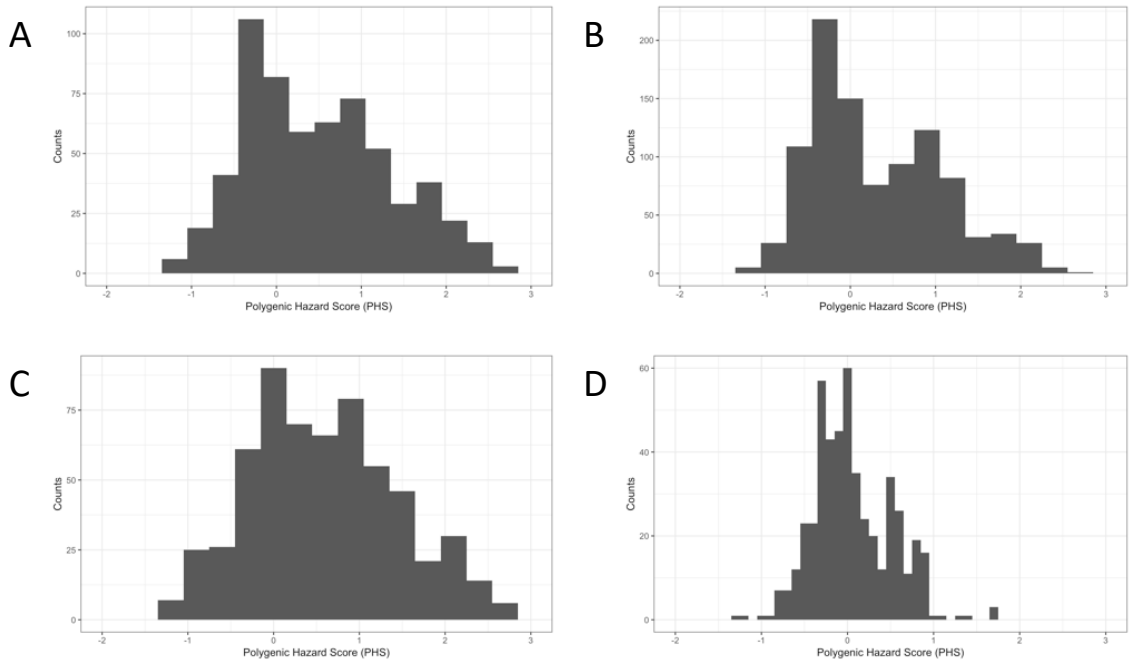
Supplementary Figure 1



Supplementary Figure 1. Distribution of polygenic hazard score (PHS) in A) ADNIGO/2, B) ADNI1, C) NACC, D) ROSMAP cohorts.

Supplementary Tables

Table 1A. Alzheimer's Disease Neuroimaging Initiative GO/2 (ADNIGO/2) demographics of participants contributing amyloid PET data by baseline diagnosis.

	Cognitively Normal (n = 323)	Mild Cognitive Impairment (n = 481)	AD dementia (n = 176)
Age at baseline ± SD	74.98 (6.57)	72.71 (7.84)	75.29 (7.75)
Education in years ± SD	16.57 (2.63)	16.19 (2.75)	15.88 (2.71)
Sex (% Female)	157 (48.60)	278 (57.80)	105 (59.66)
APOE ε4 carriers (%)	90 (27.86)	222 (46.15)	119 (67.61)
Polygenic Hazard Score ± SD	0.02 (0.61)	0.36 (0.77)	0.73 (0.78)

Table 1B. Alzheimer's Disease Neuroimaging Initiative 1 (ADNI1) demographics of participants contributing longitudinal MRI data by baseline diagnosis.

	Cognitively Normal (n = 177)	Mild Cognitive Impairment (n = 297)	AD dementia (n = 133)
Age at baseline ± SD	76.10 (4.95)	75.17 (7.17)	75.37 (7.82)
Education in years ± SD	16.18 (2.63)	15.75 (3.00)	14.86 (3.01)
Sex (% Female)	82 (46.33)	105 (35.23)	61 (46.21)
APOE ε4 carriers (%)	47 (26.56)	172 (57.72)	90 (68.18)
Polygenic Hazard Score ± SD	0.03 (0.70)	0.61 (0.82)	0.89 (0.87)

Table 1C. Religious Orders Study and Rush Memory and Aging Project (ROSMAP) demographics by final consensus cognitive diagnosis at death.

