Improving Cohort Diversity in Alzheimer's Disease Genetics Research

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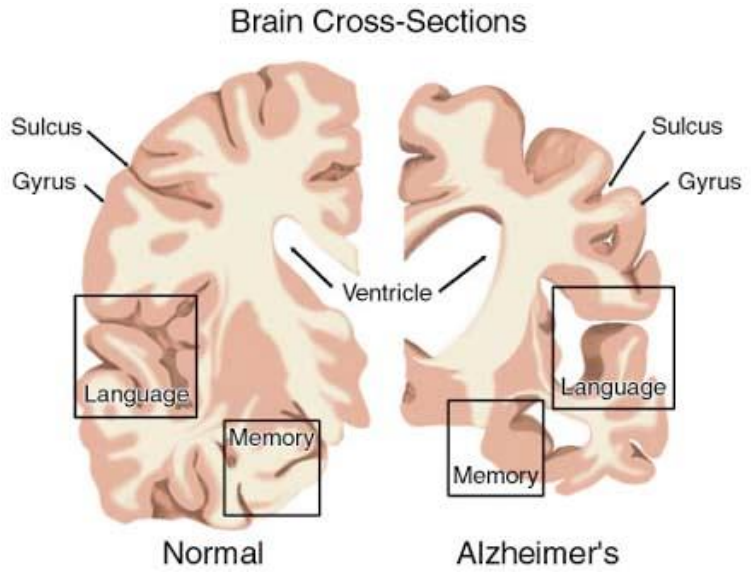
No financial conflict of interest

Alzheimer's Disease



Most common cause of dementia in seniors

Gradual, progressive loss of cognitive abilities; Extensive brain atrophy; Change of personality; Incapacitation and death

AD is a big health issue

6th topmost cause of death in US

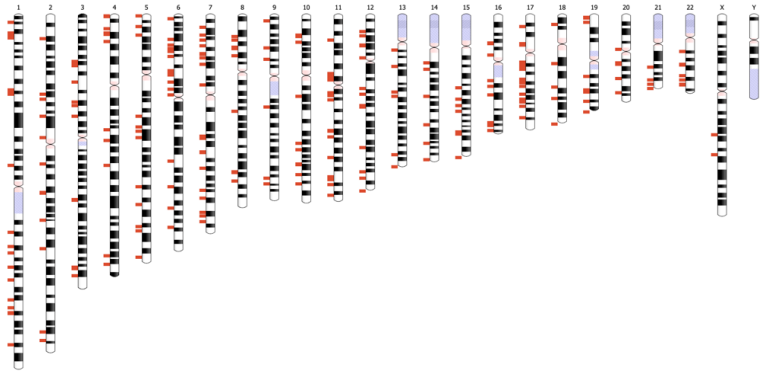
No effective cure, prevention, or means to slow progression

AD recruitment is challenging

- Hours of cognitive and neurological assessments
- CSF/Imaging to exclude other dementia causes
- Challenges in recruiting and retaining seniors in longitudinal studies

Auguste D, first AD case identified in 1901

AD Genetic Findings Are Mainly for Populations of European Ancestry



AD Variant Portal - advp.niagads.org
ADGC Publication Summary as of 2020

Population	#Variants	#Loci	#Pubs
Caucasian / White / NHW	1,687	953	117
African American / Black	90	44	9
Asian (in Asia)	53	38	7
Caribbean Hispanic	45	17	3
Arab (in Asia)	31	16	3
Hispanic	7	1	1

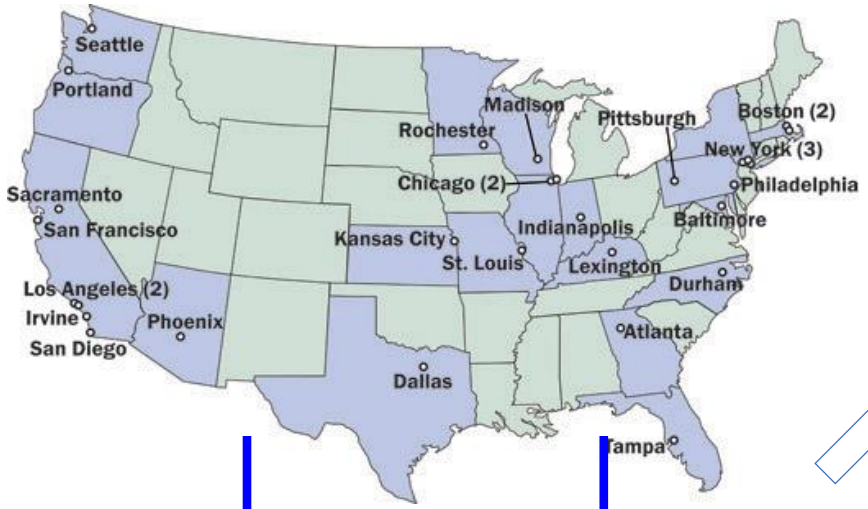
Population Specific Odds Ratio
(strongest common variant in each locus)

