Prioritization of drug targets for neurodegenerative diseases by integrating genetic and proteomic data from brain and blood

Running title: Identifying drug targets for neurodegenerative diseases

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Keywords: drug discovery; genetics; Mendelian randomization; neurodegenerative disease; omics; proteomics

Abstract

Background: Neurodegenerative diseases are among the most prevalent and devastating neurological disorders, with few effective prevention and treatment strategies. We aimed to integrate genetic and proteomic data to prioritize drug targets for neurodegenerative diseases.

Methods: We screened human proteomes through Mendelian randomization to identify causal mediators of Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), frontotemporal dementia, and Lewy body dementia. For instruments, we used brain and blood protein quantitative trait loci (pQTLs) identified from one GWAS with 376 individuals and another with 3,301, respectively. Causal associations were subsequently validated by sensitivity analyses and colocalization. The safety and druggability of identified targets were also evaluated.

Results: Our analyses showed targeting BIN1, GRN, and RET levels in blood, as well as ACE, ICA1L, MAP1S, SLC20A2, and TOM1L2 levels in brain might reduce AD risk, while ICA1L, SLC20A2, and TOM1L2 were not recommended as prioritized drugs due to the identified potential side-effects. Brain CD38, DGKQ, GPNMB, and SEC23IP were candidate targets for PD. Among them, GPNMB was the most promising target for PD with their causal relationship evidenced by studies on both brain and blood tissues. Interventions targeting FCRL3, LMAN2, MAPK3 in blood and DHRS11, FAM120B, SHMT1, TSFM in brain might affect MS risk. The risk of ALS might be reduced by medications targeting DHRS11, PSMB3, SARM1, and SCFD1 in brain.

Conclusions: Our study prioritized 22 proteins as targets for neurodegenerative diseases and provided preliminary evidence for drug development. Further studies are warranted to validate these targets.

Introduction

Neurodegenerative diseases, characterized by the progressive loss of vulnerable neurons and brain function decline, are a group of age-related disorders with highly heterogeneous pathophysiologies and clinical presentations (1). Since life expectancy has increased dramatically, neurodegenerative diseases have become more devastating and burdensome than ever before (2). Despite the compelling clinical need, effective therapeutic and prevention strategies for neurodegenerative diseases are rarely available in clinical practice. Besides, an incredibly high drug development failure rate was observed for neurodegenerative diseases (3). Fortunately, it has been shown that drug targets supported by human genetic evidence are more likely to succeed in clinical trials (4). Mendelian randomization (MR) is an analytic approach that uses genetic variants as instruments to infer causal relationships between exposures and outcomes. As genetic variants are randomly allocated at conception, the MR approach is less likely to be affected by confounding factors and reverse causality than observational studies, thus it has been considered a "natural" randomized controlled trial (RCT).

Human proteins play direct roles in biological processes and constitute the primary source of drug targets. Recent proteomic studies have identified an abundance of protein quantitative trait loci (pQTLs) in both blood and brain, enabling MR analysis at the proteomic level (5, 6). Proteomic data derived from brain and blood each have their own advantages. The human proteome in brain is more closely associated with the pathology of neurodegenerative disorders in the central nervous system, and the abundance of blood proteins is easier to be directly controlled by medications due to the blood-brain barrier. Hence, taking both brain and blood proteomic data into account would provide new insights into the drug development. In addition, it has been revealed that pQTLs located in the vicinity of the encoding genes, namely *cis*-pQTLs, are more likely to influence the protein level by directly influencing the transcription or translation. In contrast, *trans*-pQTLs might influence the protein level via indirect mechanisms (7). Thus, the use of *cis*-pQTLs for analysis would substantially minimize the pleiotropy caused by indirect pathways.

Here, we integrated genetic and proteomic data from the brain and blood to prioritize genetically-supported drug targets for neurodegenerative diseases. By combining state-of-the-art methods, we assessed the causal relationships between human proteomes and neurodegenerative diseases after taking

consistency, pleiotropy, confounding, aptamer-binding effect, linkage, and reverse causality into account (Figure S1). The potential on-target side-effects and druggability of the identified targets were also evaluated.

Methods and Materials

Study design

This study was based on publicly available summary data of QTLs and neurodegenerative diseases (Table S1). Data were collected from November 2020 to June 2021 and analyzed in 2021. A flow chart of the overall study design is presented in Figure 1. Firstly, we selected independent *cis*-pQTLs from comprehensive pQTL datasets as instruments and filtered the instruments via consistency and specificity tests. Secondly, we screened the human proteomes through MR to identify candidate causal mediators of neurodegenerative diseases. Thirdly, the identified causal relationships were further validated by multi-*cis* analysis, as well as the heterogeneity, pleiotropy, and directional tests. Fourthly, we investigated whether the protein and the disease share a common causal variant by Bayesian colocalization. Fifthly, replication and correlation analyses were conducted to estimate the consistency of results within and across brain and blood. Sixthly, we summarized the evidence of causality for all candidate drug targets and expanded our analysis pipeline to the phenome-wide to evaluate the safety by predicting the side-effects resulting from targeting the proteins. Finally, the druggability of the prioritized protein targets was checked according to two large databases.

