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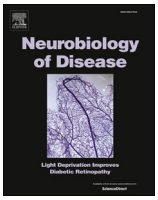

Multiple gene variants linked to Alzheimer's-type clinical dementia via GWAS are also associated with non-Alzheimer's neuropathologic entities

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ABSTRACT

The classic pathologic hallmarks of Alzheimer's disease (AD) are amyloid plaques and neurofibrillary tangles (AD neuropathologic changes, or ADNC). However, brains from individuals clinically diagnosed with "AD-type" (amnestic) dementia usually harbor heterogeneous neuropathologies in addition to, or other than, ADNC. We hypothesized that some AD-type dementia associated genetic single nucleotide variants (SNVs) identified from large genomewide association studies (GWAS) were associated with non-ADNC neuropathologies. To test this hypothesis, we analyzed data from multiple studies with available genotype and neuropathologic phenotype information. Clinical AD/dementia risk alleles of interest were derived from the very large GWAS by Bellenguez et al. (2022) who reported 83 clinical AD/dementia-linked SNVs in addition to the *APOE* risk alleles. To query the pathologic phenotypes associated with variation of those SNVs, National Alzheimer's disease Coordinating Center (NACC) neuropathologic data were linked to AD Sequencing Project (ADSP) and AD Genomics Consortium (ADGC) data. Separate data were obtained from the harmonized Religious Orders Study and the Rush Memory and Aging Project (ROSMAP). A total of 4811 European participants had at least ADNC neuropathology data and also genotype data available; data were meta-analyzed across cohorts. As expected, a subset of dementia-associated SNVs were associated with ADNC risk in Europeans—e.g., *BIN1, PICALM, CR1, MME,* and *COX7C*. Other gene variants linked to (clinical) AD dementia were associated with non-ADNC pathologies. For example, the associations of *GRN* and *TMEM106B* SNVs with limbic-predominant age-related TDP-43 neuropathologic changes (LATE-NC) were replicated. In addition, SNVs in *TNIP1* and *WNT3* previously reported as AD-related were instead associated with hippocampal sclerosis pathology. Some genotype/neuropathology association trends were not statistically significant at $P < 0.05$ after correcting for multiple testing, but were intriguing. For example, variants in *SORL1* and *TPCN1* showed trends for association with LATE-NC whereas Lewy body pathology trended toward association with *USP6NL* and *BIN1* gene variants. A smaller cohort of non-European subjects ($n = 273$, approximately one-half of whom were African-Americans) provided the basis for additional

Abbreviations: ADGC, Alzheimer's disease Genomics Consortium; ADNC, Alzheimer's disease neuropathologic change; ADRC, Alzheimer's Disease Research Center; ADSP, Alzheimer's Disease Sequencing Project; ALS, amyotrophic lateral sclerosis; FDR, false discovery rate; FTLD, frontotemporal lobar degeneration; HS, hippocampal sclerosis; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; LD, linkage disequilibrium; NACC, National Alzheimer's Coordinating Center; NFT, neurofibrillary tangle; OR, odds ratio; PCA, principal component analysis; SNV, single nucleotide (genetic) variant; ROSMAP, Rush University Religious Orders Study and the Memory and Aging Project;; WGS, whole genome sequencing.

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exploratory analyses. Overall, these findings were consistent with the hypothesis that some genetic variants linked to AD dementia risk exert their affect by influencing non-ADNC neuropathologies.

1. Introduction

Approximately 80% of Alzheimer's disease (AD) risk is heritable according to twin studies (Gatz et al., 2006), yet the biological mechanisms underlying that heritability remain poorly understood. A key goal of genetic analyses is to elucidate the individual genetic variants ("genotypes") that are associated with altered risk for the disease phenotype. However, it is increasingly clear that the clinical syndrome of AD (amnestic dementia) is influenced by many genes and multiple different neuropathologies. Thus, to understand the biology underlying the heritability of AD requires a cataloging of different genetic variants associated with dementia risk, and then a systematic analytic approach must be executed to identify how those genetic variants are associated with disease-driving phenotypes.

A definition of terms is required to avoid phenotypic ambiguity. During life, persons with amnestic dementia are usually given the clinical diagnosis of "Probable AD" (McKhann et al., 2011), or AD-type dementia (Mehta and Schneider, 2021). At autopsy, or as predicted by biomarkers, the neuropathological hallmarks of AD are amyloid-β (Aβ) plaques and tau neurofibrillary tangles (NFTs) – AD neuropathologic changes (ADNC) (Knopman et al., 2018; Montine et al., 2012).

Although the gold standard for disease instantiation and severity is neuropathologic diagnoses, it is the clinical diagnoses (lacking biomarker data) that have been used for many large surveys of AD genetics. A recent genome-wide association study (GWAS), which analyzed genomes of almost 800,000 individuals, reported 83 dementia-related single-nucleotide variants (SNVs) in addition to the *APOE* risk alleles (Bellenguez et al., 2022). The use of clinical diagnoses in this study for disease phenotyping had advantages – this strategy enabled a large sample size and facilitated inclusion of a broad range of participants. However, there are limitations, and the potential for confusion, resulting from this study design. To address these challenges requires an understanding of the underlying causes of the clinical syndrome of AD dementia.

The classification of dementia-associated neuropathologic phenotypes has been refined extensively in the past several years, partly because neuropathologies other than ADNC commonly underlie the clinical disease of AD dementia. More specifically, previous studies revealed that the clinical diagnosis of AD dementia was imperfectly predictive of ADNC (Beach et al., 2012), and only ~20% of dementia cases are "pure" ADNC at autopsy (Karanth et al., 2021; Shim et al., 2013). In attributable risk analyses of a large community-based cohort that factored in all known pathologies, ADNC accounted for <40% of all identified AD-type dementia risk (Boyle et al., 2021; Nelson et al., 2019a).