Ancestry	APOE e4	ABCA7
European	3.43	1.15
African	2.31	**1.79**
East Asian	**4.98**	1.13

PMIDs: *APOE - 32015339, 23571587, 31426376,*
ABCA7 - 24162737, 23571587, 23565137

Leverage Existing Resources for Larger Sample and More Diversity

32 NIA ADRCs recruit subjects



Phenotype

DNA

NACC

NCRAD

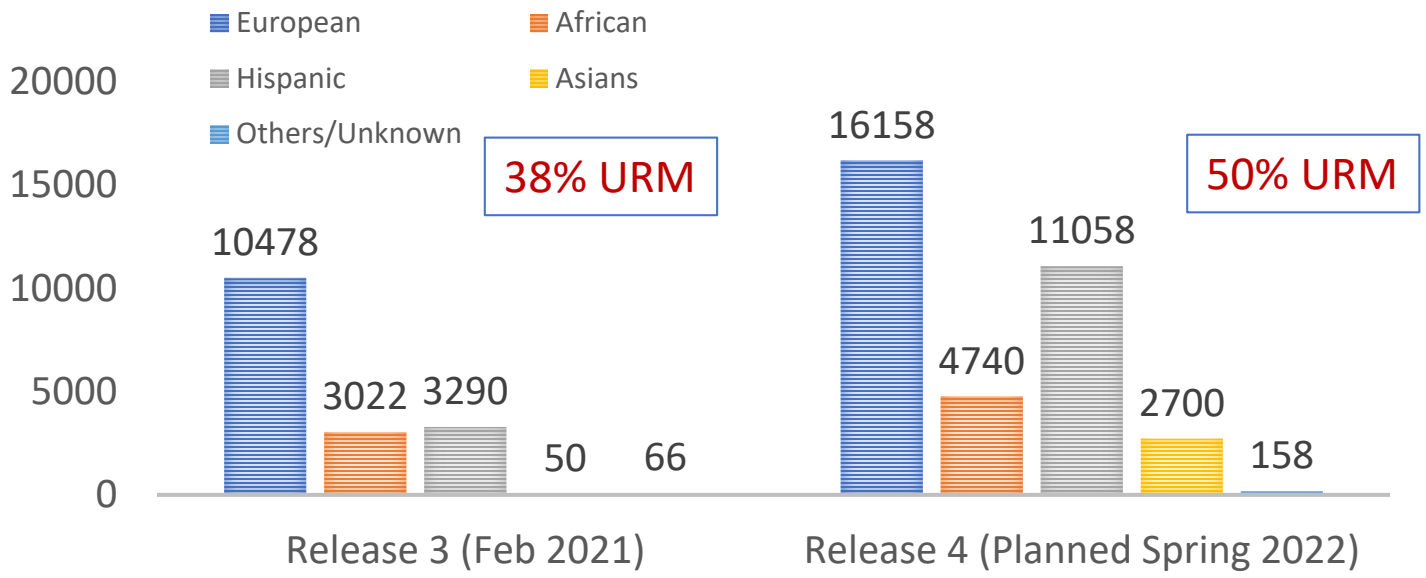
ADGC
Alzheimer's Disease Genetics Consortium

- Chooses and genotypes >10,000 subjects (Illumina 660K/OmniExpress, 500~700K SNPs)
- Collects other studies