	Cognitively normal (*n* = 194)	Mild cognitive Impairment (*n* = 23)	AD dementia (*n* = 268)
Age at death ± SD	86.79 (6.42)	91.56 (5.00)	91.14 (5.71)
Sex (% Female)	128 (65.98)	15 (65.21)	188 (70.15)
APOE ε4 carriers (%)	26 (13.40)	4 (23.53)	100 (37.31)
Polygenic Hazard Score ± SD	-0.08 (0.41)	-0.01 (0.39)	0.16 (0.46)

Table 1D. National Alzheimer's Coordinating Center (NACC) demographics by diagnosis at death

	Cognitively normal (*n* = 129)	Mild cognitive Impairment (*n* = 63)	AD dementia (*n* = 411)
Age at death ± SD	86.09 (7.33)	86.16 (8.08)	83.44 (6.88)
Sex (% Female)	74 (57.36)	32 (50.79)	193 (46.96)
APOE ε4 carriers (%)	29 (22.48)	24 (38.10)	247 (60.10)
Polygenic Hazard Score ± SD	0.20 (0.68)	0.46 (0.78)	0.78 (0.92)

Supplementary Table 2. Associations of PHS with regional amyloid PET standard uptake volume ratio (SUVR) controlling for *APOE* status.

Region of Interest (ROI)	Beta	95% CI	*p*	FDR-adjusted *p*
Rostralmiddlefrontal	0.318	(0.22 - 0.42)	1.71E-09	5.82E-08
Frontalpole	0.308	(0.20 - 0.41)	8.79E-09	1.50E-07
Inferiortemporal	0.304	(0.20 - 0.41)	1.51E-08	1.71E-07
Bankssts	0.300	(0.19 - 0.41)	3.02E-08	2.57E-07
Inferiorparietal	0.295	(0.19 - 0.40)	4.96E-08	3.37E-07
Superiortemporal	0.289	(0.18 - 0.39)	8.21E-08	3.99E-07
Middletemporal	0.286	(0.18 - 0.39)	9.38E-08	3.99E-07
Caudalmiddlefrontal	0.284	(0.18 - 0.39)	1.48E-07	5.19E-07
Parsorbitalis	0.282	(0.18 - 0.39)	1.53E-07	5.19E-07
Rostralanteriorcingulate	0.281	(0.18 - 0.38)	8.95E-08	3.99E-07
Lateraloccipital	0.278	(0.17 - 0.39)	9.00E-07	2.35E-06
Medialorbitofrontal	0.272	(0.17 - 0.37)	2.60E-07	8.03E-07
Parsopercularis	0.267	(0.16 - 0.37)	9.90E-07	2.38E-06
Parstriangularis	0.265	(0.16 - 0.37)	1.05E-06	2.38E-06
Superiorfrontal	0.264	(0.16 - 0.37)	7.58E-07	2.15E-06
Fusiform	0.264	(0.16 - 0.37)	1.49E-06	2.98E-06
Transversetemporal	0.263	(0.16 - 0.37)	1.58E-06	2.98E-06
Precuneus	0.260	(0.16 - 0.36)	1.32E-06	2.80E-06
Isthmuscingulate	0.245	(0.14 - 0.35)	6.51E-06	1.07E-05
Lateralorbitofrontal	0.243	(0.14 - 0.35)	6.10E-06	1.07E-05
Posteriorcingulate	0.242	(0.14 - 0.35)	6.62E-06	1.07E-05
Superiorparietal	0.241	(0.13 - 0.35)	1.24E-05	1.75E-05
Supramarginal	0.239	(0.13 - 0.35)	1.22E-05	1.75E-05
Caudalanteriorcingulate	0.238	(0.13 - 0.34)	9.84E-06	1.52E-05
Insula	0.237	(0.13 - 0.34)	1.43E-05	1.95E-05
Temporalpole	0.219	(0.11 - 0.33)	8.45E-05	1.10E-04
Entorhinal	0.217	(0.10 - 0.33)	1.57E-04	1.91E-04
Lingual	0.213	(0.10 - 0.32)	1.77E-04	2.08E-04
Postcentral	0.211	(0.10 - 0.32)	1.51E-04	1.90E-04
Parahippocampal	0.205	(0.10 - 0.32)	2.61E-04	2.86E-04
Paracentral	0.203	(0.09 - 0.31)	2.41E-04	2.73E-04
Precentral	0.192	(0.08 - 0.30)	7.05E-04	7.49E-04
Pericalcarine	0.184	(0.07 - 0.30)	1.29E-03	1.33E-03
Cuneus	0.178	(0.07 - 0.29)	2.05E-03	2.05E-03

Supplementary Table 3. Associations of PHS with regional amyloid PET standard uptake volume ratio (SUVR) in cognitively normal (CN) individuals, not controlling for *APOE* status.

