 in Belloy et al., rs4364769 in our study) are located 270,925 bp away and their LD (r^2) is 0 in the EADB-core dataset.
This could be due to several reasons:

a) some of the loci are false positives; a higher rate of false positives is expected among signals with X-chromosome-wide significance rather than genome-wide significance.
b) the winner's curse: signals are expected to be slightly inflated in the study which identified them.
c) a difference in power.
d) the Belloy et al. study did not perform statistical tests under the e-XCI model, although there was a general assessment of e-XCI.
e) the phenotype definition. The Belloy et al study analyzed 15,081 clinical-AD cases (10.9% of their total raw number of cases), 41,091 registry-AD and ADD cases (29.7%) and 82,386 proxy-ADD cases (59.5%) (ADD=Alzheimer's disease and dementia). In our main analysis, we included 52,214 clinical-AD cases (45%), 7,759 registry-AD cases (6.7%) and 55,868 proxy-ADD cases (48%). We note that, while there are 3 levels of AD definition in FinnGen, we used the stricter one (G6_Alzheimer), while Belloy et al. used the most lenient one (AD-wide). Additionally, the MVP registry cases used in the Belloy et al. study, are ADD registry cases rather than AD registry cases. Overall, our study is made up of a much larger proportion of clinical-AD cases and uses a stricter definition of registry-AD cases compared to the Belloy et al. study. There could be a higher proportion of non-AD dementia cases in the Belloy et al. study, which could lead to different genetic signals. Additionally, the proxy definition is also quite different in the two studies. We used a definition very similar to the classical one, initially proposed for autosomes (Liu et al, 2017), while Belloy et al. used a much more complex definition, leading to a different correction factor applied to the XWAS summary statistics.

F. List of software

Softwares:
bcftools (v1.9) (Danecek et al., 2021)
Eagle v2.4 (Loh et al. 2016)
IMPUTE2 (Howie et al. 2009)
METAL (Willer at al., 2010)
Minimac4 (v4-1.0.2) (Das et al. 2016)
SAIGE (v1.0.9) (Zhou et al. 2018)
SHAPEIT3 (Delaneau et al. 2012)
SNPTEST (v2.5.6) (Marchini et al., 2007)
REGENIE (v2.2.4) (Mbatchou et al., 2021)
PLINK (v1.9) (Purcell et al., 2007)

R packages:
coloc (v5.2.3) (Giambartolomei et al., 2014)
geepack (Halekoh et al., 2006)
GWAF (v2.2) (Chen et al., 2009)
metafor (Viechtbauer, 2010)
mvtmeta (Gasparrini et al., 2012)
snpStats (v1.44.0) (snpStats, 2023)

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University of Pittsburgh, P50 AG005133, AG030653, AG041718, AG07562, AG02365; University of Southern California, P50 AG005142; University of Texas Southwestern, P30 AG012300; University of Miami, R01 AG027944, AG010491, AG027944, AG021547, AG019757; University of Washington, P50 AG005136, R01 AG042437; University of Wisconsin, P50 AG033514; Vanderbilt University, R01 AG019085; and Washington University, P50 AG005681, P01 AG03991, P01 AG026276. HP was supported by AG025711. ER was supported by CCNA. The Kathleen Price Bryan Brain Bank at Duke University Medical Center is funded by NINDS grant # NS39764, NIMH MH60451 and by Glaxo Smith Kline. Support was also from the Alzheimer's Association (LAF, IIRG-08-89720; MP-V, IIRG-05- 14147), the US Department of Veterans Affairs Administration, Office of Research and Development, Biomedical Laboratory Research Program, and BrightFocus Foundation (MP-V, A2111048). P.S.G.-H. is supported by Wellcome Trust, Howard Hughes Medical Institute, and the Canadian Institute of Health Research. Genotyping of the TGEN2 cohort was supported by Kronos Science. The TGen series was also funded by NIA grant AG041232 to AJM and MJH, The Banner Alzheimer's Foundation, The Johnnie B. Byrd Sr. Alzheimer's Institute, the Medical Research Council, and the state of Arizona and also includes samples from the following sites: Newcastle Brain Tissue Resource (funding via the Medical Research Council, local NHS trusts and Newcastle University), MRC London Brain Bank for Neurodegenerative Diseases (funding via the Medical Research Council), South West Dementia Brain Bank (funding via numerous sources including the Higher Education Funding Council for England (HEFCE), Alzheimer's Research Trust (ART), BRACE as well as North Bristol NHS Trust Research and Innovation department and DeNDRoN), The Netherlands Brain Bank (funding via numerous sources including Stichting MS Research, Brain Net Europe, Hersenstichting Nederland Breinbrekend Werk, International Parkinson Fonds, Internationale Stiching Alzheimer Onderzoek), Institut de Neuropatologia, Servei Anatomia Patologica, Universitat de Barcelona. ADNI data collection and sharing was funded by the National Institutes of Health Grant U01 AG024904 and Department of Defense award number W81XWH-12-2-0012. ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative

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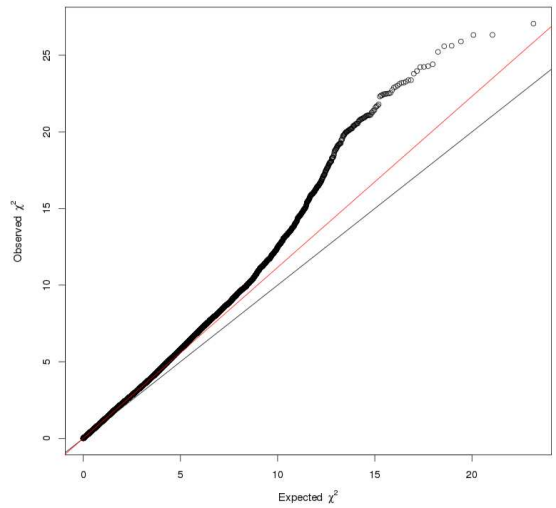
(www.veripalvelu.fi/verenluovutus/biopankkitoiminta), Terveystalo Biobank (www.terveystalo.com/fi/Yritystietoa/Terveystalo-Biopankki/Biopankki/) and Arctic Biobank (https://www.oulu.fi/en/university/faculties-and-units/faculty-medicine/northern-finland-birth-cohorts-and-arctic-biobank). All Finnish Biobanks are members of BBMRI.fi infrastructure (www.bbmri.fi). Finnish Biobank Cooperative -FINBB (https://finbb.fi/) is the coordinator of BBMRI-ERIC operations in Finland. The Finnish biobank data can be accessed through the Fingenious® services (https://site.fingenious.fi/en/) managed by FINBB.

I. Supplementary Figures

a)



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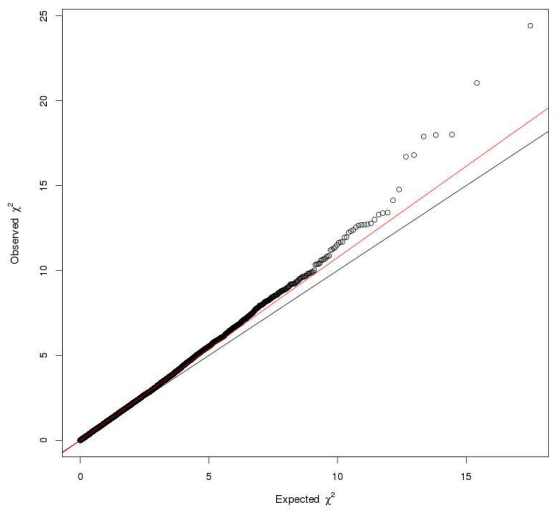

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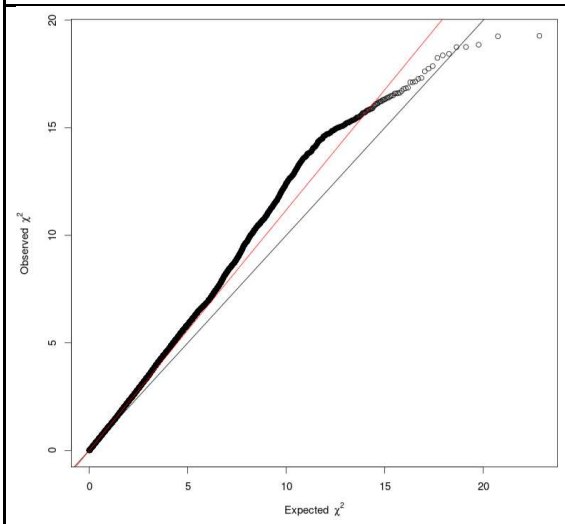

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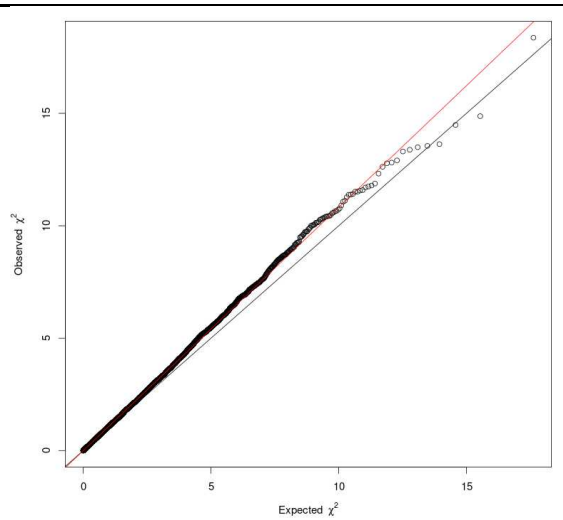

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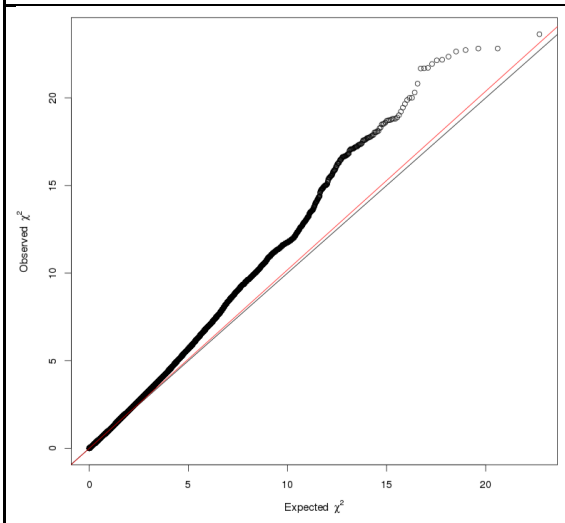