NIH National Institute on Aging

Alzheimer's Disease Sequencing Project

#Genomes



PAR-16-406: Additional Sequencing for the Alzheimer's Disease Sequencing Project

PAR-21-212: Alzheimer's Disease Sequencing Project Follow-Up Study 2.0 (ADSP FUS 2.0): The Diverse Population Initiative

adsp Alzheimer's Disease Sequencing Project

NIH National Institute on Aging

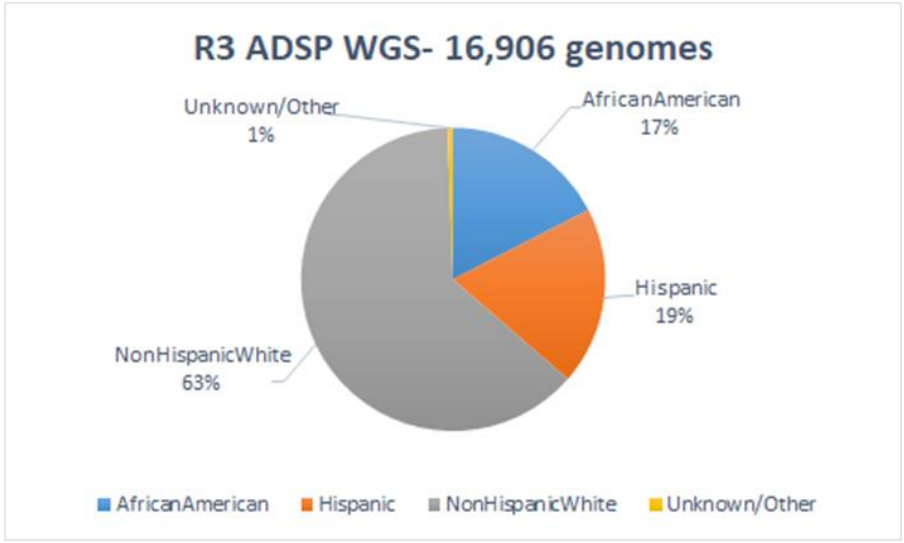
- Adult Changes in Thought (ACT)
- Erasmus Rucphen Family (ERF)
- Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA)
- Indianapolis Ibadan (IIAA)
- National Cell Repository for Alzheimer's Disease Family (NCRAD Family)
- National Institute on Aging Late Onset of Alzheimer's Disease Family (NIA-LOAD)
- NIA Alzheimer Disease Centers (ADC)
- University of Miami (MIA)
- Washington Heights and Inwood Community Aging project (WHICAP)
- Alzheimer's Disease Neuroimaging Initiative (ADNI)
- Puerto Rican 10/66 Study (PR1066)
- Vanderbilt University (VAN)
- Stanford Extreme Phenotypes in AD (StEP AD)
- Atherosclerosis Risk in Communities (ARIC)
- Chicago Health and Aging Project (CHAP)
- Cardiovascular Health Study (CHS)
- Framingham Heart Study (FHS)
- Genetic Differences (GenDiff)
- Religious Orders Study/Memory and Aging Project (ROSMAP)
- Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE)
- Rotterdam Study (RS)
- Texas Alzheimer's Research and Care Consortium (TARCC)
- University of Toronto
- University of Washington Families (RAS)
- Mayo Clinic (MAYO)

AAPI is the fastest growing minority in US

- Fastest growing minority in the US
  - 14.6 Million as of 2010
  - 20.9 Million as of 2016
- Subpopulations by ancestry as of 2010

Ancestry	Population 2010
Chinese	3,535,382
Indian	2,918,807
Filipino	2,649,973
Vietnamese	1,632,717
Korean	1,463,474
Japanese	841,824
Pakistani	382,994

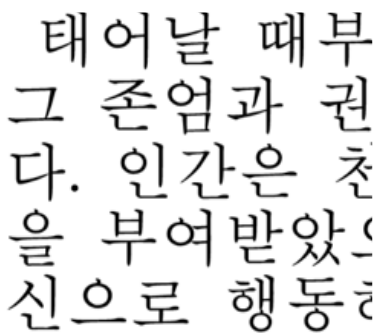
50 (0.3%) AAPI out of 16,906 R3 ADSP samples



Doan et al. 2019: … 529 clinical research projects focused on Asian American, Native Hawaiian, and Pacific Islander participants funded by the NIH ***between 1992 and 2018, composing 0.17% of the total NIH budget.***

Challenges in Recruiting AAPIs for AD Genetics Research

Research institutions may not be located in the AAPI community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신으로 행동

AAPI are heterogeneous in languages/dialect, cultures, etc.