What other neuropathologies can underlie AD-type dementia? An important dementia-associated brain disease of aging is limbic-predominant age-related TDP-43 encephalopathy (LATE). The pathological hallmark of LATE neuropathologic changes (LATE-NC) is TDP-43 proteinopathy (Neumann et al., 2006) that is mostly restricted to the medial temporal lobes. Approximately one-third of people aged 85 or older have LATE-NC (Nelson et al., 2022). People with LATE-NC are also at elevated risk for comorbid hippocampal sclerosis (HS), a diagnostic term that implies atrophy and cell loss in the hippocampal formation, and HS is associated with added cognitive impairment (Boyle et al., 2019; Gauthreaux et al., 2022; Nelson et al., 2010). Another major subtype of pathology associated with amnestic dementia is Lewy body disease (Boyle et al., 2019). Lewy body pathologies comprise a heterogeneous group of neurological disorders with the common element of misfolded α-synuclein protein (Attems et al., 2021).

The neurodegenerative disease phenotypes are even more complex because findings at brain autopsy are usually characterized by neuropathologic combinations as opposed to "pure" isolated neuropathologies (Brenowitz et al., 2017; Jack Jr et al., 2016; James et al., 2016; Jellinger et al., 2015; Kryscio et al., 2016; Nelson et al., 2007; Nelson et al., 2016; Neltner et al., 2016; Whitwell et al., 2007). Genetics may contribute to these phenomena because specific genetic variants often influence more than one subtype of neuropathology. As a conspicuous example, different neuropathologies have been linked to gene variants of the *APOE* dementia-associated ε4 risk allele (Cykowski et al., 2022; Dugan et al., 2021; Kukull et al., 1996; O'Meara et al., 1997; Tsuang et al., 2005).

For the reasons stated above, it is clear that a considerable proportion of amnestic dementia in the human population is associated with neuropathologies other than ADNC. Yet only a few studies have examined the influence of genetic risk factors on non-ADNC neuropathologies underlying AD-type dementia (Beecham et al., 2014; Farfel et al., 2016). In the present study, we hypothesized that some of the SNVs reported to be associated with risk for AD-type dementia by Bellenguez et al. (Bellenguez et al., 2022) are actually associated with other pathologies. We gathered extensive genotype and neuropathologic phenotype data from >4000 research participants to evaluate the associations between AD dementia-linked SNVs and the neuropathologies that each SNV was associated with.

2. Material and methods

2.1. Participants

The National Alzheimer's Coordinating Center (NACC) phenotype data were derived from 37 different United States (U.S.) Alzheimer's Disease Research Centers (ADRCs) with autopsy data scored using NACC Neuropathology (NP) v10–11 forms through the March 2022 data freeze (https://www.alz.washington.edu/). Autopsies were performed within each of the contributory ADRCs. The NACC NP data were linked to ADRC genetic data including whole genome sequencing (WGS) data produced under the Alzheimer's Disease Sequencing Project (ADSP) and genotype data were provided by the Alzheimer's Disease genetic Consortium (ADGC). These data sets were described in detail previously (Crane et al., 2017; Dugan et al., 2021; Naj et al., 2018; Naj et al., 2017). Duplicated participants were removed from the ADGC genotype data, and thus the study sample in the WGS data was independent of those in the ADGC genotype data (hereafter referred to as "ADSP WGS" and "ADGC", respectively). Harmonized data from two cohorts (the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP)) are referred to as the ROSMAP study (Bennett et al., 2018). Again, duplicates were removed so that the study samples were non-overlapping. We performed principal component analysis (PCA) implemented in PLINK v1.90a (Chang et al., 2015; Purcell et al., 2007) with the "–pca" option using a linkage disequilibrium (LD) pruned subset of markers (pairwise $r^2 < 0.2$) merged to 1000 Genomes Project Phase 3 (Genomes Project et al., 2010) data after removing symmetric SNVs and flipping SNVs discordant for DNA strands between the two datasets. Based on the first and second PC plot, we split participants into two ancestry groups: European ancestry and other ancestries (Supplementary Figs. 1–3, Supplementary Tables 1–3). For our primary analysis, we excluded participants who had at least one of 19 rare brain diseases diagnosed at autopsy (see Fig. 1 and (Katsumata et al., 2020)) from ADSP WGS and ADGC datasets in people with European ancestry. The excluded rare brain diseases included frontotemporal lobar degeneration (FTLD), chronic traumatic encephalopathy, multiple sclerosis, multiple system atrophy, amyotrophic lateral sclerosis, triplet repeat (e.

g., Huntington's and other) diseases, and prion diseases. These exclusions involved removing 98 participants from initial analyses. Data from all participants (including those with rare disease) were investigated as a sensitivity analysis. Similar exclusion criteria were not applied to ROSMAP due to lack of data availability and to ADSP WGS and ADGC in people with other ancestries due to small sample sizes.

2.2. Neuropathology data

Data were included related to the following neuropathologic features: ADNC including neocortical neuritic plaques (Consortium to Establish a Registry for Alzheimer's Disease (CERAD) rating (Mirra, 1997)) and Braak NFT stages (Braak and Braak, 1991), Lewy body pathologies identified using α-synuclein immunohistochemistry (Attems et al., 2021), whereas LATE-NC was operationalized by TDP-43 pathology (Dugan et al., 2021; Nelson et al., 2019a; Neumann et al., 2006), which is often comorbid with (but separate from) HS (Dugan et al., 2021; Nelson et al., 2011). The neuropathological data were dichotomized: ADNC/NFT was represented by 0 = Braak NFT stage 0 to IV and 1 = Braak NFT stage V or VI (Braak and Braak, 1991); neocortical neuritic plaques with 0 = none to moderate and 1 = frequent (Mirra et al., 1991); TDP-43 pathology with 0 = none and 1 = present in any brain regions including amygdala, hippocampus, entorhinal/inferior temporal cortex, and neocortex; Lewy body pathology with 0 = none and 1 = present in any brain regions including brainstem, limbic, amygdala, olfactory bulb, and neocortex; and HS with 0 = none and 1 = present either unilaterally or bilaterally. Additional post hoc sensitivity analyses were performed, using different cut-points for diagnostic operationalizations, to evaluate the findings when other pathologic criteria were applied.