Region of Interest (ROI)	Beta	95% CI	*p*	FDR-adjusted *p*
Rostralanteriorcingulate	0.343	(0.45 - 0.05)	2.36E-10	4.02E-09
Rostralmiddlefrontal	0.341	(0.24 - 0.44)	1.69E-10	4.02E-09
Caudalanteriorcingulate	0.333	(0.23 - 0.44)	8.15E-10	7.25E-09
Posteriorcingulate	0.331	(0.23 - 0.43)	8.53E-10	7.25E-09
Medialorbitofrontal	0.326	(0.22 - 0.43)	1.83E-09	1.04E-08
Superiorfrontal	0.325	(0.22 - 0.43)	1.84E-09	1.04E-08
Precuneus	0.316	(0.21 - 0.42)	4.71E-09	1.89E-08
Inferiorparietal	0.313	(0.21 - 0.42)	5.02E-09	1.89E-08
Parstriangularis	0.313	(0.21 - 0.42)	6.00E-09	2.04E-08
Frontalpole	0.312	(0.21 - 0.42)	2.62E-09	1.27E-08
Isthmuscingulate	0.312	(0.21 - 0.41)	8.29E-09	2.56E-08
Caudalmiddlefrontal	0.306	(0.20 - 0.41)	1.72E-08	4.50E-08
Middletemporal	0.303	(0.20 - 0.41)	1.47E-08	4.17E-08
Parsopercularis	0.297	(0.19 - 0.40)	5.57E-08	1.26E-07
Supramarginal	0.294	(0.19 - 0.40)	5.27E-08	1.26E-07
Paracentral	0.292	(0.19 - 0.40)	6.10E-08	1.30E-07
Superiortemporal	0.292	(0.19 - 0.40)	8.41E-08	1.68E-07
Inferiortemporal	0.286	(0.18 - 0.39)	9.32E-08	1.76E-07
Bankssts	0.285	(0.18 - 0.39)	1.43E-07	2.44E-07
Superiorparietal	0.282	(0.18 - 0.39)	1.80E-07	2.92E-07
Parsorbitalis	0.281	(0.18 - 0.38)	1.34E-07	2.39E-07
Insula	0.280	(0.17 - 0.39)	4.01E-07	5.93E-07
Lateralorbitofrontal	0.278	(0.17 - 0.38)	3.20E-07	4.95E-07
Postcentral	0.267	(0.16 - 0.37)	6.89E-07	9.76E-07
Transversetemporal	0.246	(0.14 - 0.35)	8.31E-06	1.13E-05
Precentral	0.239	(0.13 - 0.34)	1.24E-05	1.56E-05
Lateraloccipital	0.235	(0.13 - 0.34)	1.06E-05	1.39E-05
Parahippocampal	0.230	(0.12 - 0.34)	3.18E-05	3.86E-05
Fusiform	0.221	(0.12 - 0.33)	4.85E-05	5.68E-05
Temporalpole	0.205	(0.10 - 0.31)	1.43E-04	1.62E-04
Cuneus	0.201	(0.09 - 0.31)	2.46E-04	2.70E-04
Entorhinal	0.162	(0.05 - 0.27)	3.32E-03	3.52E-03
Pericalcarine	0.156	(0.05 - 0.26)	4.11E-03	4.23E-03
Lingual	0.154	(0.05 - 0.26)	4.38E-03	4.38E-03

Supplementary Table 4. Beta estimates of the interaction between PHS and time on longitudinal regional cortical volume change controlling for *APOE* status.