Lack of funding / active recruitment

Limited outreach, trust, community partnerships with AAPI

We need resources to invest in the infrastructure and networks to meaningfully include AAPIs in ADRD genetics and other clinical and caregiving research

ACAD

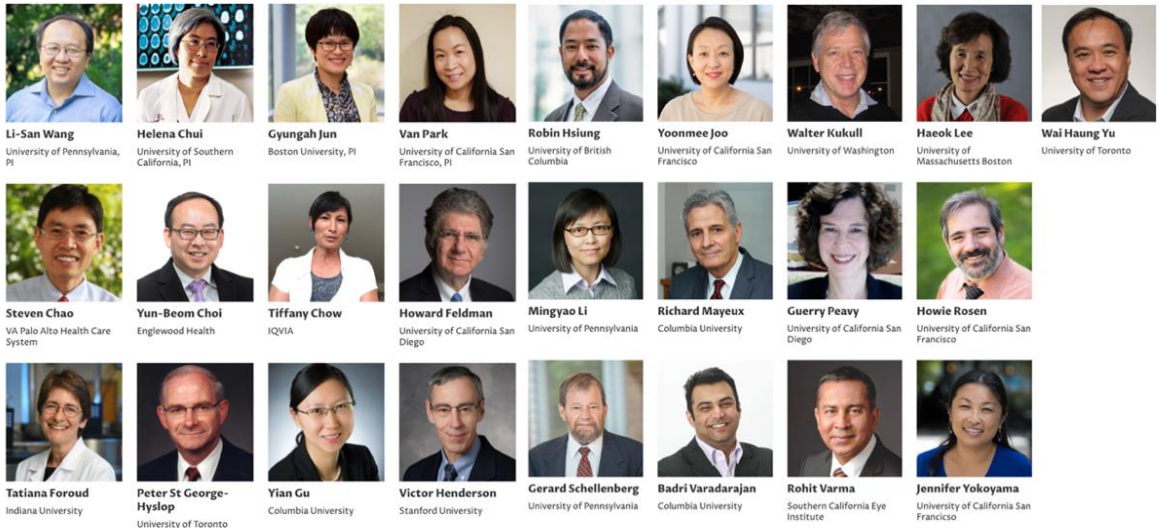
Asian Cohort for Alzheimer's Disease

acadstudy.org

NIA R56 AG 069130

ACAD Strategy

- Sponsored by a two-year NIA R56 award
  - 3-Part Data Collection Packet based on NACC UDS; translated into Chinese, Vietnamese, Korean
  - Translated validated cognitive test instruments
  - Training/outreach material and REDCap data capture
  - Recruitment started in August; >200 signed up
- Community-Based Participatory Research (CBPR)
- Interdisciplinary team/international collaboration
- Engaging multiple populations: Respect diversity among AAPIs while working together to have a bigger voice



Summary

- Diverse cohorts increase statistical power for gene discovery
- Leverage existing cohorts/infrastructure to increase sample size quickly
- Long term investment for minority populations underrepresented in medical research
- Culturally sensitive assessment protocols and recruitment strategies; build trust with communities

Acknowledgement

We are grateful to participants, families/caregivers and staff of the contributing cohorts

We thank the contributions by researchers from these projects (partial list):

- Alzheimer's Disease Genetics Consortium (ADGC)
- CHARGE Consortium
- International Genomics of Alzheimer's Project (IGAP)
- Alzheimer's Disease Sequencing Project (ADSP)
- NHGRI Centers for Common Disease Genomics (CCDG)
- NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS)
- Genome Center for Alzheimer's Disease (GCAD)
- Asian Cohort for Alzheimer's Disease (ACAD)

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Department of Pathology and Laboratory Medicine and all the research support offices, University of Pennsylvania

The Alzheimer's Disease Sequencing Project (ADSP) is comprised of two Alzheimer's Disease (AD) genetics consortia and three National Human Genome Research Institute (NHGRI) funded Large Scale Sequencing and Analysis Centers (LSAC). The two AD genetics consortia are the Alzheimer's Disease Genetics Consortium (ADGC) funded by NIA (U01 AG032984), and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) funded by NIA (R01 AG033193), the National Heart, Lung, and Blood Institute (NHLBI), other National Institute of Health (NIH) institutes and other foreign governmental and non-governmental organizations. The Discovery Phase analysis of sequence data is supported through UF1AG047133 (to Drs. Schellenberg, Farrer, Pericak-Vance, Mayeux, and Haines); U01AG049505 to Dr. Seshadri; U01AG049506 to Dr. Boerwinkle; U01AG049507 to Dr. Wijsman; and U01AG049508 to Dr. Goate and the Discovery Extension Phase analysis is supported through U01AG052411 to Dr. Goate, U01AG052410 to Dr. Pericak-Vance and U01 AG052409 to Drs. Seshadri and Fornage.