2.3. Genetic data

ADSP WGS data were provided from NIH/ADSP collaborators. We obtained variant calling data ($n = 16{,}785$) for SNVs and short insertions/deletions in VCF data file formats mapped to Genome Reference Consortium Human Build 38 (GRCh38). We also obtained ADGC and ROSMAP genotype data (PLINK format file sets). These genotype data were imputed using the TOPMed Imputation Server (https://imputation.biodatacatalyst.nhlbi.nih.gov/) (Taliun et al., 2019) based on GRCh38. We reran the PCA for each neuropathology outcome to derive orthogonal PCs which were used as covariates in the subsequent analyses. When SNV data were missing, we used the proxy which was in perfect LD (i.e., $r^2 = 1$ and $D' = 1$) identified using LDLink (ldlink.nci.nih.gov) (Machiela and Chanock, 2015) by querying the LDproxy Tool in the relevant population.

2.4. Statistical analysis

For each of the neuropathology outcomes, we performed association

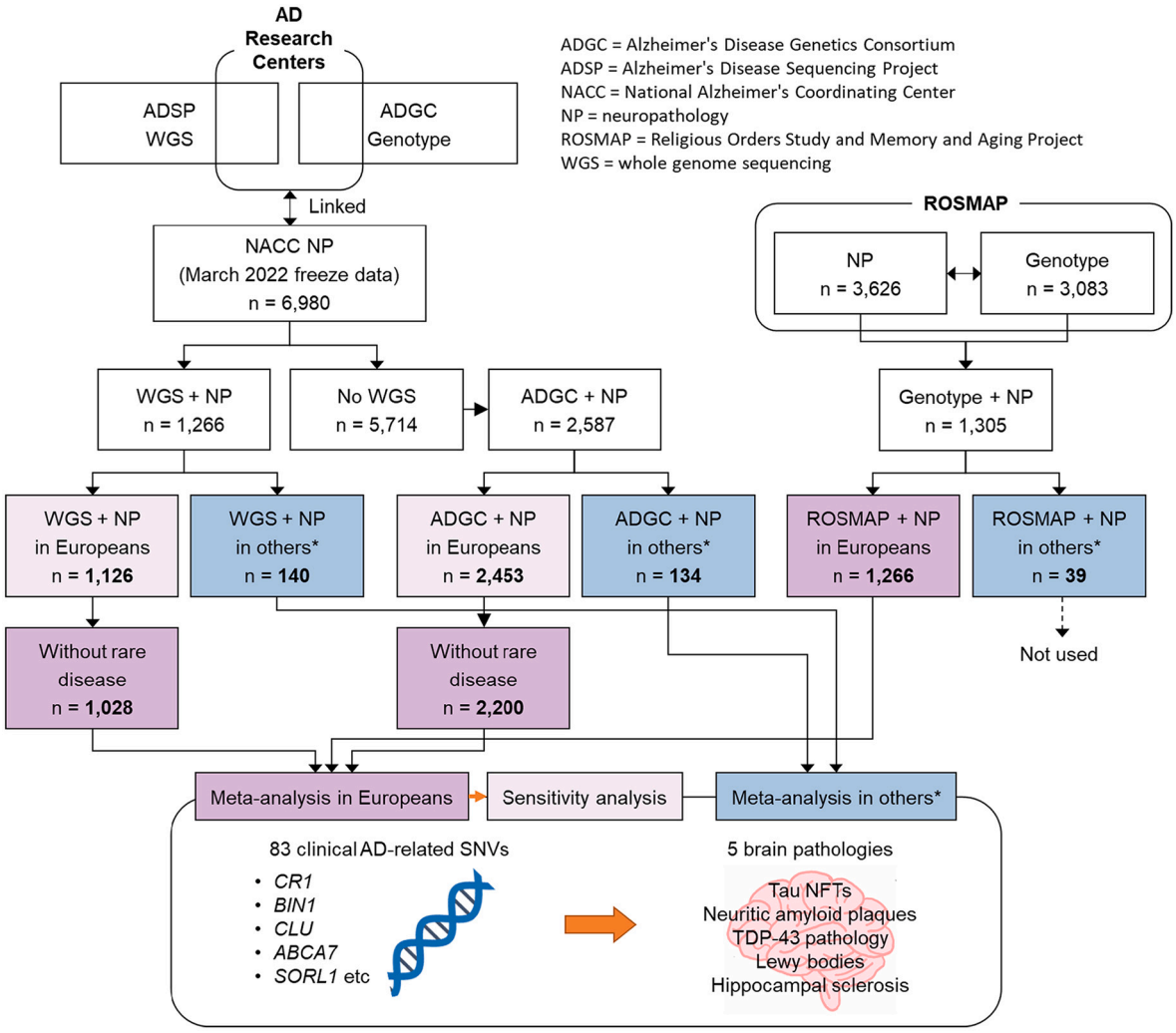

Fig. 1. Work flow diagram of the present study. * "Others" includes other ancestries than Europeans (i.e., Africans, Admixed Americans, East Asians, and South Asians).

tests of clinical AD-related SNVs reported in the Bellenguez et al. (2022) study (Supplementary Table 4) under an additive mode of inheritance using logistic regression adjusted for age at death, sex, and the top three PCs computed in PLINK v1.90a. We then combined results across the three datasets (ADSP WGS, ADGC, and ROSMAP) for European ancestry in a fixed-effect meta-analysis with weighted *Z*-score-based *p*-values implemented in PLINK v1.90a with the "–meta-analysis weighted-z" option. Since the sample size in the other ancestries from the ROSMAP dataset was too small, we performed meta-analysis for other ancestries using the results from the two datasets, ADSP WGS and ADGC. We created clustered heatmaps for p-values with the pheatmap R package. We set statistical significance at false discovery rate (FDR) adjusted p-value (i.e., Q-value) < 0.05 using the Benjamini-Hochberg procedure in each of the neuropathology outcomes.