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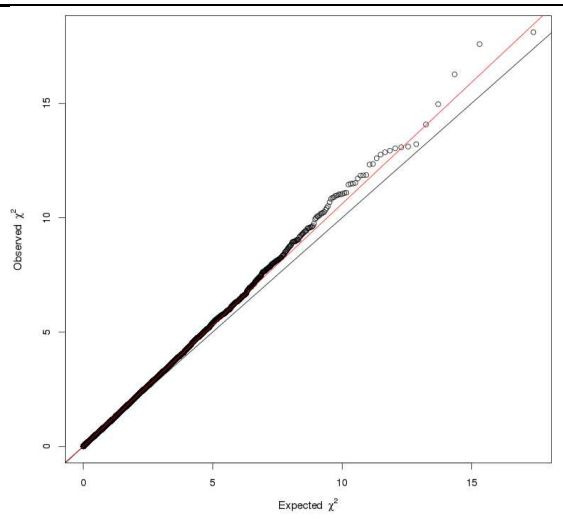

Figure S1: QQ-plots of the r-XCI approach meta-analyses. The black line represents the affine function (y=x) and the red line a regression of observed values against expected values. The left column (a), c) and e)) shows QQ-plots with only common variants (MAF > 0.01), and the right column (b), d) and f)) the QQ-plots with only independent common variants (MAF > 0.01 and variants selected with the PLINK pruning procedure applied on EADB-core variants, which keeps only one variant from each pair of variants with r^2>0.2 and within 500 kb from each other, considering only female samples). Figures a) and b) are QQ-plots of the r-XCI meta-analysis including AD-proxy cases, with lambda = 1.116 and 1.074, respectively. Figures c) and d) are QQ-plots of the r-XCI meta-analysis including only diagnosed AD-cases, with lambda = 1.118 and 1.082, respectively. Figures e) and f) are QQ-plots of the r-XCI meta-analysis excluding biobanks, with lambda = 1.019 and 1.061, respectively.

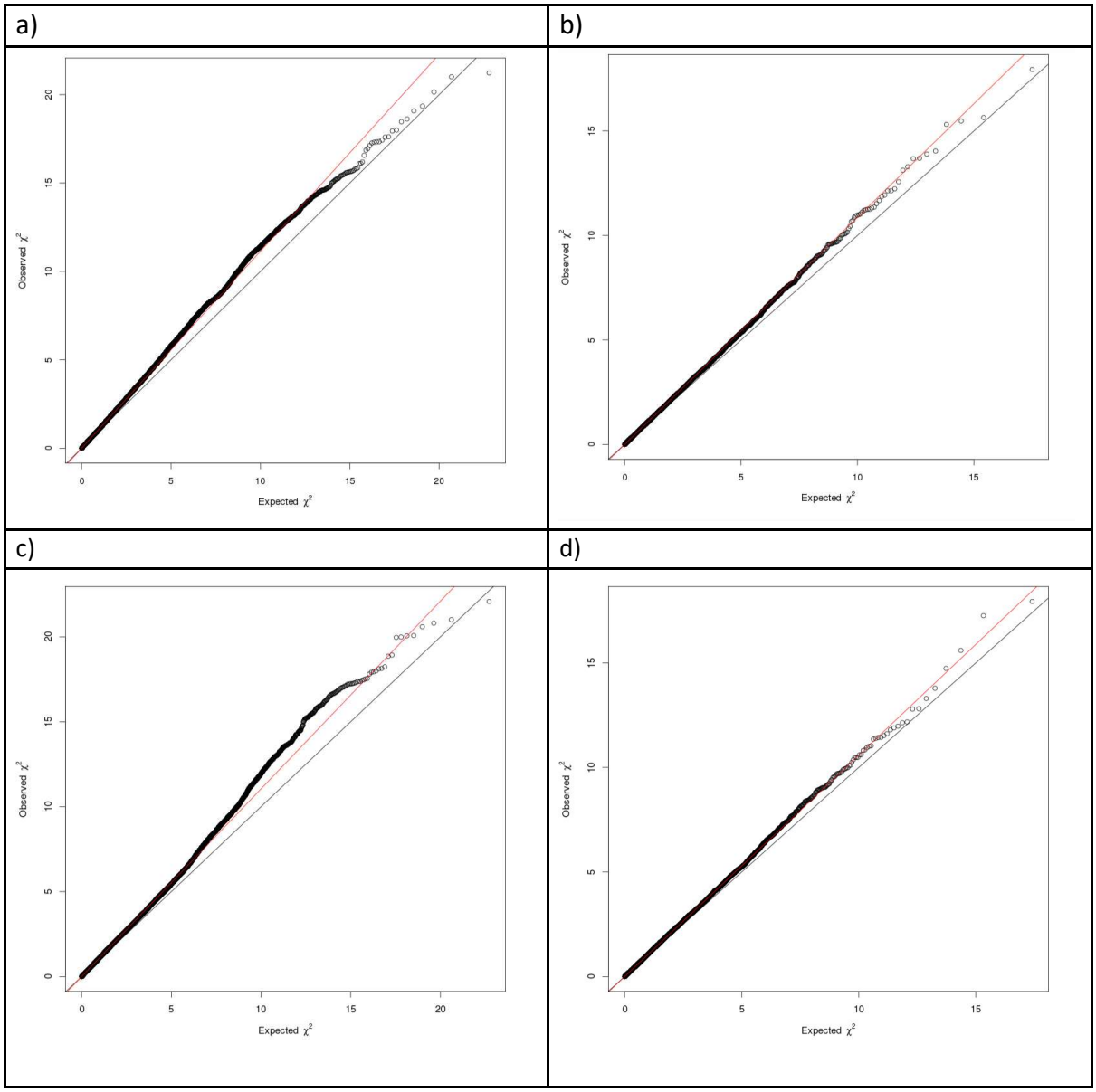

Figure S2: QQ-plots of the e-XCI approach meta-analyses. The black line represents the affine function (y=x) and the red line a regression of observed values against expected values. The left column (a) and c)) shows QQ-plots with only common variants (MAF > 0.01), and the right column (b) and d)) the QQ-plots with only independent common variants (MAF > 0.01 and variants selected with the PLINK pruning procedure applied on EADB-core variants, which keeps only one variant from each pair of variants with r^2>0.2 and within 500 kb from each other, considering only female samples). Figures a) and b) are QQ-plots of the e-XCI meta-analysis including only diagnosed AD-cases, with lambda = 1.114 and 1.087, respectively. Figures c) and d) are QQ-plots of the e-XCI meta-analysis excluding biobanks, with lambda = 1.105 and 1.059, respectively.

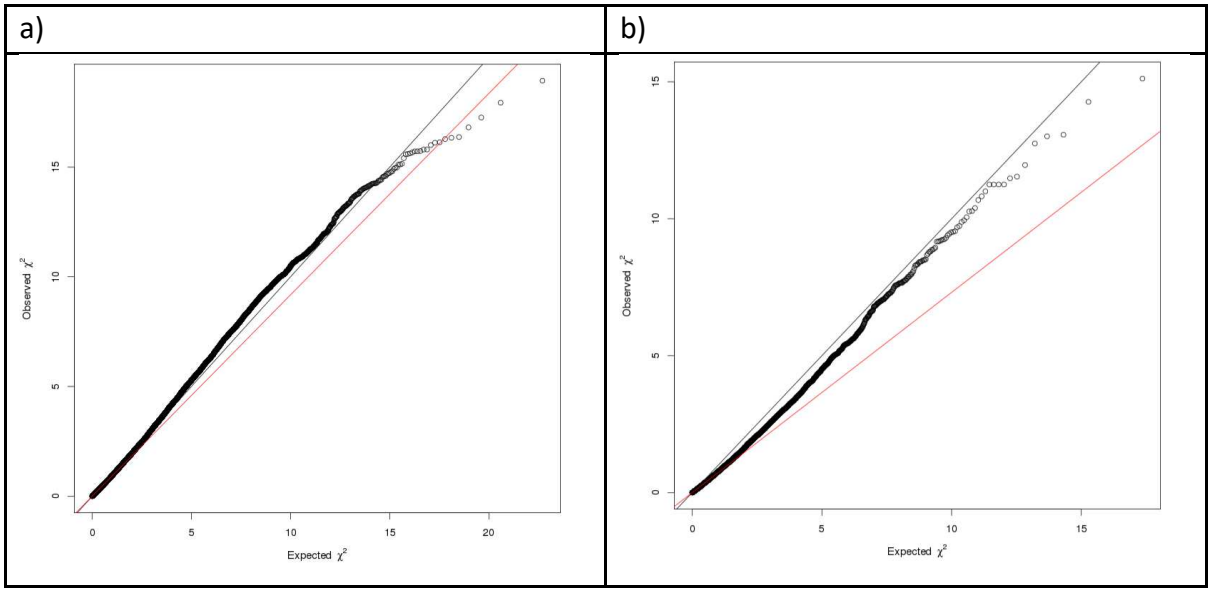

Figure S3: QQ-plots of the s-XCI approach meta-analysis, including only case-control studies, with lambda = 0.914 and 0.735, respectively. The black line represents the affine function (y=x) and the red line a regression of observed values against expected values. The left column (a) shows QQ-plots with only common variants (MAF > 0.01), and the right column (b) the QQ-plots with only independent common variants (MAF > 0.01 and variants selected with the PLINK pruning procedure applied on EADB-core variants, which keeps only one variant from each pair of variants with r^2>0.2. and within 500 kb from each other, considering only female samples).