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The ADGC cohorts include: Adult Changes in Thought (ACT) (UO1 AG006781, UO1 HG004610, UO1 HG006375, U01 HG008657), the Alzheimer's Disease Centers (ADC) (P30 AG019610, P30 AG013846, P50 AG008702, P50 AG025688, P50 AG047266, P30 AG010133, P50 AG005146, P50 AG005134, P50 AG016574, P50 AG005138, P30 AG008051, P30 AG013854, P30 AG008017, P30 AG010161, P50 AG047366, P30 AG010129, P50 AG016573, P50 AG016570, P50 AG005131, P50 AG023501, P30 AG035982, P30 AG028383, P30 AG010124, P50 AG005133, P50 AG005142, P30 AG012300, P50 AG005136, P50 AG033514, P50 AG005681, and P50 AG047270), the Chicago Health and Aging Project (CHAP) (R01 AG11101, RC4 AG039085, K23 AG030944), Indianapolis Ibadan (R01 AG009956, P30 AG010133), the Memory and Aging Project (MAP) (R01 AG17917), Mayo Clinic (MAYO) (R01 AG032990, U01 AG046139, R01 NS080820, RF1 AG051504, P50 AG016574), Mayo Parkinson's Disease controls (NS039764, NS071674, 5RC2HG005605), University of Miami (R01 AG027944, R01 AG028786, R01 AG019085, IIRG09133827, A2011048), the Multi-Institutional Research in Alzheimer's Genetic Epidemiology Study (MIRAGE) (R01 AG09029, R01 AG025259), the National Cell Repository for Alzheimer's Disease (NCRAD) (U24 AG21886), the National Institute on Aging Late Onset Alzheimer's Disease Family Study (NIA- LOAD) (R01 AG041797), the Religious Orders Study (ROS) (P30 AG10161, R01 AG15819), the Texas Alzheimer's Research and Care Consortium (TARCC) (funded by the Darrell K Royal Texas Alzheimer's Initiative), Vanderbilt University/Case Western Reserve University (VAN/CWRU) (R01 AG019757, R01 AG021547, R01 AG027944, R01 AG028786, P01 NS026630, and Alzheimer's Association), the Washington Heights-Inwood Columbia Aging Project (WHICAP) (RF1 AG054023), the University of Washington Families (VA Research Merit Grant, NIA: P50AG005136, R01AG041797, NINDS: R01NS069719), the Columbia University HispanicEstudio Familiar de Influencia Genetica de Alzheimer (EFIGA) (RF1 AG015473), the University of Toronto (UT) (funded by Wellcome Trust, Medical Research Council, Canadian Institutes of Health Research), and Genetic Differences (GD) (R01 AG007584). The CHARGE cohorts are supported in part by National Heart, Lung, and Blood Institute (NHLBI) infrastructure grant HL105756 (Psaty), RC2HL102419 (Boerwinkle) and the neurology working group is supported by the National Institute on Aging (NIA) R01 grant AG033193.