3. Results

The numbers of included participants are shown in Fig. 1. Since there were missing values, the samples sizes differed for each of the neuropathologies (Supplementary Table 1). The ROSMAP study included more females, fewer *APOE* ε4 carriers, fewer people with high ADNC, more people with TDP-43 pathology, and fewer people with Lewy body pathology and hippocampal sclerosis compared with the ADSP WGS and ADGC studies in both participants with European and other ancestries (Table 1 and Supplementary Table 3).

Table 1
Characteristics in subjects of European ancestry.

Characteristic	ADRC		ROSMAP ($n = 1266$)
	ADSP WGS ($n = 1028$)	ADGC ($n = 2200$)	
Age at death, mean ± SD	82.5 ± 10.5	82.2 ± 10.6	89.7 ± 6.5
Years in education, mean ± SD	16.5 ± 9.1	16.3 ± 8.2	16.3 ± 3.7
Sex, n (%)			
Male	529 (51.5)	1173 (53.3)	412 (32.5)
Female	499 (48.5)	1027 (46.7)	854 (67.5)
APOE, n (%)			
−/−	526 (51.2)	1155 (52.5)	952 (75.2)
−/ε4	438 (42.6)	798 (36.3)	293 (23.1)
ε4/ε4	64 (6.2)	247 (11.2)	21 (1.7)
Braak NFT stage, n (%)			
0 – IV	374 (36.5)	909 (41.5)	916 (72.4)
V/VI	652 (63.5)	1282 (58.5)	350 (27.6)
Neocortical neuritic plaques, n (%)			
No – moderate	466 (45.3)	1072 (48.8)	840 (66.4)
Frequent	562 (54.7)	1123 (51.2)	426 (33.6)
TDP-43 in any brain regions, n (%)			
No	273 (75.0)	520 (65.2)	554 (47.1)
Yes[a]	91 (25.0)	277 (34.8)	622 (52.9)
Lewy bodies in any brain regions, n (%)			
No	661 (64.6)	1388 (63.5)	927 (75.7)
Yes[b]	362 (35.4)	797 (36.5)	298 (24.3)
Hippocampal sclerosis, n (%)			
No	418 (87.4)	962 (86.7)	1133 (91.1)
Yes[c]	60 (12.6)	147 (13.3)	111 (8.9)

Abbreviations: ADGC = Alzheimer's Disease Genetics Consortium; ADRC = Alzheimer's Disease Research Center; ADSP = Alzheimer's Disease Sequencing Project; NFT = neurofibrillary tangle; ROSMAP = Religious Orders Study (ROS) and Memory and Aging Project (MAP); SD = standard deviation; TDP-43 = TAR DNA binding protein 43 kDa; WGS = whole genome sequencing.

[a] Observed in any regions including amygdala, hippocampus, entorhinal/inferior temporal cortex, and neocortex.

[b] Observed in any brain regions including brainstem-predominant, limbic, neocortical, amygdala predominant, and olfactory bulb.

[c] Observed in either unilateral or bilateral.

The associations of the non-*APOE* SNVs with the individual neuropathologies are displayed in Supplementary Tables 5–10 in people with primarily European ancestry and Supplementary Tables 11–16 in people with other ancestries. The meta-analyzed association results in people with European ancestry are shown in Table 2 (summarized results) and Supplementary Table 10 (full results). In the meta-analysis for European ancestry, rs6733839 in *BIN1* was strongly associated with AD-related neuropathology (OR = 1.30 and *P*-value = 2.6×10^{-8} in Braak NFT stage and OR = 1.21 and P-value = 3.9×10^{-5} in neocortical neuritic plaques). The SNVs in *MME* and *EED/PICALM* were also associated with both Braak NFT stage and neocortical neuritic plaques. The SNV in *TMEM106B* was detected as a signal of TDP-43 pathology (OR = 0.78 and P-value = 1.0×10^{-4} in the A allele of rs13237518) and HS (OR = 0.64 and P-value = 9.3×10^{-7} in the A allele of rs13237518). The T allele of rs5848 in *GRN* was associated with HS (OR = 1.53 and P-value = 2.1×10^{-6}). The G allele of rs74685827 in *SORL1* and the C allele of rs6489896 in *TPCN1* were rather genetic risk factors of TDP-43 pathology; however, these associations were not statistically significant after FDR adjustment (Q-values were 0.062 and 0.085, respectively). The SNVs in *WNT3* and *TNIP1* were significantly associated with HS but not associated with AD-related neuropathologies (Table 2). These SNVs were separated into TDP-43/HS related clusters including *TMEM106B*, *GRN*, *TPCN1*, *SORL1*, *WNT3*, *TNIP1*, *ACE*, and *SCIMP* and AD-related clusters including *FERMT2*, *RBCK1*, *PTK2B*, *INPP5D*, *APH1B*, *EED/PICALM*, *SPI1*, *COX7C*, *MME*, and *CR1* (Fig. 2 and Supplementary Fig. 4–5).

It is possible that some genetic variants underlie the tendency for ADNC and LATE-NC to co-exist in the same brains. In a post-hoc analysis, we examined the two SNVs (linked nominally to LATE-NC risk) in *SORL1* and *TPCN1* for comorbid phenotypes with LATE-NC and ADNC using ADSP WGS data. As shown in Table 3, the G allele of rs74685827 in *SORL1* was associated with both (comorbid) widespread NFTs (Braak NFT stages V/VI) and TDP-43 pathology (P-value = 0.034) in this sample.