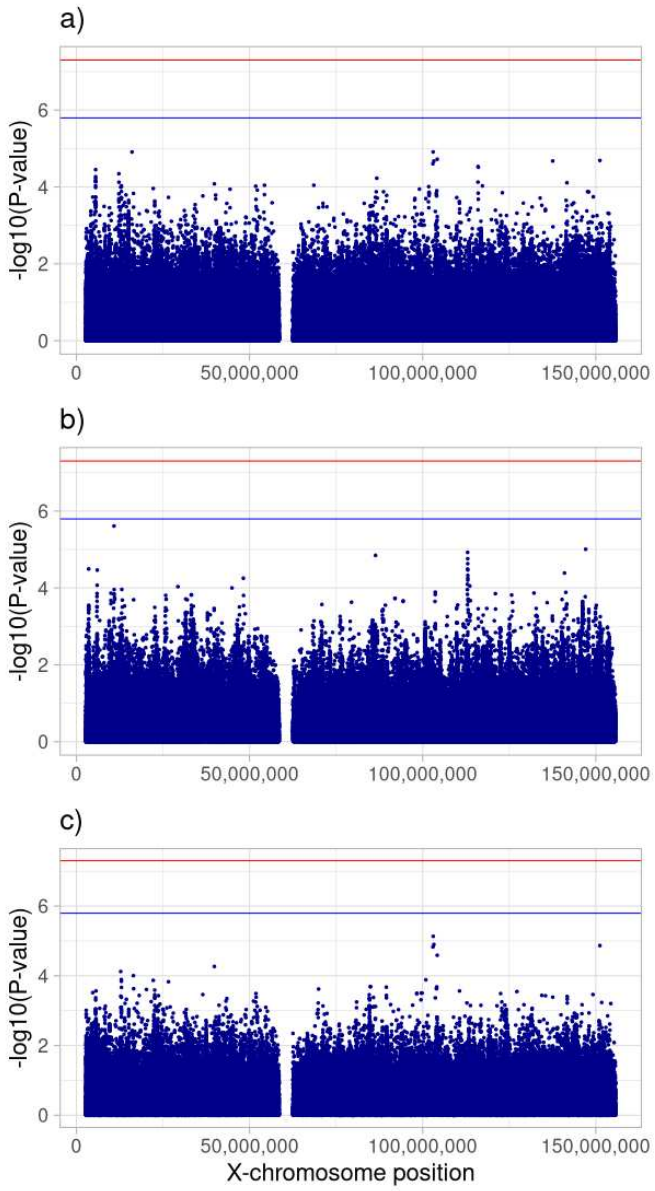

Figure S4: Manhattan plot of the a) female-only, b) male-only and c) interaction between genotype and sex in the meta-analysis excluding AD-proxy cases. The red and blue lines represent the genome-wide significant threshold (5 x 10^{-8}) and the X-chromosome-wide significant threshold (1.6 x 10^{-6}), respectively.

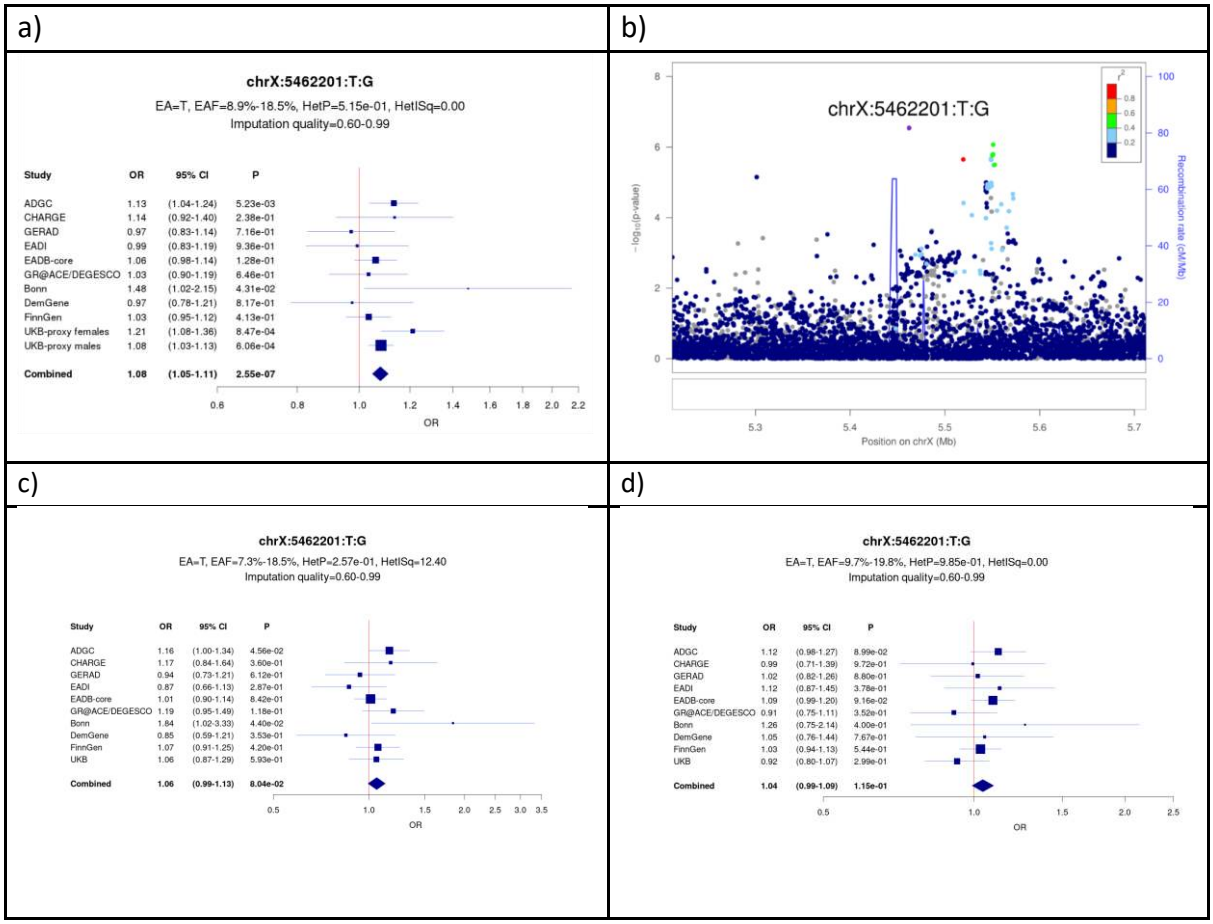

Figure S5: Forest plots and locus zoom of rs4364769 (chrX:5462201:T:G): a) forest plot and b) locus zoom in the r-XCI meta-analysis including AD-proxy, c) forest plot of female-only models excluding AD-proxy, where genotypes were coded G = {0, 0.5, 1} and d) forest plot of male-only models excluding AD-proxy, where genotypes were coded G = {0, 1}. The variant in purple is rs4364769. The positions are in GRCh38 Assembly. OR: odds ratio, CI: confidence interval, EA: effect allele, EAF: effect allele frequency range across all studies, HetP: heterogeneity P value, HetISq: heterogeneity statistic.

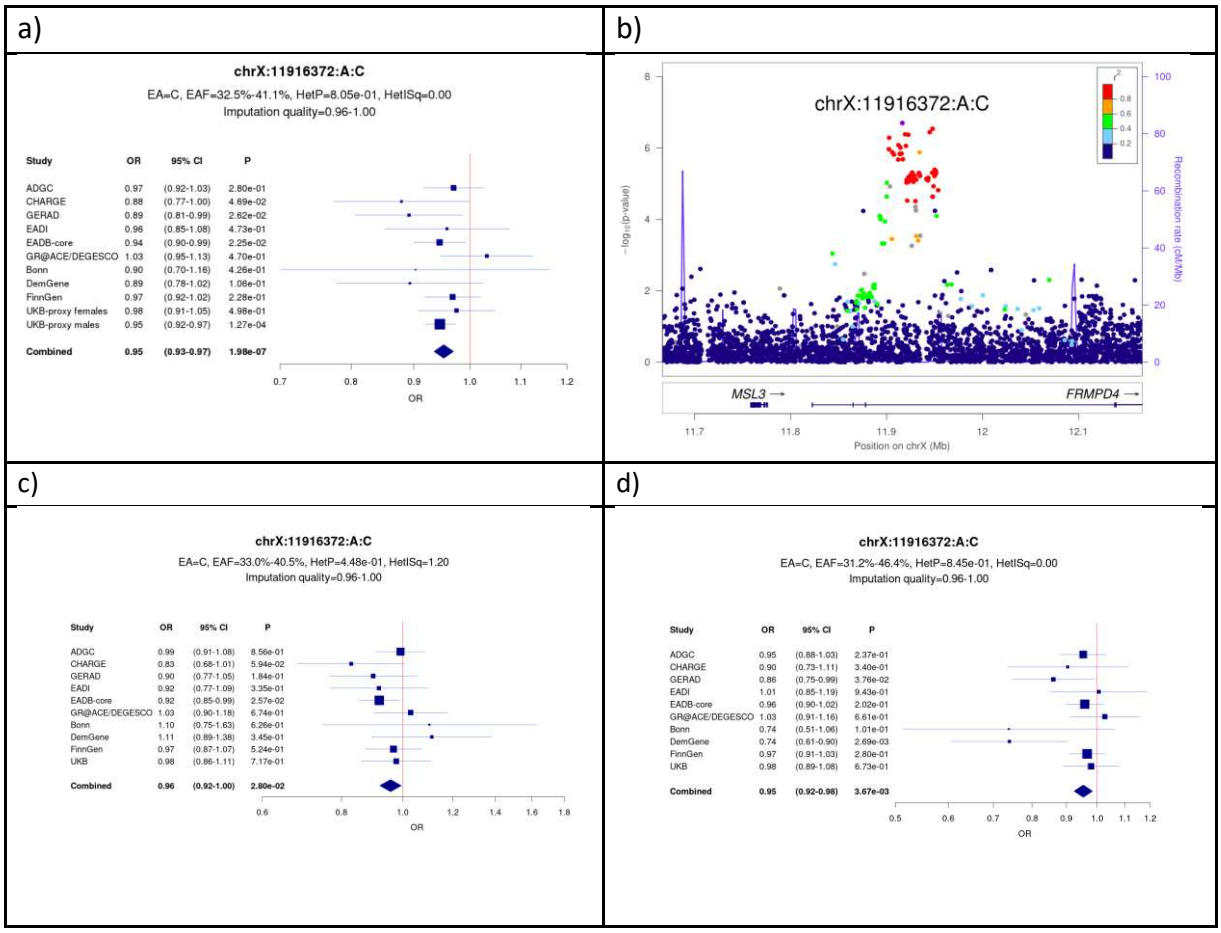

Figure S6: Forest plot and locus zoom of rs5933929 (chrX:11916372:A:C): a) forest plot and b) locus zoom in the r-XCI meta-analysis including AD-proxy, c) forest plot of female-only models excluding AD-proxy, where genotypes were coded G = {0, 0.5, 1} and d) forest plot of male-only models excluding AD-proxy, where genotypes were coded G = {0, 1}. The variant in purple is rs5933929. The positions are in GRCh38 Assembly. OR: odds ratio, CI: confidence interval, EA: effect allele, EAF: effect allele frequency range across all studies, HetP: heterogeneity P value, HetISq: heterogeneity statistic.