Region of Interest (ROI)	PHS*time Beta	95% CI	*p*	FDR-adjusted *p*
Entorhinal	-0.194	(-0.28 – -0.11)	1.59E-05	0.000524119
Inferiorparietal	-0.142	(-0.23 – -0.05)	1.73E-03	0.028570466
Middletemporal	-0.134	(-0.22 – -0.05)	4.50E-03	0.030624189
Temporalpole	-0.134	(-0.23 – -0.04)	3.18E-03	0.030624189
Inferiortemporal	-0.128	(-0.22 – -0.04)	4.64E-03	0.030624189
Bankssts	-0.119	(-0.21 – -0.03)	8.59E-03	0.047232081
Precuneus	-0.118	(-0.21 – -0.03)	1.16E-02	0.047750791
Parahippocampal	-0.114	(-0.20 – -0.03)	1.03E-02	0.047750791
Isthmuscingulate	-0.104	(-0.19 – -0.01)	2.19E-02	0.080237526
Fusiform	-0.102	(-0.19 – -0.01)	2.43E-02	0.080237526
Posteriorcingulate	-0.097	(-0.19 – 0.00)	4.04E-02	0.121308587
Caudalmiddlefrontal	-0.086	(-0.18 – 0.01)	7.38E-02	0.185043327
Supramarginal	-0.086	(-0.18 – 0.01)	7.85E-02	0.185043327
Superiorparietal	-0.085	(-0.18 – 0.01)	7.38E-02	0.185043327
Superiorfrontal	-0.071	(-0.17 – 0.02)	1.47E-01	0.32415702
Rostralmiddlefrontal	-0.062	(-0.16 – 0.03)	2.12E-01	0.410850928
Parstriangularis	-0.06	(-0.16 – 0.03)	2.05E-01	0.410850928
Lateraloccipital	-0.049	(-0.14 – 0.05)	3.07E-01	0.563530415
Caudalanteriorcingulate	-0.044	(-0.14 – 0.05)	3.45E-01	0.599421505
Parsopercularis	-0.042	(-0.14 – 0.05)	3.78E-01	0.608323306
Superiortemporal	-0.037	(-0.13 – 0.06)	3.87E-01	0.608323306
Paracentral	-0.037	(-0.14 – 0.06)	4.38E-01	0.657132868
Parsorbitalis	-0.035	(-0.13 – 0.06)	4.60E-01	0.660214071
Lateralorbitofrontal	-0.024	(-0.12 – 0.07)	4.86E-01	0.667980809
Rostralanteriorcingulate	-0.018	(-0.12 – 0.08)	6.24E-01	0.824257685
Medialorbitofrontal	-0.013	(-0.11 – 0.08)	6.57E-01	0.834106378
Postcentral	0.000	(-0.10 – 0.10)	7.50E-01	0.84465576
Lingual	0.008	(-0.09 – 0.10)	7.93E-01	0.84465576
Pericalcarine	0.014	(-0.09 – 0.12)	7.84E-01	0.84465576
Cuneus	0.016	(-0.08 – 0.12)	7.24E-01	0.84465576
Precentral	0.018	(-0.08 – 0.12)	7.13E-01	0.84465576
Frontalpole	0.023	(-0.08 – 0.12)	8.69E-01	0.896075112
Transversetemporal	0.047	(-0.05 – 0.15)	0.9928667	0.992866764

Supplementary Table 5. Associations of polygenic hazard score (PHS) with regional postmortem amyloid load and neurofibrillary tangles controlling for *APOE* status.

Region of Interest (ROI)	Amyloid load			Neurofibrillary tangles		
	Beta (95% CI)	SE	*P*	Beta (95% CI)	SE	*p*
Angular gyrus	0.26 (0.07 – 0.45)	0.10	6.55×10^{-3}	0.32 (0.10 – 0.20)	0.11	4.36×10^{-3}
Calcarine cortex	0.29 (0.14 – 0.43)	0.07	8.91×10^{-5}	0.10 (0.01 – 0.20)	0.05	3.49×10^{-2}
Anterior cingulate cortex	0.36 (0.14 – 0.57)	0.11	1.14×10^{-3}	0.32 (0.10 – 0.53)	0.11	3.71×10^{-3}
Entorhinal cortex	0.36 (0.18 – 0.55)	0.09	8.81×10^{-5}	0.27 (0.02 – 0.52)	0.13	3.11×10^{-2}
Hippocampus	0.25 (0.12 – 0.38)	0.06	1.25×10^{-4}	0.3 (-0.01 – 0.60)	0.15	0.055
Inferior temporal cortex	0.32 (0.13 – 0.48)	0.09	5.01×10^{-4}	0.53 (0.22 – 0.83)	0.15	7.03×10^{-4}
Midfrontal cortex	0.27 (0.08 – 0.46)	0.10	5.22×10^{-3}	0.32 (0.13 – 0.51)	0.10	1.11×10^{-3}
Superior frontal cortex	0.31 (0.11 – 0.51)	0.10	2.03×10^{-3}	0.29 (0.06 – 0.51)	0.11	1.25×10^{-2}