There were different analytic strategies that may have been used. Therefore, we performed two relevant post hoc sensitivity analyses. The first sensitivity analysis used data from all participants with or without rare disease (i.e., included all subjects before applying exclusion criteria) in people with European ancestry. The ORs from the sensitivity analyses were similar with those in people who did not have any rare disease (Supplementary Table 17). In the second sensitivity analysis, we changed the operationalization (cut-points) for severities in neuropathologies: 0 = Braak NFT stage 0 to III and 1 = Braak NFT stage IV to VI; neocortical neuritic plaques with 0 = none or sparse and 1 = moderate or frequent; TDP-43 pathology with 0 = none or present in amygdala (i.e. LATE-NC stages 0/1) and 1 = present in hippocampus, entorhinal/inferior temporal cortex, or neocortex (LATE-NC stages 2/3); Lewy body pathology data with 0 = none or present in other regions and 1 = present in neocortex. The results of this sensitivity analysis are shown in Supplementary Table 18. Notably, the odds ratios were larger, and *P*-values smaller, for *GRN* (rs5848) and *SORL1* (rs74685827) SNVs' association with LATE-NC using the revised operationalization (i.e., LATE-NC stages 0/1 vs 2/3) of TDP-43 pathology.

An ad hoc grouping of non-European research subjects was composed of approximately one-half African-Americans in addition to other ethnoracial groups as defined by genetic PCA analyses (Supplemental Figs. 1–3). Among this heterogeneous subsample, the numbers of subjects were small, and no SNV was associated with any of the surveyed neuropathology phenotypes after FDR adjustment (Table 4 for summary results, Supplementary Tables 11–15 for individual neuropathologies, and full results are shown in Supplementary Table 16). Notably, rs12151021 in *ABCA7* was the top SNV in ADNC (plaques and tangles)

Table 2
Summary of association from meta-analysis in people with European ancestry.

Gene	Variant	MAF[a]	AD-OR[b]	Meta-analysis		
				NP-OR	P-value	Q-value[c]
Braak NFT stage						
BIN1	rs6733839	0.38	1.17	1.30	2.6×10^{-8}	1.5×10^{-6}
CR1	rs679515	0.17	1.13	1.24	3.8×10^{-4}	0.011
MME	rs16824536	0.032	0.92	0.70	9.8×10^{-4}	0.016
COX7C	rs62374257	0.21	1.07	1.20	0.0011	0.016
SPI1	rs10437655	0.38	1.06	1.13	0.0064	0.071
EED/PICALM	rs3851179	0.37	0.90	0.88	0.0089	0.075
INPP5D	rs10933431	0.23	0.93	0.86	0.0094	0.075
Neocortical neuritic plaques						
BIN1	rs6733839	0.38	1.17	1.21	3.9×10^{-5}	0.0022
EED/PICALM	rs3851179	0.37	0.90	0.85	0.0010	0.021
MME	rs16824536	0.032	0.92	0.70	0.0011	0.021
APH1B	rs117618017	0.14	1.11	1.23	0.0020	0.026
RBCK1	rs1358782	0.27	0.95	0.85	0.0023	0.026
FERMT2	rs17125924	0.080	1.10	1.25	0.0047	0.044
PTK2B	rs73223431	0.35	1.07	1.13	0.0088	0.071
TDP-43 in any brain regions						
TMEM106B	rs13237518	0.40	0.96	0.78	1.0×10^{-4}	0.0059
SORL1	rs74685827	0.015	1.19	1.85	0.0042	0.092
GRN	rs5848	0.30	1.07	1.22	0.0049	0.092
TPCN1	rs6489896	0.094	1.08	1.42	0.0071	0.10
Lewy bodies in any brain regions						
BIN1	rs6733839	0.38	1.17	1.16	0.0012	0.068
USP6NL	rs7912495	0.45	1.06	1.14	0.0043	0.12
Hippocampal sclerosis						
TMEM106B	rs13237518	0.40	0.96	0.64	9.3×10^{-7}	5.2×10^{-5}
GRN	rs5848	0.30	1.07	1.53	2.1×10^{-6}	5.8×10^{-5}
WNT3	rs199515	0.22	0.94	0.69	0.0014	0.025
TNIP1	rs871269	0.34	0.96	0.75	0.0018	0.025
ACE	rs4277405	0.37	0.94	1.12	0.0082	0.089
SCIMP	rs7225151	0.14	1.08	1.36	0.0095	0.089

Abbreviations: AD = Alzheimer's disease; MAF = minor allele frequency; NFT = neurofibrillary tangle; NP = neuropathology; OR = odds ratio; TDP-43 = TAR DNA binding protein 43 kDa.

[a] MAFs are calculated from 1000 genome phase 3 in Europeans (EUR) population.

[b] AD-OR represents clinical AD related odds ratios reported in "New insights into the genetic etiology of Alzheimer's disease and related dementias" (Bellenguez et al., 2022).

[c] Q-value indicates the false discovery rate (FDR) adjusted p-value with the Benjamini-Hochberg procedure.

neuropathology for non-Europeans. The C allele of *CLU* was risk for HS rather than protective. *ANK3, ABCA7,* and *BIN1* made an ADNC-related cluster, *MME*, *RBCK1*, and *USP6NL* were in a cluster for Braak NFT stage, and *PLCG2*, *ANKH*, and *CLU* were separated into the TDP-43/HS cluster (Fig. 3 and Supplementary Fig. 6).

Finally, we confirmed the associations between *APOE* diplotype determined with rs429358 and rs7412 and each of the NPs (Supplementary Table 19). As we expected, the ε2/ε3 diplotype had protective effects on Braak NFT stage and neocortical neuritic plaques, but did not have on TDP-43, Lewy body, and HS pathologies. The ε4 allele was strongly associated with all the neuropathologies in people with European ancestry, and with ADNC in people with other ancestries.

4. Discussion

In the current study, genotype and pathologic endophenotype data were meta-analyzed together based on the AD-related SNVs identified and/or replicated in the large GWAS of (Bellenguez et al., 2022). More specifically, we combined neuropathologic and genotype data from three high-quality data sets: ADSP, ADGC, and ROSMAP. As expected, some of the dementia-linked SNVs were indeed associated with ADNC risk, e.g., SNVs in or near *BIN1*, *PICALM*, and *CR1*. Also replicated were the SNVs associated previously with LATE-NC risk in *GRN* and *TMEM106B* genes. In terms of novel findings, SNVs in or near *TNIP1* and *WNT3* that were previously reported as AD-related variants were instead associated with HS pathology. Overall, our findings underscore that non-ADNC neuropathologies can contribute substantially to AD-type amnestic dementia clinically.