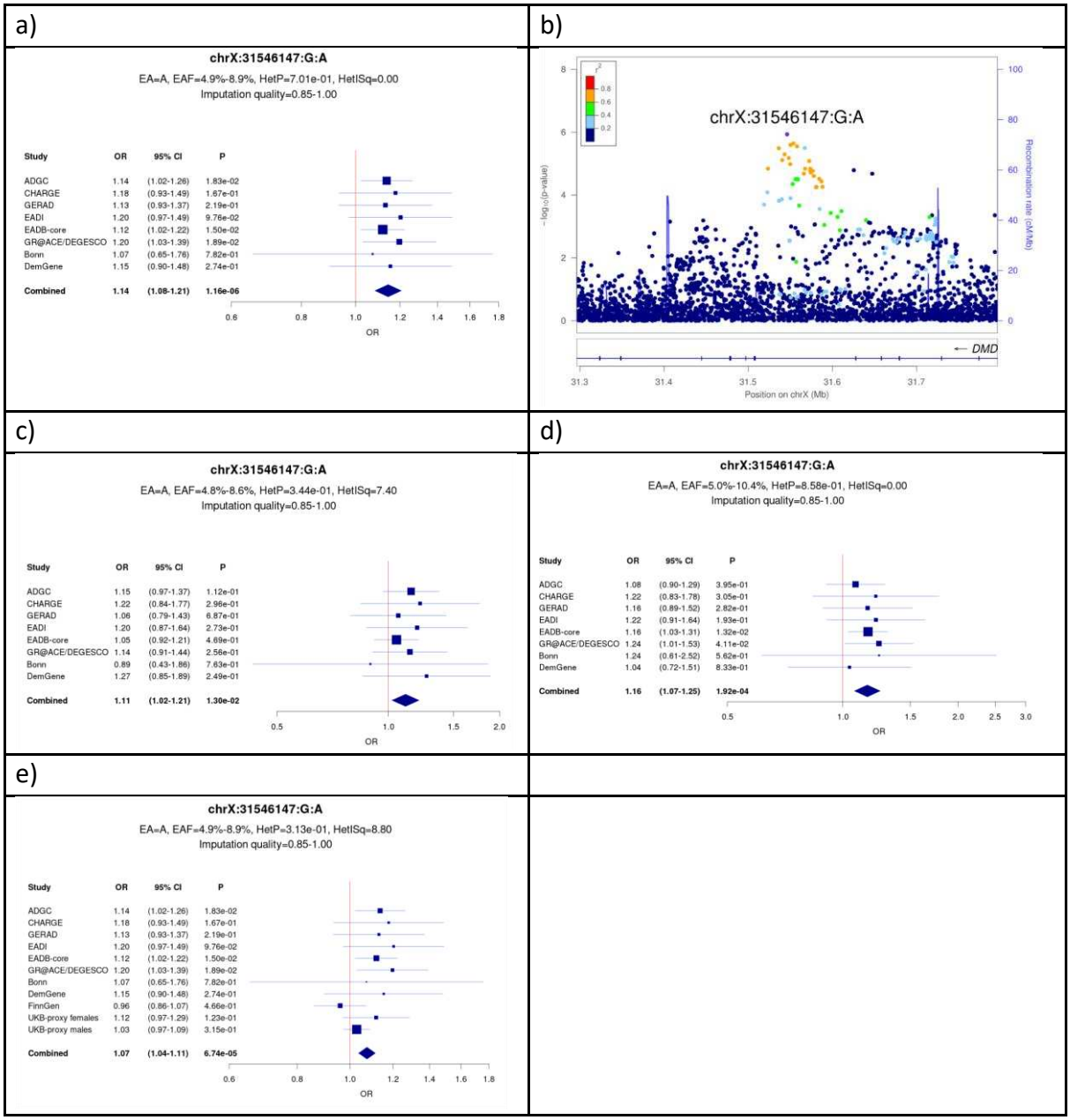

Figure S7: Forest plot and locus zoom of rs5972406 (chrX:31546147:G:A): a) forest plot of the r-XCI meta-analysis excluding biobanks, b) locus zoom in the r-XCI meta-analysis excluding biobanks, c) forest plot of the female-only meta-analysis excluding biobanks and d) forest plot of the male-only meta-analysis excluding biobanks, e) forest plot of the r-XCI meta-analysis including AD-proxy cases. The variant in purple is rs5972406. The female-only and the male-only models were coded G = {0, 0.5, 1} and G = {0, 1}, respectively. The positions are in GRCh38 Assembly. OR: odds ratio, CI: confidence interval, EA: effect allele, EAF: effect allele frequency range across all studies, HetP: heterogeneity P value, HetISq: heterogeneity statistic.

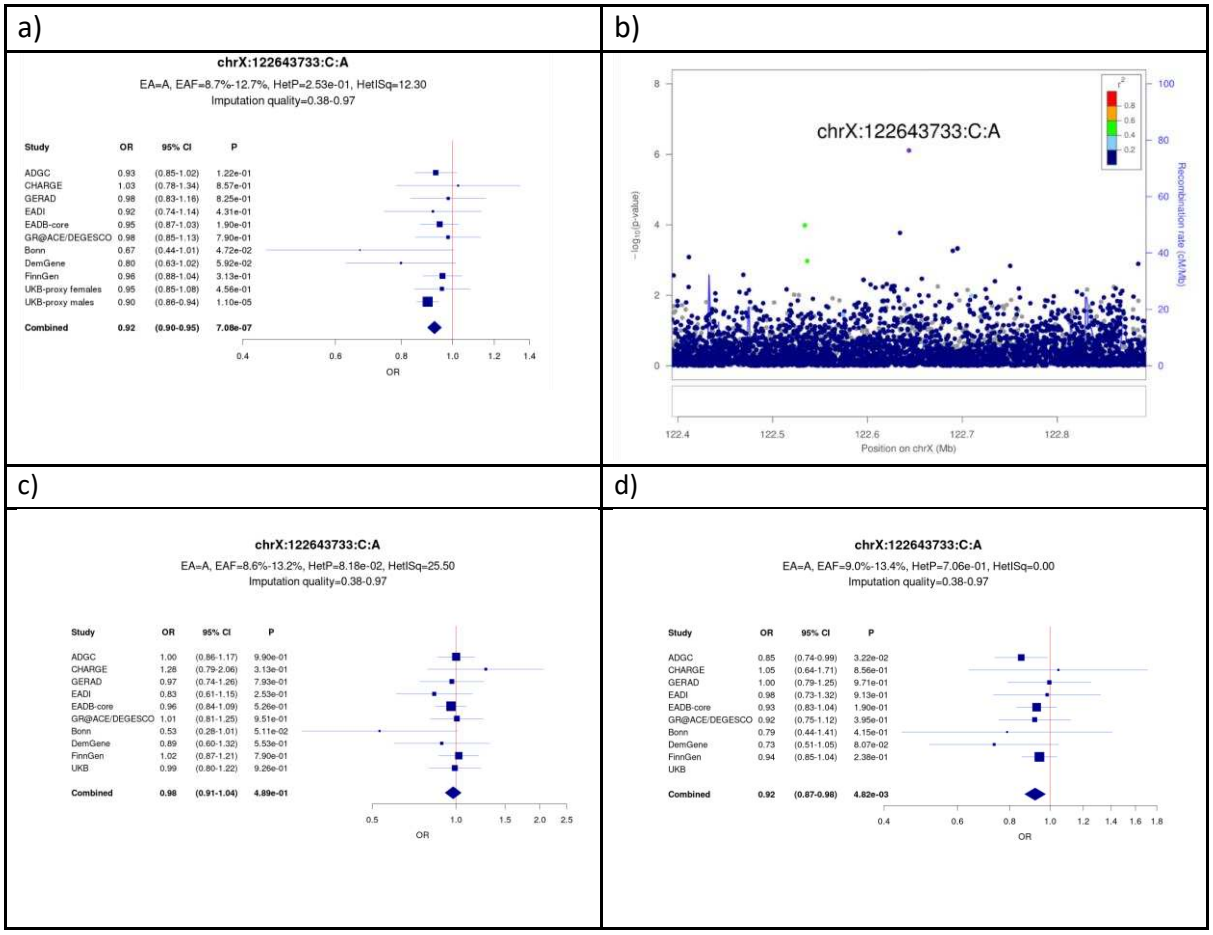

Figure S8: Forest plot and locus zoom of rs191195705 (chrX:122643733:C:A): a) forest plot and b) locus zoom in the r-XCI meta-analysis including AD-proxy, c) forest plot of female-only models excluding AD-proxy, where genotypes were coded G = {0, 0.5, 1}, and d) forest plot of male-only models excluding AD-proxy, where genotypes were coded G = {0, 1}. The variant in purple is rs191195705. The positions are in GRCh38 Assembly. OR: odds ratio, CI: confidence interval, EA: effect allele, EAF: effect allele frequency range across all studies, HetP: heterogeneity P value, HetISq: heterogeneity statistic.