The CHARGE cohorts participating in the ADSP include the following: Austrian Stroke Prevention Study (ASPS), ASPS-Family study, and the Prospective Dementia Registry-Austria (ASPS/PRODEM-Aus), the Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), the Erasmus Rucphen Family Study (ERF), the Framingham Heart Study (FHS), and the Rotterdam Study (RS). ASPS is funded by the Austrian Science Fond (FWF) grant number P20545-P05 and P13180 and the Medical University of Graz. The ASPS-Fam is funded by the Austrian Science Fund (FWF) project I904),the EU Joint Programme - Neurodegenerative Disease Research (JPND) in frame of the BRIDGET project (Austria, Ministry of Science) and the Medical University of Graz and the Steiermärkische Krankenanstalten Gesellschaft. PRODEM-Austria is supported by the Austrian Research Promotion agency (FFG) (Project No. 827462) and by the Austrian National Bank (Anniversary Fund, project 15435. ARIC research is carried out as a collaborative study supported by NHLBI contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). Neurocognitive data in ARIC is collected by U01 2U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, 2U01HL096917 from the NIH (NHLBI, NINDS, NIA and NIDCD), and with previous brain MRI examinations funded by R01-HL70825 from the NHLBI. CHS research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grants U01HL080295 and U01HL130114 from the NHLBI with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629, R01AG15928, and R01AG20098 from the NIA. FHS research is supported by NHLBI contracts N01-HC-25195 and HHSN268201500001I. This study was also supported by additional grants from the NIA (R01s AG054076, AG049607 and AG033040 and NINDS (R01 NS017950). The ERF study as a part of EUROSPAN (European Special Populations Research Network) was supported by European Commission FP6 STRP grant number 018947 (LSHG-CT-2006-01947) and also received funding from the European Community's Seventh Framework Programme (FP7/2007-2013)/grant agreement HEALTH-F4- 2007-201413 by the European Commission under the programme "Quality of Life and Management of the Living Resources" of 5th Framework Programme (no. QLG2-CT-2002- 01254). High-throughput analysis of the ERF data was supported by a joint grant from the Netherlands Organization for Scientific Research and the Russian Foundation for Basic Research (NWO-RFBR 047.017.043). The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the municipality of Rotterdam. Genetic data sets are also supported by the Netherlands Organization of Scientific Research NWO Investments (175.010.2005.011, 911-03-012), the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), and the Netherlands Genomics Initiative (NGI)/Netherlands Organization for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA), project 050-060-810. All studies are grateful to their participants, faculty and staff. The content of these manuscripts is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the U.S. Department of Health and Human Services.

The FUS cohorts include: the Alzheimer's Disease Centers (ADC) (P30 AG019610, P30 AG013846, P50 AG008702, P50 AG025688, P50 AG047266, P30 AG010133, P50 AG005146, P50 AG005134, P50 AG016574, P50 AG005138, P30 AG008051, P30 AG013854, P30 AG008017, P30 AG010161, P50 AG047366, P30 AG010129, P50 AG016573, P50 AG016570, P50 AG005131, P50 AG023501, P30 AG035982, P30 AG028383, P30 AG010124, P50 AG005133, P50 AG005142, P30 AG012300, P50 AG005136, P50 AG033514, P50 AG005681, and P50 AG047270), Alzheimer's Disease Neuroimaging Initiative (ADNI) (U19AG024904), Amish Protective Variant Study (RF1AG058066), Cache County Study (R01AG11380, R01AG031272, R01AG21136, RF1AG054052), Case Western Reserve University Brain Bank (CWRUBB) (P50AG008012), Case Western Reserve University Rapid Decline (CWRURD) (RF1AG058267, NU38CK000480), CubanAmerican Alzheimer's Disease Initiative (CuAADI) (3U01AG052410), Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA) (5R37AG015473, RF1AG015473, R56AG051876), Genetic and Environmental Risk Factors for Alzheimer Disease Among African Americans Study (GenerAAtions) (2R01AG09029, R01AG025259, 2R01AG048927), Gwangju Alzheimer and Related Dementias Study (GARD) (U01AG062602), Hussman Institute for Human Genomics Brain Bank (HIHGBB) (R01AG027944, Alzheimer's Association "Identification of Rare Variants in Alzheimer Disease"), Ibadan Study of Aging (IBADAN) (5R01AG009956), Mexican Health and Aging Study (MHAS) (R01AG018016), Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) (2R01AG09029, R01AG025259, 2R01AG048927), Northern Manhattan Study (NOMAS) (R01NS29993), Peru Alzheimer's Disease Initiative (PeADI) (RF1AG054074), Puerto Rican 1066 (PR1066) (Wellcome Trust (GR066133/GR080002), European Research Council (340755)), Puerto Rican Alzheimer Disease Initiative (PRADI) (RF1AG054074), Reasons for Geographic and Racial Differences in Stroke (REGARDS) (U01NS041588), Research in African American Alzheimer Disease Initiative (REAAADI) (U01AG052410), Rush Alzheimer's Disease Center (ROSMAP) (P30AG10161, R01AG15819, R01AG17919), University of Miami Brain Endowment Bank (MBB), and University of Miami/Case Western/North Carolina A&T African American (UM/CASE/NCAT) (U01AG052410, R01AG028786).

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