Supplementary acknowledgements

ADNI: Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (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.; Cogstate; 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 Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

ADGC: The National Institutes of Health, National Institute on Aging (NIH-NIA) supported this work through the following grants: ADGC, U01 AG032984, RC2 AG036528; NACC, U01 AG016976; NCRAD, U24 AG021886; NIA LOAD, U24 AG026395, U24 AG026390; Banner Sun Health Research Institute P30 AG019610; Boston University, P30 AG013846, U01 AG10483, R01 CA129769, R01 MH080295, R01 AG017173, R01 AG025259, R01AG33193; Columbia University, P50 AG008702, R37 AG015473; Duke University, P30 AG028377, AG05128; Emory University, AG025688; Group Health Research Institute, UO1 AG06781, UO1 HG004610; Indiana University, P30 AG10133; Johns Hopkins University, P50 AG005146, R01 AG020688; Massachusetts General Hospital, P50 AG005134; Mayo Clinic, P50 AG016574; Mount Sinai School of Medicine, P50 AG005138, P01 AG002219; New York University, P30 AG08051, MO1RR00096, UL1 RR029893, 5R01AG012101, 5R01AG022374, 5R01AG013616, 1RC2AG036502, 1R01AG035137; Northwestern University, P30 AG013854; Oregon Health & Science University, P30 AG008017, R01 AG026916; Rush University, P30 AG010161, R01 AG019085, R01 AG15819, R01 AG17917, R01 AG30146; TGen, R01 NS059873; University of Alabama at Birmingham, P50 AG016582, UL1RR02777; University of Arizona, R01 AG031581; University of California, Davis, P30 AG010129; University of California, Irvine, P50 AG016573, P50, P50 AG016575, P50 AG016576, P50 AG016577; University of California, Los Angeles, P50 AG016570; University of California, San Diego, P50 AG005131; University of California, San Francisco, P50 AG023501, P01 AG019724; University of Kentucky, P30 AG028383, AG05144; University of Michigan, P50 AG008671; University of Pennsylvania, P30 AG010124; University of Pittsburgh, P50 AG005133, AG030653; 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; Vanderbilt University, R01 AG019085; and

Washington University, P50 AG005681, P01 AG03991. The Kathleen Price Bryan Brain Bank at Duke University Medical Center is funded by NINDS grant # NS39764, NIMH MH60451 and by Glaxo Smith Kline. Genotyping of the TGEN2 cohort was supported by Kronos Science. The TGen series was also funded by NIA grant AG034504 to AJM, 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 Funding for ADNI is through the Northern California Institute for Research and Education by grants from Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace, Inc., Merck and Co., Inc., Novartis AG, Pfizer Inc, F. Hoffman-La Roche, Schering-Plough, Synarc, Inc., Alzheimer's Association, Alzheimer's Drug Discovery Foundation, the Dana Foundation, and by the National Institute of Biomedical Imaging and Bioengineering and NIA grants U01 AG024904, RC2 AG036535, K01 AG030514. We thank Drs. D. Stephen Snyder and Marilyn Miller from NIA who are *ex-officio* ADGC members. Support was also from the Alzheimer's Association (LAF, IIRG-08-89720; MP-V, IIRG-05-14147) and the US Department of Veterans Affairs Administration, Office of Research and Development, Biomedical Laboratory Research Program. P.S.G.-H. is supported by Wellcome Trust, Howard Hughes Medical Institute, and the Canadian Institute of Health Research. Data for this study were prepared, archived, and distributed by the National Institute on Aging Alzheimer's Disease Data Storage Site (NIAGADS) at the University of Pennsylvania (U24-AG041689-01), funded by the National Institute on Aging.

NACC: The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIAfunded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Steven Ferris, PhD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG016570 (PI Marie-Francoise Chesselet, MD, PhD), P50 AG005131 (PI Douglas Galasko, MD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD) , P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P50 AG005136 (PI Thomas Montine,

MD, PhD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), and P50 AG047270 (PI Stephen Strittmatter, MD, PhD).