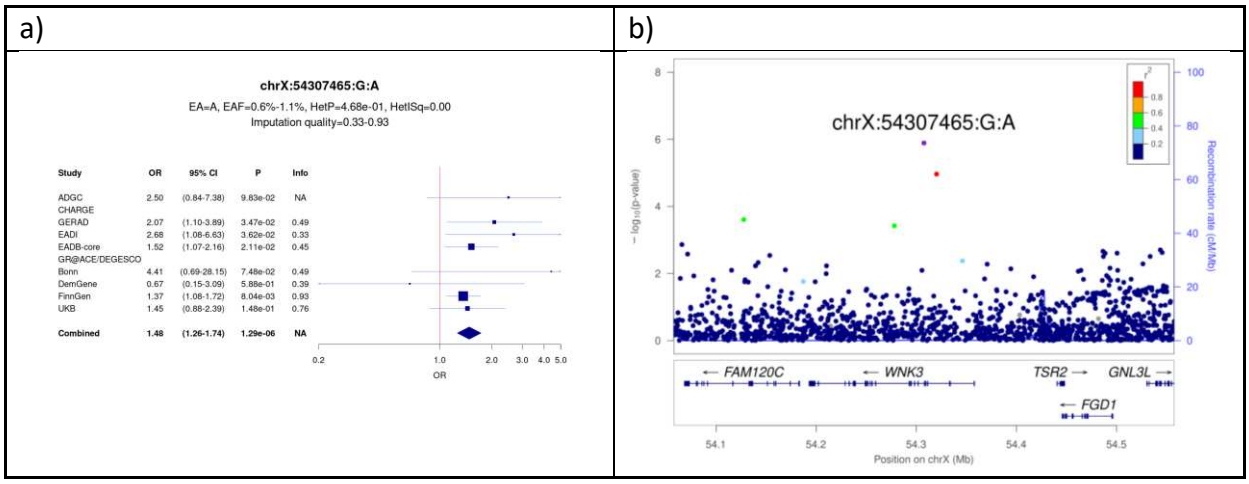

Figure S9: Forest plot and locus zoom of rs189139822 (chrX:54307465:G:A) in the r-XCI meta-analysis including only diagnosed AD-cases: a) forest plot, b) locus zoom. The variant in purple is rs189139822. The positions are in GRCh38 Assembly. OR: odds ratio, CI: confidence interval, EA: effect allele, EAF: effect allele frequency range across all studies, HetP: heterogeneity P value, HetISq: heterogeneity statistic.

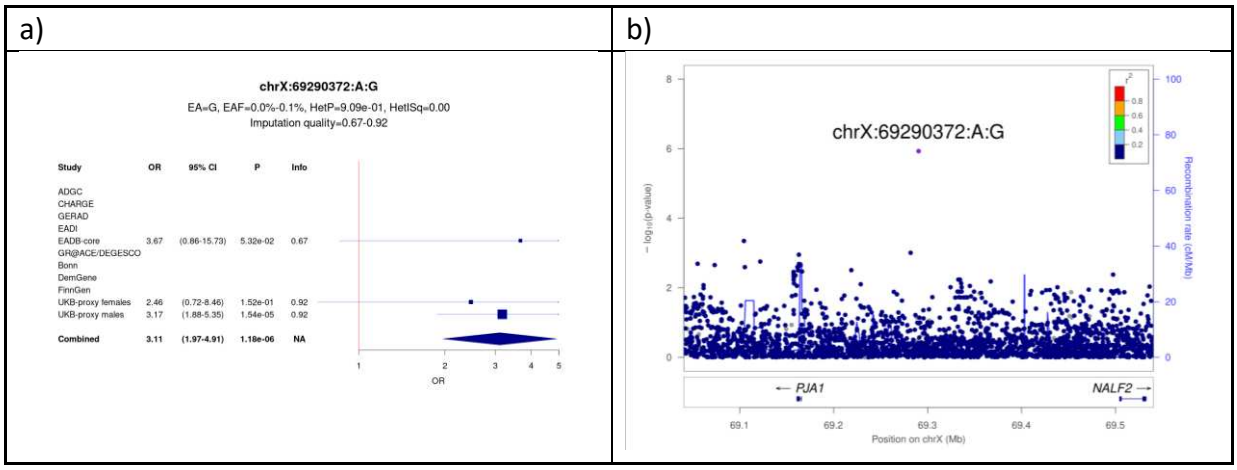

Figure S10: Forest plot and locus zoom of rs771148434 (chrX:69290372:A:G) in the r-XCI meta-analysis including AD-proxy: a) forest plot, b) locus zoom. The variant in purple is rs771148434. The positions are in GRCh38 Assembly. OR: odds ratio, CI: confidence interval, EA: effect allele, EAF: effect allele frequency range across all studies, HetP: heterogeneity P value, HetISq: heterogeneity statistic.

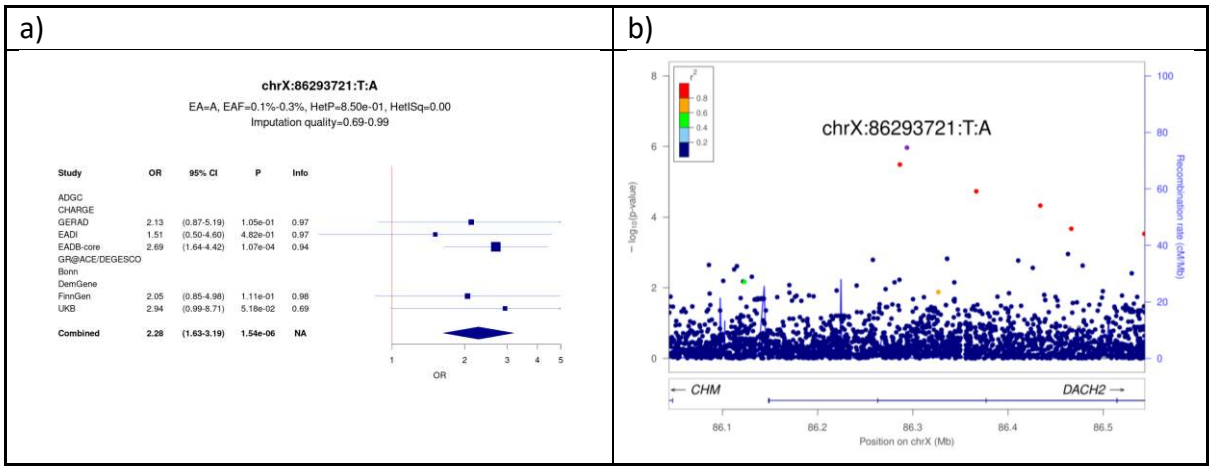

Figure S11: Forest plot and locus zoom of rs1326297223 (chrX:86293721:T:A) in the r-XCI meta-analysis. including AD-proxy: a) forest plot, b) locus zoom. The variant in purple is rs1326297223. The positions are in GRCh38 Assembly. OR: odds ratio, CI: confidence interval, EA: effect allele, EAF: effect allele frequency range across all studies, HetP: heterogeneity P value, HetISq: heterogeneity statistic.

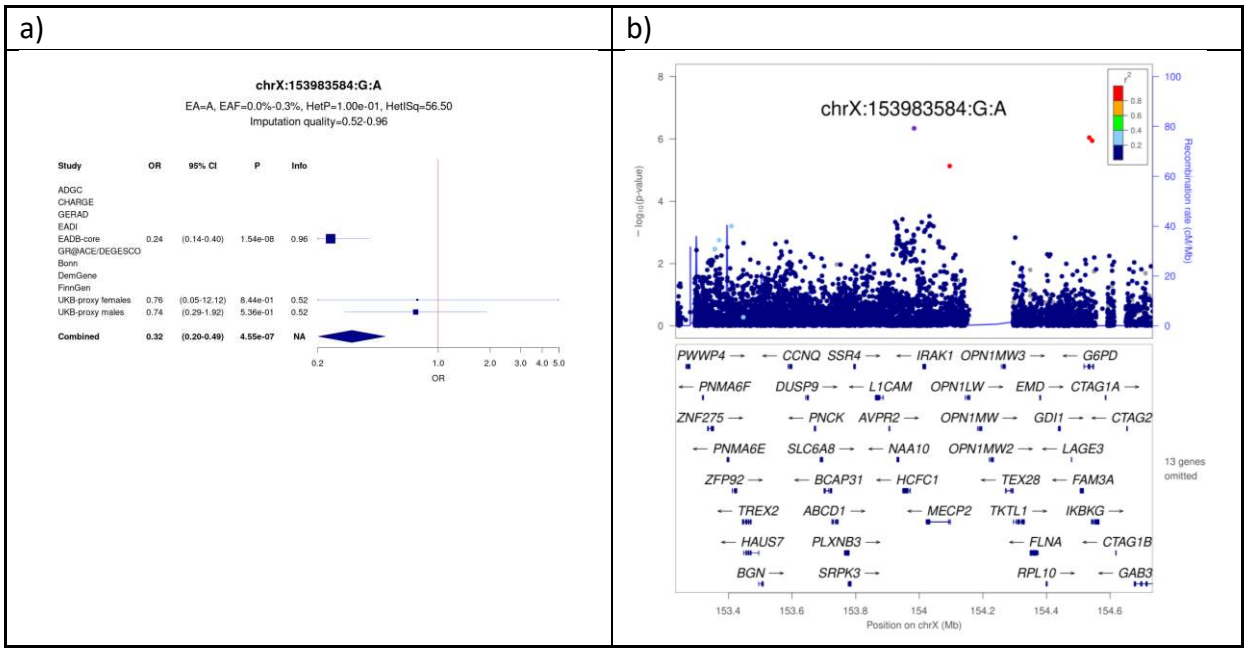

Figure S12: Forest plot and locus zoom of rs782044000 (chrX:153983584:G:A) in the r-XCI meta-analysis including AD-proxy: a) forest plot of the r-XCI meta-analysis, b) locus zoom. The variant in purple is rs782044000. The positions are in GRCh38 Assembly. OR: odds ratio, CI: confidence interval, EA: effect allele, EAF: effect allele frequency range across all studies, HetP: heterogeneity P value, HetISq: heterogeneity statistic.

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K. Appendix – Analysis plans

An analysis plan for the X-chromosome wide association study for Alzheimer's disease was provided to each study, including:

1. an overall XWAS for Alzheimer's disease analysis plan,
2. an X-chromosome Quality control and TopMed imputation analysis plan,
3. Instructions to use bcftools plugin fix-GP-males,
4. Instructions to use bcftools plugin fix-GT-males,
5. bcftools plugin fix-GP-males C code,
6. snpStats R script for X-chromosome wide association.

The documents 1-4 are also provided in this section, in this order. Documents 5 and 6 are provided in Zenado (https://doi.org/10.5281/zenodo.14001011).

X-chromosome association analysis plan for Alzheimer's Disease

The objective of this analysis is to identify new genetic risk factors on the non-PAR region of the X-chromosome.