There have been several prior GWA-based studies focusing on multiple AD dementia-related risk alleles and/or non-ADNC related neuropathologic endophenotypes (Beecham et al., 2014; Farfel et al., 2016; Yang et al., 2020). For example, Beecham et al. previously confirmed the expected associations between ADNC phenotypes (Braak NFT stages and CERAD neuritic amyloid plaques scores) for *BIN1, PICALM,* and *CR1*. That study also included some phenotypes related to cerebrovascular pathologies (e.g., cerebral amyloid angiopathy and "vascular brain injury"), that were not included in the current study. Beecham et al. also reported evidence of a novel gene variant in *KCNMB2* (rs9637454) linked to HS risk (Beecham et al., 2014), that was not evaluated in the current study but was assessed in a similar data set as was analyzed in the current study (Dugan et al., 2021).

In a separate study of ROSMAP data, the associations were analyzed between various neuropathologies and 22 gene variants linked to AD dementia by GWAS (Farfel et al., 2016). The endophenotypes assessed also included cerebrovascular pathologies. Several suggestive findings were made in this study including an association between *ZCWPW1* SNV

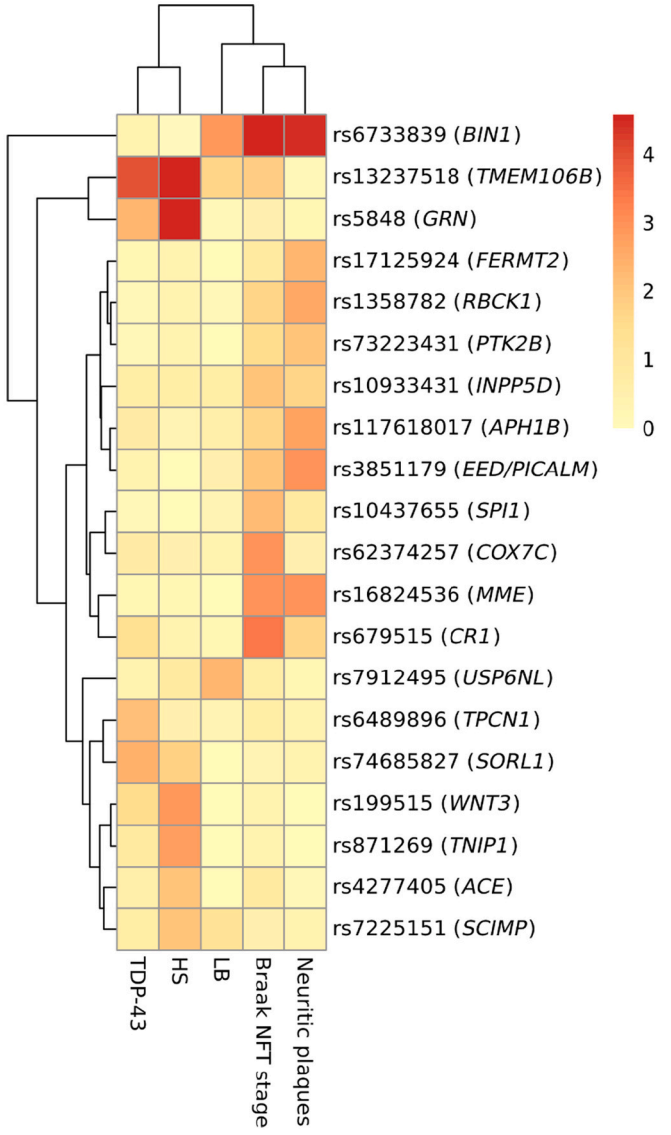

Fig. 2. Heatmap for -log10 transformed *p*-values of single nucleotide variants with p < 0.01 among people with European ancestry. Abbreviations: TDP-43 = TAR DNA binding protein 43 kDa; HS = hippocampal sclerosis; LB = Lewy bodies; NFT = neurofibrillary tangle.

Table 3
Participant counts comparing single nucleotide variants in *SORL1* and *TPCN1* and comorbid neuropathologies of limbic-predominant age-related TDP-43 encephalopathy (LATE) and Alzheimer's disease (AD) in ADSP WGS participants with European ancestry.

	LATE + AD	Others	P-value[a]
rs74685827 in *SORL1*			
T/T	71	283	0.034
G/T	5	5	

[a] P-value calculated with Fisher's exact test.

and HS pathology, whereas a SNV in the *CELF1* gene was associated with both micro-infarcts and Lewy body pathology. This study (Farfel et al., 2016) also emphasized that far larger sample sizes may be required for confident hypothesis-testing to link dementia-associated SNVs with neuropathologic features.

The current study built on prior published work by incorporating additional parameters in both the genotype and phenotype portions of the analytic equation, due to new information being made available in the past several years. In terms of SNVs linked to AD-type (amnestic) dementia risk, the paper by Bellenguez et al. (2022) identified dozens of novel putative risk alleles. It should also be emphasized that the prior AD/dementia-associated genetic variants were mostly replicated by this study (Bellenguez et al., 2022).

As to the neuropathologic phenotypes, a relatively recent development is the classification of LATE-NC (Nelson et al., 2019a), which is a common pathology linked to the amnestic dementia clinical syndrome. Here we focus on several of the novel putative risk alleles that were associated with LATE-NC or HS risk in the current study. Each of these provides opportunities for further research. The estimated effect sizes of these genetic variants' linkages to neuropathologies were in the "same direction" (same risk-associated allele) and effect sizes ascertained were larger than those of clinical diagnosed AD reported (Bellenguez et al., 2022). We discuss these associations agnostic about the impacts of the genetic variants themselves, mindful of the fact that GWAS can identify proxy markers that are indicative of a co-inherited genetic characteristic (e.g., structural variants or repeat sequences), may affect splicing, or could modulate expression of another gene or genes (possibly far away on the chromosome) underlying the phenotype(s). With those caveats in mind, we were intrigued by findings of putative risk-associated genetic variation in or near the genes *SORL1, TNIP/GPX3,* and *WNT3*.