This document describes the association analysis steps for the X-chromosome nonPAR region for the IGAP-EADB-UKBB studies (studies with and without related individuals).

Please provide a paragraph describing your study and its specificities to include in the "Sample description" of the X-chromosome paper.

Summary

Appendix

1. Analysis strategies

Three approaches will be considered:

1) XCI: The main analysis will be conducted under the hypothesis of random X-chromosome inactivation (XCI).
2) eXCI: Given that some genes escape inactivation (eXCI), we will estimate male and female effects separately given coding scheme disparities.
3) sXCI: As the choice of the inactivated X-chromosome copy can be skewed toward a specific copy (sXCI), we will estimate female effect under a general model.

2. Data

Raw genotype data: We use the same sample and variant QC as described in the EADB-GSA paper pipeline (https://www.nature.com/articles/s41588-022-01024-z), but including additionally the following steps:

- Samples showing high missingness on the X-chromosome, male samples showing high level of heterozygosity and samples for which genetic gender cannot be determined should be excluded.
- X-chromosome non-PAR variants showing high missingness in either males or females, variants showing high heterozygosity in males should be excluded.

Imputation panel: Preferably **TopMed.**

A more detailed X-chromosome specific quality control and TOPMed imputation analysis plan can be provided if needed.

Subjects: Individuals with European ancestry.

Phenotype: Alzheimer's disease (AD) status (AD cases = 1, controls = 0). Other dementia should be excluded for all studies.

Exposure: Self-reported sex coded as 0 = male, 1 = female. When missing, use genetically determined sex.

Exclusions: Remove controls aged under 30 and individuals with missing Alzheimer's disease status.

UKBioBank related samples (up to 3rd degree) should be excluded.

GERAD samples related with EADB-core or Bonn should be excluded.

Genetic data format: Dosage or genotype probabilities (GP). Females should be coded (AA=0, AB=1, BB=2) and males should be coded as homozygous females (A=0, B=2). Thus, when using GPs, female genotypes are encoded (GP1 = P(AA), GP2 = P(AB), GP3 = P(BB))

and male genotypes are encoded (GP1 = P(A), GP2 = 0, GP3 = P(B)). When using dosage, females should have D = P(AB) + 2 * P(BB) and males D = 2 * P(B).

For vcf format: As TOPMed imputed data on Michigan Imputation Server codes males as hemizygous (A=0, B=1, with only P(A) and P(B)), a bcftools plugin was created by Benjamin Grenier-Boley to modify males GP ploidy in a vcf file ("fix-GP-chrX-nonPAR-males"). As the preferred software SNPTEST requires a consistent ploidy between GP and genotype (GT) (even if you use only GP), we advise to correct males GT as well with the "fixploidy" bcftools plugin.

The plugin "fix-GP-chrX-nonPAR-males" is attached along with a how-to-use file for both "fix-GP-chrX-nonPAR-males" and "fixploidy".

For any other format: Please, make sure that males are coded as homozygous females (A=0, B=2).

3. Covariate adjustments

The following covariates will be considered in at least one of the adjustments:

- Principal components or/and center as necessary (both types of variables are referred to as PCs below);
- Sex;
- Age (for cases, use age at onset, but when missing use age at last exam, then age baseline, then age at death; for controls, use age at last exam);
- APOE e4 and e2. The number of alleles should be coded 0, 1 ou 2 (or in dosage if imputed). If unavailable in the clinical data, APOE status can be defined using the imputed data, if the two APOE variants have a good imputation quality. For a given individual, genotypes of the two APOE variants should only be considered if their probability is higher than 0.8. This means that there can be missing APOE status even after imputation.

The following adjustments will be included for studies without related individuals:

- A1_PC: PCs (main model)
- A2_age_PC: PCs + age
- A3_APOE_age_PC: PCs + age + APOE4 + APOE2

The following adjustments will be included for studies with related individuals:

- A1_PC: PCs
- A2_age_PC: PCs + age
- A3_APOE_age_PC: PCs + age + APOE4 + APOE2
- A4_sex_PC: PCs + sex (main model)

4. Association tests

To limit the computational burden, all adjustments will not be considered for all models.

Note: We require the same models for studies with and without related individuals, except for the first model (M1). For studies without related individuals, we require a sex-combined model with a robust variance adjusted on PCs (M1_ADD_robust) and for studies with related individuals, we require a sex-combined model adjusted on sex and PCs (M1_ADD_combined).

Studies without related individuals

The following models and adjustments will be considered for studies without related individuals:

1) M1_ADD_robust: logistic regression of AD status in males and females combined with additive genetic model and a robust variance estimation (Appendix model 1).
   + A1_PC
2) M2_female_ADD: logistic regression of AD status in females only with additive genetic model (Appendix model 2).
   + A1_PC
   + A2_age_PC
   + A3_APOE_age_PC
3) M2_male_ADD: logistic regression of AD status in males only with additive genetic model (Appendix model 2).
   + A1_PC
   + A2_age_PC
   + A3_APOE_age_PC
4) M3_female_GEN: logistic regression of AD status in females only with general genetic model (Appendix model 3).
   + A1_PC
   + A2_age_PC
   + A3_APOE_age_PC

We thus are requiring 10 analyses for each case-control study.

Model	M1_ADD_robust	M2_female_ADD	M2_male_ADD	M3_female_GEN
Males coding	0/2	/	0/2	/
Robust variance	yes	no	no	no
A1_PC	yes	yes	yes	yes
A2_age_PC	no	yes	yes	yes
A3_APOE_age_PC	no	yes	yes	yes

Studies with related individuals (including UKBB)

The following models and adjustments will be considered for studies with related individuals and the UKBioBank (even if related individuals are excluded from the UKBioBank):

1) M1_ADD_combined: logistic regression of AD status in males and females combined with additive genetic model (Appendix model 1).
   + A4_sex_PC
2) M2_female_ADD: logistic regression of AD status in females only with additive genetic model (Appendix model 2).
   + A1_PC
   + A2_age_PC
   + A3_APOE_age_PC
3) M2_male_ADD: logistic regression of AD status in males only with additive genetic model (Appendix model 2).
   + A1_PC
   + A2_age_PC
   + A3_APOE_age_PC
4) M3_female_GEN: logistic regression of AD status in females only with general genetic model (Appendix model 3). As several methods exist to perform a general model, please use the coding specified in Appendix model 3.
   + A1_PC
   + A2_age_PC
   + A3_APOE_age_PC

We thus are requiring 10 analyses for each family study.

Model	M1_ADD_combined	M2_female_ADD	M2_male_ADD	M3_female_GEN
Males coding	0/2	/	0/2	/
Robust variance	no	no	no	no
A1_sex_PC	yes	yes	yes	yes
A2_age_PC	no	yes	yes	yes
A3_APOE_age_PC	no	yes	yes	yes

Note: We did not find an option in SAIGE and GEE R-packages to compute a general model for M3_female_GEN. If this model can not be performed in SAIGE or in any other package for genome-wide association tests in large-scale data sets for the UKBioBank or in any GEE package for studies with related individuals, please only provide the other models (M1_ADD_combined, M2_female_ADD and M2_female_ADD).

5. Software for association analysis

Studies without related individuals

1) For studies without related individuals M2_female_ADD, M2_male_ADD and M3_female_GEN analysis, the preferred software is SNPTEST, (v2.5.6) (https://www.well.ox.ac.uk/~gav/snptest/) using the method 'newml'.

Be careful that sample order in the phenotype file should be the same as in the vcf file.

Be careful that SNPTEST requires a consistent ploidy between GP and GT (even if you use only GP). As males should be coded as homozygous females for GP, we advise to correct males GT with the +fixploidy bcftools plugin.

Examples of SNPTEST command line:
For M2_female_ADD and M2_male_ADD analysis:
- cov_names cov1 cov2
- data data_file_name sample_file_name # the phenotype is AD status
- exclude_samples Individual_exclusion_file_name # usual exclusion and exclude all males for M3_female_ADD or all females for M3_male_ADD
- frequentist 1 # 1 corresponds to an additive genetic model
- genotype_field GP # for vcf input data format as genotype probability
- method newml
- minimum_predictor_count 1
- o output_file_name
- pheno AD_status_variable_name
(note : the option -stratifiy_on of SNPTEST v2.5.6 does not seem to be working)

For M3_female_GEN analysis:
- cov_names cov1 cov2
- data data_file_name sample_file_name # the phenotype is AD status
- exclude_samples Individual_exclusion_file_name # usual exclusion and exclude all males
- frequentist 4 # 4 correspond to a general genetic model
- genotype_field GP #for vcf input data format as genotype probability
- method newml
- minimum_predictor_count 1
- o output_file_name
- pheno AD_status_variable_name
(note : the option -stratifiy_on of SNPTEST v2.5.6 does not seem to be working)

2) For studies without related individuals M1_ADD_robust analysis, the preferred software is the snpStats package in R (https://www.bioconductor.org/packages/release/bioc/html/snpStats.html).

The snpStats package can only read genotype probabilities in impute2 format (an example of an impute2 row: "--- variant_id variant_position variant_ref variant_alt GP_sample1 GP_sample2 ... "). Vcf data can be formatted into impute2 format with bcftools.

Example of bcftools command line:
bcftools query -S list_samples_included -f '--- %CHROM:%POS:%REF:%ALT\t%POS\t%REF\t%ALT[\t%GP]\n' -o impute2_data_file_name initial_vcf_data_file_name

With list_samples_included a text file containing the list of the included samples, and initial_vcf_data_file_name, the initial vcf file.

The snpStats package does not provide allele frequencies and allele count, be sure to compute this information.

See an example of snpStats script attached.

In the case you use any other software than SNPTEST for M2_female_ADD, M2_male_ADD and M3_female_GEN and snpStats (R) for M1_ADD_robust, please ensure all required information can be extracted.

Studies with related individuals

For studies with related individuals, several R packages are available (such as geepack, gee, or geeM). The software MMAP (https://mmap.github.io/) may also be used, but was not tested.

UKBioBank

The following pipeline should be used for both UKB diagnosed and UKB proxy.

We recommend using SAIGE as the pipeline is already set up from previous projects (with SAIGE v.1.0.5, documentation: https://github.com/saigegit/SAIGE, https://saigegit.github.io/SAIGE-doc/).