The *SORL1* (Sortilin Related Receptor 1) gene is located on human Chromosome 11 and *SORL1* is a well-known AD dementia-linked gene (Barthelson et al., 2020; Campion et al., 2019). This gene stands out because both highly-penetrant *SORL1* rare genetic variants are associated with early-onset AD, and other more common *SORL1* genetic variants are linked to late-onset "sporadic" AD dementia–including

Table 4
Summary of association from meta-analysis in people with other ancestries.

Gene	Variant	MAF[a]	AD-OR[b]	Meta-analysis		
				NP-OR	P-value	Q-value[c]
Braak NFT stage						
ABCA7	rs12151021	0.38	1.1	1.68	0.0072	0.42
MME	rs16824536	0.12	0.92	0.54	0.021	0.53
RBCK1	rs1358782	0.14	0.95	0.58	0.029	0.53
BIN1	rs6733839	0.40	1.17	1.49	0.046	0.53
USP6NL	rs7912495	0.37	1.06	1.48	0.049	0.53
Neocortical neuritic plaques						
ABCA7	rs12151021	0.38	1.1	1.73	0.0046	0.18
BIN1	rs6733839	0.40	1.17	1.74	0.0063	0.18
ANK3	rs7068231	0.46	0.95	0.59	0.012	0.23
TDP-43 in any brain regions						
PLCG2	rs12446759	0.49	0.95	0.35	0.0042	0.23
Lewy bodies in any brain regions						
MS4A4A	rs1582763	0.23	0.91	0.45	0.0078	0.45
BIN1	rs6733839	0.40	1.17	1.60	0.020	0.58
Hippocampal sclerosis						
ANKH	rs112403360	0.058	1.09	5.82	0.0048	0.27
CLU	rs11787077	0.38	0.91	2.83	0.0096	0.27

Abbreviations: AD = Alzheimer's disease; MAF = minor allele frequency; NFT = neurofibrillary tangle; NP = neuropathology; OR = odds ratio; TDP-43 = TAR DNA binding protein 43 kDa.

[a] MAFs are calculated from 1000 genome phase 3 in other populations (AFR, African; AMR, Admixed American; EAS, East Asian; SAS, South Asian).

[b] AD-OR represents clinical AD related odds ratios reported in "New insights into the genetic etiology of Alzheimer's disease and related dementias" (Bellenguez et al., 2022).

[c] Q-value indicates the false discovery rate (FDR) adjusted p-value with the Benjamini-Hochberg procedure.

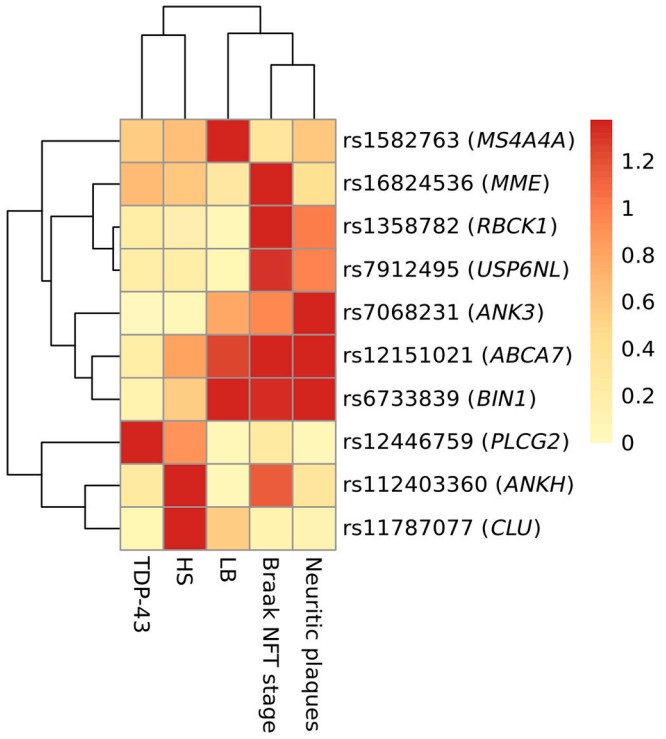

Fig. 3. Heatmap for -log10 transformed *p*-values of single nucleotide variants with $p < 0.05$ among people with non-European ancestries. Abbreviations: TDP-43 = TAR DNA binding protein 43 kDa; HS = hippocampal sclerosis; LB = Lewy bodies; NFT = neurofibrillary tangle.

pathologically confirmed ADNC cases (Thonberg et al., 2017). The SORL1 protein is involved in amyloid-β clearance so has a highly credible functional link to ADNC (Willnow and Andersen, 2013). *SORL1* mutations have also been linked to FTLD (Benussi et al., 2021). In the current study, we found a nominally statistically significant signal for association between *SORL1* variation and LATE-NC, but no association was found between the *SORL1* SNVs and ADNC. Note that despite our null result for the association between ADNC and *SORL1* variants in this dataset, this is not an "either/or" scenario; rather, *SORL1* variant(s) may drive a subtype of LATE-NC with comorbid ADNC. Consistent with that hypothesis, a post-hoc analysis indicated that the rs74685827 *SORL1* risk allele was associated with the ADNC+LATE-NC phenotype.

Another genetic locus associated with a non-ADNC pathology was the SNV rs199515 in the *WNT3* (Wnt Family Member 3) gene, which was associated with HS risk. HS is an important pathological phenotype indicating neuronal cell death in the hippocampus, often seen at autopsy in brains with comorbid LATE-NC (Amador-Ortiz et al., 2007), and also associated with substantial additional clinical impairment (Gauthreaux et al., 2022). There has been prior indications that genetic variation associated with LATE-NC and HS pathologies overlap incompletely (Dugan et al., 2021; Nelson et al., 2014; Nelson et al., 2015). The WNT3 protein serves as a ligand for members of the frizzled receptors family and functions in the canonical Wnt signaling pathway that results in activation of transcription factors relevant to neurodevelopment (Katoh, 2008; Min et al., 2022). Previously linked to FTLD and Parkinson's disease risk (Ferrari et al., 2017; Li et al., 2022; Liu et al., 2011), *WNT3* resides in an intriguing portion of human Chromosome 17, ~1 MB in the telomeric direction from the potentially pathogenetic *MAPT* locus, which is an additional ~1 MB distance telomeric from the *GRN* gene.

A third intriguing genetic association identified in the current study is the SNV rs871269 in the Chromosome 5 *TNIP1* (TNFAIP3 Interacting Protein 1) gene, which also was linked to altered risk for HS. Mutations in the *TNIP1* gene region were previously associated with altered risk for amyotrophic lateral sclerosis (ALS) (Benyamin et al., 2017; Restuadi et al., 2022). The ALS-linked SNV in *TNIP1* (rs10463311) is located ~20 kb away from the AD/dementia-associated SNV evaluated in the current study. One prior study concluded that the *TNIP1*-region genetic risk allele rs10463311 may exert its effect on ALS risk by modulating expression of the nearby *GPX3* (Glutathione Peroxidase 3) gene (Restuadi et al., 2022). Functionally, the TNIP1 protein is an inflammation modulatory protein that exerts its influence by regulating nuclear factor kappa-B activation (Shamilov and Aneskievich, 2018). The GPX3 protein, by contrast, is active in protecting cells from reactive oxygen species and has been connected functionally with superoxide dismutase (Chang et al., 2020).

There were a number of limitations in our study design. Potential confounding factors may bias ascertainment of neuropathologic endophenotypes and thereby distort our genetic association results. We ignored cognitive status in this study, and were only concerned with the correlations between SNV status and neurodegenerative pathologies. We also note that the present work is not a replication or validation study, because many of the cases included from ADGC and NACC data sets were also incorporated in the Bellenguez et al. (2022), albeit studying non-identical phenotypes and the numbers of overlap being <1% of the overall sample size of the latter study. We note however that the large majority of the Bellenguez sample were not neuropathologically characterized as far as we are aware.

There is no autopsy cohort with perfect (or even near-perfect) population representation or 100% autopsy rate. Moreover, sex, race, and socioeconomic factors are known to influence subject recruitment, and practices vary among neuropathologists (Haneuse et al., 2009). The analyses performed on non-Europeans was largely exploratory due to restricted sample sizes (<300 subjects combining cases and controls) and caution is required in over-interpreting such data (Ighodaro et al., 2017). However, the findings were suggestive: the SNV which with the strongest nominal association with dementia-related neuropathology was in the *ABCA7* gene, which previously was linked to AD dementia risk, particularly in African-Americans (Hohman et al., 2016; Liao et al., 2014; Logue et al., 2011; Reitz et al., 2013). We also highlighted intriguing possible novel associations such as the finding of a trend for association between *PLCG2* SNV variation and LATE-NC risk in non-Europeans.

In addition to recruitment biases, there are other potential confounders that pertain to this study. >30 different research centers contributed research subject data for this study. Neuropathologic practices (specific techniques, diagnostic cut-points applied, etc.) differ between research centers and add variation to the results (Besser et al., 2018). The nosology of LATE-NC is a somewhat contentious area (Josephs et al., 2019; Nelson et al., 2019b). "Border zones" between LATE-NC, FTLD, and ADNC are not universally agreed on; we are mindful of other perspectives and recognize that terminology and underlying scientific assumptions will probably continue to evolve.

From a statistical perspective, we applied multiple statistical tests with a sample size in the low thousands of European cases and controls. Thus, even with applying the sharpened endophenotype of the diagnostic "gold standard" (neuropathology), relatively few genotype/phenotype associations were robust enough to survive correction for multiple comparisons. Future studies may also be required to generate a better analytic framework for polygenic risk profiles for each pathological endophenotype. Nonetheless, there were multiple indications of a valid analytic workflow with suggestive results: (1) The strongest association signals were seen in the expected genetic loci that have been replicated consistently with the same specific neuropathologies in the past, e.g., *BIN1* and *EED/PICALM* SNVs were associated with ADNC risk, whereas *TMEM106B* and *GRN* SNVs were associated with risk for LATE-NC; (2) In the subset of SNVs that trended to association with nominal $P < 0.01$, the genetic variation was consistently associated with dementia-related pathologies in the same direction (same risk allele), but with larger effect sizes (odds ratios) in comparison to the prior large AD/

dementia (mostly clinical data) GWAS; and, (3) The pattern of "hit" SNVs related to ADNC, Lewy body pathology, and LATE-NC/HS conformed generally to the known distribution of attributable risk for AD-type dementia in community-based cohorts (Boyle et al., 2019).

In conclusion, some gene variants that were previously identified as contributing to clinical dementia risk appear to exert their influence via non-ADNC neuropathologies. Among the new findings of our study were novel associations between specific AD-linked genes and the LATE-NC/HS phenotype(s). Although further replication of these results is required, our findings were consistent with the hypothesis that non-ADNC neuropathologies can contribute substantially to amnestic dementia, and to its heritability.

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CRediT authorship contribution statement

Yuriko Katsumata: Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Resources, Writing – original draft, Writing – review & editing. **Lincoln M. Shade:** Data curation, Formal analysis, Writing – review & editing. **Timothy J. Hohman:** Data curation, Writing – review & editing. **Julie A. Schneider:** Data curation, Writing – review & editing. **David A. Bennett:** Data curation, Project administration, Writing – review & editing. **Jose M. Farfel:** Data curation, Writing – review & editing. **Walter A. Kukull:** Data curation, Project administration, Resources, Writing – review & editing. **David W. Fardo:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Resources, Writing – original draft, Writing – review & editing. **Peter T. Nelson:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Resources, Writing – original draft, Writing – review & editing.

Data availability

Data will be made available on request.

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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.

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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's disease Among African Americans Study (GenerAAtions) (2R01AG09029, R01AG025259, 2R01AG048927), Gwangju Alzheimer's 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),

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Appendix A. Supplementary data

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