The GRM (step1) should be constructed considering only variants passing REGENIE filtering criteria (471,762 genotyped SNPs) and additional classical filtering. For the step1 input file (PLINK file), consider only variants:

- in autosomes
- genotyped
- with MAF ≥1%
- with HWE P >= 1 × 10−15
- with missingness < 0.01
- not involved in inter-chromosomal LD (list of those variants in Supplementary Table 19 of REGENIE paper, Mbatchou, J. et al. Computationally efficient whole-genome regression for quantitative and binary traits. Nat Genet 53, 1097–1103 (2021).)
- not in the APOE region (40 to 50 Mb on chromosome 19 in GRCh37 and GRCh38)
- not in regions of high LD (positions provided in the table below; please note that the start position is 0-base: https://www.ensembl.org/info/website/upload/bed.html)
- remaining after LD pruning using a r^2 threshold of 0.9 with a window size of 1,000 markers and a step size of 100 markers.

Table of the positions of the regions of high LD

chromosome	position_start	position_end	description
chr1	48227412	52227412	Price2008_LongRangeLD
chr2	86146488	101133568	Price2008_LongRangeLD
chr2	134783529	138283530	Price2008_LongRangeLD
chr2	183291754	190291755	Price2008_LongRangeLD
chr3	47524995	50024996	Price2008_LongRangeLD
chr3	83417309	86917310	Price2008_LongRangeLD
chr3	88917309	96017310	Price2008_LongRangeLD
chr5	44464242	50464243	Price2008_LongRangeLD
chr5	97972099	100472101	Price2008_LongRangeLD
chr5	128972100	131972101	Price2008_LongRangeLD
chr5	135472100	138472101	Price2008_LongRangeLD
chr6	25392020	33392022	Price2008_LongRangeLD
chr6	56892040	63942041	Price2008_LongRangeLD
chr6	139958306	142458307	Price2008_LongRangeLD
chr7	55032505	66362565	Price2008_LongRangeLD
chr8	7962589	11962591	Price2008_LongRangeLD
chr8	42880842	49837447	Price2008_LongRangeLD
chr8	111930823	114930824	Price2008_LongRangeLD
chr10	36959993	43679994	Price2008_LongRangeLD
chr11	46043423	57243424	Price2008_LongRangeLD
chr11	87860351	90860352	Price2008_LongRangeLD
chr12	33108732	41713733	Price2008_LongRangeLD
chr12	111015616	113515617	Price2008_LongRangeLD
chr20	32536338	35066586	Price2008_LongRangeLD
chr2	129883529	140283530	LCT_region_on_2q21
chr6	24092020	38892022	HLA_region
chr8	6612591	13455629	Inversion_on_8p23
chr17	40546473	44644684	Inversion_on_17q21.31

Note that REGENIE additionally removes variants in low-complexity regions.

Do not analyse variants with imputation quality < 0.3.

Example of SAIGE command line:
Step 1:
Fit the null model using a full GRM.

```
Rscript step1_fitNULLGLMM.R     \
    --plinkFile=./input/nfam_100_nindep_0_step1_includeMoreRareVariants_poly_22chr  \
    --phenoFile=./input/pheno_1000samples.txt_withdosages_withBothTraitTypes.txt \
    --phenoCol=y_binary \
    --covarColList=x1,x2,a9,a10 \
    --qCovarColList=a9,a10  \      ##specify which covariates are categorical
    --sampleIDColinphenoFile=IID \
```

```
    --traitType=binary        \
    --outputPrefix=./output/example_binary \
    --nThreads=24   \
```

Step 2

```
Rscript step2_SPAtests.R        \
        --vcfFile=./input/genotype_100markers.vcf.gz    \
        --vcfFileIndex=./input/genotype_100markers.vcf.gz.csi     \
        --vcfField=DS  \
        --SAIGEOutputFile=./output/genotype_100markers_marker_vcf.txt \
        --chrom=1       \
        --minMAF=0 \
        --minMAC=20 \
        --GMMATmodelFile=./output/example_binary.rda \
        --varianceRatioFile=./output/example_binary.varianceRatio.txt   \
        --is_output_moreDetails=TRUE
        --is_Firth_beta=TRUE    \
        --pCutoffforFirth=0.1  \
        --is_imputed_data=TRUE      ## can be omitted I think, may save time
```

Do not analyse variants with imputation quality < 0.3.

Note: For both step1 and step 2, LOCO=TRUE is not necessary as only one chromosome is analyzed.

6. Output format instructions

The ID of the variant should be in the format chr:position:REF:ALT.

TOPMed imputed data are in GRCh38. If your results are from another build, provide results in that build. Liftover (position + alleles) will be performed centrally.

Results files can be provided per batch.

Please compress files before uploading using gzip (.gz file).

Please do not exclude any variants as they will be filtered centrally.

Files should be named
IGAP_ModelX_AdjX_YOURSTUDYNAME_chrX_batchX_YYYYMMDD.tsv.gz where:

- "ModelX" can be M1_ADD_XCI, M4_female_ADD, M4_male_ADD or M3_female_GEN.
- "AdjX" can be A1_PC, A2_age_sex_PC or A3_APOE_age_sex_PC.
- "YYYYMMDD" is the date of upload.
- "chrX" is the chromosome.
- "batchX" is the batch number (optional). It can be 00.00, 01.00 ... etc.

The preferred option is to provide raw output files from SNPTEST or SAIGE for the UKBB, together with the imputation quality files. Raw output files from other software are

also fine, as soon as the information given below can be extracted. In this case, please give us a description of the file you provide. We will reformat the file ourselves. Otherwise, please use the following format:

Column Header	Description
variant_id	The ID of the variant should be in the format chr:position:REF:ALT
chr	Chromosome Number
position	Position of the variant
imp_quality	A value (range 0-1) corresponding to the imputation quality measure.
effect_allele	Allele for which the effect has been estimated (character A/C/T/G or using a combination of those letters for Indels)
other_allele	The other allele
EAF	Analysis-specific allele frequency of the effect_allele
MAC	Minor allele Count
beta_snp	Beta-coefficient for the association of the variant with the phenotype (genetic additive variable)
se_snp	Standard error for the association of the variant with the phenotype
P_snp	P-value for the association of the variant with the phenotype. When using SNPTEST, prefer the LRT p-value rather than the Wald p-value in the case of additive models (all but M3_female_GEN).
beta_het	For M3_female_GEN, beta-coefficient for the association of the variant dominance variable with the phenotype (fill with NA if the model is not general) (see Appendix model 3).
se_het	For M3_female_GEN, standard error for the association of the variant dominance variable with the phenotype (fill with NA if the model is not general) (see Appendix model 3).
P_het	For M3_female_GEN, p-value for the association of the variant dominance variable with the phenotype (fill with NA if the model is not general) (see Appendix model 3).
P_joint	For M3_female_GEN, p-value for the joint effect of variant additive and dominance variable (fill with NA if the model is not general) (see Appendix model 3).
cov_het_snp	For M3_female_GEN, covariance between beta_snp and beta_het (fill with NA if the model is not general)
N_total	Total number of subjects included in the model
N_cases	Number of phenotype cases included in the model
N_control	Number of phenotype controls included in the model

7. Study description file per sex

Provide descriptive statistics of the analysis and dataset for each sex separately. Please provide a file for female samples statistics and a file for male samples statistics using the following format. Statistics should only include data on samples used in association analysis.

Either for female samples or for male samples:

Information to provide	Description
Short_name	The acronym or abbreviation preferred for referring to the dataset
Genotype_Chip	The type of genotype chip(s) used to genotype the dataset. If multiple chips were used, please indicate N cases and controls per chip.
Assembly	The assembly used for the variant position, for example GRCh38 or GRCh37
Imputation_panel	Imputation panel used and its version
Imputation_software	Phasing/imputation software used. If multiple software, separate by semicolon,for example (shapeit2;impute2)
Analysis_software	Software used to perform association test. Please include the version of the software used (ex : SNPTEST_v2.5.6). Same format as Imputation software.
N_Principal_components	The principal components used for the adjustment, for example PC1, PC3, PC5. Also indicate if an adjustment on center was considered, for example PC1, PC3, PC5, center
N	Number of subjects analyzed
N_Cases	The number of AD cases analyzed
N_Cases_APOE4_0	The number of cases with 0 copies of the APOE ε4 allele
N_Cases_APOE4_1	The number of cases with 1 copies of the APOE ε4 allele
N_Cases_APOE4_2	The number of cases with 2 copies of the APOE ε4 allele
N_Cases_APOE4_miss	The number of cases missing data on the number of copies of the APOE ε4 allele
Mean_AAO_Cases	The mean value of age-at-onset among cases (if available)
SD_AAO_Cases	The value for the standard deviation of the mean of age-at-onset among cases (if available)
MEAN_AAE_Cases	The mean value of age-at-exam among cases (if available). “Age-at-exam” corresponds to age at the time of the most recent exam performed
SD_AAE_Cases	The value for the standard deviation of the mean of age-at-exam among cases (if available)
N_Controls_APOE4_0	The number of AD controls with 0 copies of the APOE ε4 allele
N_Controls_APOE4_1	The number of AD controls with 1 copies of the APOE ε4 allele
N_Controls_APOE4_2	The number of AD controls with 2 copies of the APOE ε4 allele
N_Controls_APOE4_miss	The number of AD controls missing data on the number of copies of the APOE ε4 allele
MEAN_AAE_Controls	The mean value of age-at-exam among controls (if available). “Age-at-exam” corresponds to age at the time of the most recent exam performed
SD_AAE_Controls	The value for the standard deviation of the mean of age-at-exam among controls (if available)

Appendix:

Position regions X-chromosome:
PAR1 (b38) = 10001 - 2781478
PAR2 (b38) = 155701384 - 156030895
nonPAR (b38) = 2781479 - 155701383

PAR1 (b37) = 60001 - 2699520
PAR2 (b37) = 154931044 - 155270560
nonPAR (b37) = 2699521 - 154931043

MODEL 1
Model 1 is a logistic regression with an additive genetic model and an XCI coding scheme.

$Y \sim G + C$

1) Y is the status (Alzheimer's disease or control).
2) G is the additive coding. (AA=0, AB=1, BB=2) for females and (A=0, B=2) for males.
3) C is a vector of covariates.

MODEL 2
Model 2 is a logistic regression with an additive genetic model. Model 2 will be run twice, once with only female subjects and once with only males.

$Y \sim G + C$

1) Y is the status (Alzheimer's disease or control).
2) G is the additive coding. (AA=0, AB=1, BB=2) for females and (A=0, B=2) for males.
3) C is a vector of covariates.

MODEL 3
Model 2 is a logistic regression under the general genetic model including only females. It corresponds to an additive model including a dominance variable (D).

$Y \sim G + D + C$

1) Y is the status (Alzheimer's disease or control).
2) G is the additive coding. (AA=0, AB=1, BB=2).
3) D is the dominance variable, corresponding to heterozygous coding: (AA=0, AB=1, BB=0).
4) C is a vector of covariates.

X chromosome quality control and TOPMed imputation

This document describes the quality control (QC) and TOPMed imputation steps for the X-chromosome.

1. Quality Control

A. Sample quality control for autosomes

The samples failing autosome sample QC will be excluded in the X-chromosome analysis as well.

We use the same sample QC as described in the EADB-GSA paper pipeline (https://www.nature.com/articles/s41588-022-01024-z). The sample QC steps are the following:

Pre-quality control.
Heterozygosity and missingness.
Population outliers.
Sex-check.
Relatedness.
Possibly problematic chips batch.

For the following X-chromosome QC, all samples failing the heterozygosity and missingness and sex-check QC were removed. From this point, we replace missing self-reported sex by genetic sex.

B. Sample quality control specific to X-chromosome

Pre-quality control. All variants failing pre-QC were excluded to all the following sample QC steps.
Were excluded in the pre-QC:

- PAR (pseudo autosomal region) (see the positions of X-chromosome regions in Appendix) variants showing departure from the Hardy-Weinberg equilibrium (HWE) in controls (p-value < 1e-15) (using PLINK v1.9 (https://www.cog-genomics.org/plink2/) --hardy option);
- non-PAR variants showing departure from the HWE in female controls (p-value < 1e-15) (or in female cases and controls if the number of controls is too low) (using PLINK v1.9 --hardy option);
- Variants showing high missingness globally (> 0.025) (using PLINK v1.9 --missing option).

Sample QC. Were excluded:

- Samples showing missingness > 0.05 on the X-chromosome (using PAR and non-PAR X-chromosome variants) (using PLINK v1.9 --missing option);
- Male samples showing high level of heterozygosity (more than 1%) in non-PAR variants (using PLINK v1.9 --het option).

- Samples for which genetic gender cannot be determined. The genetic sex was generated in the sex-check sample QC step.

C. Variant quality control specific to X-chromosome

For the variant QC, the initial set of X-chromosome variants was used (re-integrating the variants failing the pre-QC of the sample QC). All samples failing the general sample QC or the X-chromosome specific sample QC were removed for the X-chromosome variant QC.

non-PAR regions. All the analyses of this step were computed on non-PAR variants of X-chromosome using PLINK (v1.9). Were excluded:
- Variants showing high missingness in either males or females (> 0.05) (variants missingness was computed on males and females separately using --missing option);
- Variants showing high heterozygosity in males (> 0.01) (the heterozygosity was computed in males only from the --hwe option outputs);
- Variants failing the HWE test (P-value < 5e-8) in female controls (or in female cases and controls if the number of controls is too low) (using --hardy option);
- Variants showing a differential missingness between cases and controls (Fisher's exact test P-value < 5e-8) (using --test-missing option);

PAR regions. All the analyses of this step were computed on PAR variants of X-chromosome using PLINK. Were excluded (same exclusion criteria as for autosomes):
- Variants showing high missingness (> 0.05) (using --missing option);
- Variants failing the HWE tests (P-value < 5e-8) in controls (using --hardy option);
- Variants showing a differential missingness between cases and controls (Fisher's exact test P-value < 5e-8) (using --test-missing option).

PAR and non-PAR regions. The same QC checks as in EADB-GSA autosomes were applied (detailed in EADB-GSA paper) for the frequency test, ambiguous variants and duplicated variants QC. Following is a reminder of those steps:
- Frequency checks QC. Population outliers were excluded for this step. A frequency test comparing the study with the panels gnomAD (only non-finnish) and HRC and TOPMed, if the variant is not present in either panel, was performed. Were removed variant with a Chisq test higher than the chosen threshold (the threshold used is adapted to sample size). Ambiguous variants are removed if the frequency difference is higher than 0.1 in either panel (as ambiguous variants present more disparities). If you do not have access to gnomAD, HRC or TOPMed panel frequencies, it is possible to send us your data frequencies and we will perform the exclusion.
- Ambiguous variants check QC. All ambiguous variants (A/T or C/G) with MAF > 0.4 were removed.
- Duplicated variants check QC. For duplicated variants of the chip, only the copy with the minimum missingness was kept if both copies pass previous variant QC.

2. TOPMed Imputation

A. Imputation input file

The imputation input file format recommended is .vcf.gz.

All samples and variants passing the QC were used as the input of the imputation process. Related samples and population outliers were not excluded for the imputation.

All remaining heterozygous non-PAR variants in males should be set as missing. A bcftools command example for this operation:
bcftools filter -e "GT[@path_to_male_samples_list_file]='het' " -S. path_to_nonPAR_vcf_file

Males should be set as haploid in the non-PAR region (using "fixploidy" bcftools plugin for instance).

We recommand to anonymize the sample names in the file uploaded in the imputation server.

B. Michigan Imputation Server

The imputation was performed by the Michigan Imputation Server (MIS) 104 where the TOPMed Freeze5 reference panel was granted to the EADB consortium. The server version used was the 1.2.4 with Eagle v2.4 105 as the phasing software and Minimac4 v4-1.0.2 as the imputation software.

If the study has several batches (genotyping chips for example) that have to be imputed separately, a global imputation quality will be recomputed after the imputation process. A merged imputation quality including all samples can be obtained using the bcftools "impute_info" plugin.

Instructions fix-GP-chrX-nonPAR-males bcftools plugin

This document describes the bcftools plugin “fix-GP-chrX-nonPAR-males” created by Benjamin Grenier-Boley, how to install it and how to use it.

Description:

The plugin “fix-GP-chrX-nonPAR-males” allows to set males genotype probabilities (GP) as homozygous female in the non-PAR region of the X-chromosome.

It outputs a vcf file with males coded as homozygous females by adding a 0 probability for the heterozygous genotype.

This plugin was tested using bcftools v1.13 but should work for any version.

Installation:

The plugin file (fix-GP-chrX-nonPAR-males.c) must be copied into the “plugins” subdirectory of bcftools. Once copied, bcftools must be recompiled using make. In the following line, all command lines begin with “~$”

Following is an example of installation :

```
~$ cp fix-GP-chrX-nonPAR-males.c /home/user/software/bcftools/plugins
~$ cd /home/user/software/bcftools
~$ make
```

At the end of the compilation process, the file fix-GP-chrX-nonPAR-males.so should be created inside the plugins subdirectory. Do not forget that the environment variable BCFTOOLS_PLUGINS must be set in order to use plugins.

Setting BCFTOOLS _PLUGINS using the last example :

```
~$ BCFTOOLS_PLUGINS=/home/user/software/bcftools/plugins
```

Input files format:

1. input_vcf_file: A vcf file of the non-PAR region of the X-chromosome genetic data with males as hemizygous (A=0, B=1). The format can be vcf, vcf.gz or bcf.

Thus, in the input vcf file, males have:

- GT = 0 or 1
- only two GP
- only one HDS

While females are coded (AA=0, AB=1, BB=2) and have:

- GT = 0/0 or 0/1 or 1/0 or 1/1

- three GP
- two HDS

2. male_file: a list of all the males samples, one per line. The males samples names must match the ones present in the vcf file.

Command lines example:

Print the help:

```
~$ bcftools +fix-GP-chrX-nonPAR-males -h
```

Basic usage:

```
~$ bcftools +fix-GP-chrX-nonPAR-males -o ${output_file} ${input_vcf_file} -- -M ${male_file}
```

In addition, all general options relative to the output format or multi-threading can be used. For example to output a bcf file using 5 threads:

```
~$ bcftools +fix-GP-chrX-nonPAR-males --threads 5 -Ob -o ${output_file} ${input_vcf_file} -- -M ${male_file}
```

Instructions fixploidy bcftools plugin

This document describes the bcftools plugin “fixploidy” and how to use it.

Description:

The plugin “fixploidy” allows modify the ploidy of a vcf file. We use it to set males genotype (GT) as homozygous female in the non-PAR region of the X-chromosome.

Installation:

Setting BCFTOOLS _PLUGINS using the last example:
```
~$ BCFTOOLS_PLUGINS=/home/user/software/bcftools/plugins
```

Input files format:

1. input_vcf_file: A vcf file of the non-PAR region of the X-chromosome genetic data with males as hemizygous (A=0, B=1). The format can be vcf, vcf.gz or bcf. Thus, in the input vcf file, males have GT = 0 or 1, while females are coded (AA=0, AB=1, BB=2) and have GT = 0/0 or 0/1 or 1/0 or 1/1.
2. sample_sex: a list of samples, one per line, with two column : "NAME SEX" (M to indicate a male and F for a female). The males samples names must match the ones present in the vcf file.
3. ploidy_file: A space/tab-delimited list of CHROM,FROM,TO,SEX,PLOIDY

A command to create a ploidy_file that sets all samples and all variants to diploid:
```
~$ echo -e "*\t*\t*\t*\t2" > ${ploidy_file}
```

Command lines example:

Setting BCFTOOLS _PLUGINS using the last example :
```
~$ BCFTOOLS_PLUGINS=/home/user/software/bcftools/plugins
```

Print the help:
```
~$ bcftools +fixploidy -h
```

Basic usage:
```
~$ bcftools +fix-GP-chrX-nonPAR-males -o ${output_file} ${input_vcf_file} -- -s ${sample_sex} -p ${ploidy_file}
```

In addition, all general options relative to the output format or multi-threading can be used. For example to output a bcf file using 5 threads :
```
~$ bcftools +fix-GP-chrX-nonPAR-males --threads 5 -Ob -o ${output_file} ${input_vcf_file} -- -s ${sample_sex} -p ${ploidy_file}
```