Data Sources

The discovery brain pQTL data were generated from post-mortem samples of the dorsolateral prefrontal cortex (dPFC) donated by 376 individuals in ROS/MAP (8). The proteomic profiles included 8,356 proteins labeled by isobaric tandem mass tag peptide and analyzed by liquid chromatography coupled to mass spectrometry (LC-MS) (9, 10). The discovery blood pQTL data originated from the INTERVAL study, and the proteomic profiles were generated from 3,301 blood donors and included 3,622 plasma proteins measured by SOMAscan (5). We also obtained two brain and two blood pQTL datasets from independent cohorts for replication (11, 12), as well as an eQTL data for the analysis of aptamer-binding effects (13). Details of the replication datasets are presented in the Supplementary Methods.

The summary statistics of GWAS for Alzheimer's disease (AD, n_{cases} = 75,024, $n_{controls}$ = 397,844) (14), Parkinson's disease (PD, n_{cases} = 33,674, $n_{controls}$ = 449,056) (15), amyotrophic lateral sclerosis (ALS, n_{cases} = 27,205, $n_{controls}$ = 110,881) (16), multiple sclerosis (MS, n_{cases} = 14,802, $n_{controls}$ = 26,703) (17), frontotemporal dementia (FTD, n_{cases} = 2,154, $n_{controls}$ = 4,308) (18), and Lewy body dementia (LBD, n_{cases} = 2,981, $n_{controls}$ = 2,173) (19) were obtained from large consortia. All individuals of GWAS included in this study were of predominantly European descent. No sample overlap between QTL datasets and GWAS for neurodegenerative diseases was detected. Detailed descriptions of all GWAS used in this study can be found in Table S1.

Instrument selection and validation

We first mapped the genetic variants to genome build GRCh37/hg19 and selected *cis*-pQTLs from the brain and blood proteomes according to Ensembl v104 (http://grch37.ensembl.org). The *cis*-pQTLs were defined as genome-wide significant ($P < 5 \times 10^{-8}$) and LD-independent genetic variants fell within 500 kb upstream or downstream of the transcription start site of the gene encoding the protein. LD clumping was achieved based on $r^2<0.001$ using the 1000G European reference panel. All rare variants with minor allele frequency (MAF) less than 0.01 were excluded from further analysis. Variants located within the human major histocompatibility complex region (chr6:26-34MB) were removed before analysis.

Next, we performed the cross-study consistency and specificity tests to validate the identified instruments. We checked the LD of sentential *cis*-pQTLs and the direction of effect estimates to evaluate the instrument consistency across proteomic studies. For instrument specificity, the number of proteins associated with each instrument ($P < 5 \times 10^{-8}$) was counted. If an instrument and its proxies ($r^2 > 0.8$) were associated with more than five proteins, the instrument was considered highly pleiotropic and thus excluded from further analysis. The PhenoScanner was used to help identify other known genotype-protein associations in blood (9, 11, 20-23). We manually counted the number of brain proteins associated with each instrument (6, 9, 24). Specifically, if *cis*-pQTL data from more than one SOMAmer reagent of a certain protein were available, we chose the reagent with the highest instrument consistency and specificity. If different SOMAmers shared the same *cis*-pQTL, we would select the one with the lowest *P*-value for the following analysis. Instrument strength was measured by the F-statistic, while an F-statistic of at least 10 indicates the instrument is not weak (25).

Mendelian randomization

After validation of the genetic instruments, we extracted the effect estimates of the same variants or their proxies in GWAS of neurodegenerative diseases for data harmonization. The primary MR analysis was performed using the Wald ratio or inverse-variance weighted (IVW) method, depending on the number of independent *cis*-pQTLs for each protein. Bonferroni correction for the number of proteins was conducted to control multiple comparisons (Bonferroni threshold: 0.05/608 for brain and 0.05/613 for blood).

MR results with a single instrument of a protein might be distorted if the instrument was an outlier. To address this concern and boost statistical power, we next conducted the multi-*cis* MR analysis using *cis*-acting genome-wide significant instruments in weak LD ($r^2 < 0.6$) for the associations identified by primary analysis (clumping at $r^2 < 0.001$) (26). Multiple MR analytical approaches, including IVW, Egger, weighted median, and weighted mode were applied for validation, of which IVW was chosen as the primary approach according to the recommendation (27). The heterogeneity was quantified by the IVW Q statistic, and the pleiotropy was evaluated by the MR-Egger intercept. The causal direction was assessed by two analytical approaches, the Steiger filtering and the reverse MR. Reverse MR could only be performed with blood proteins due to data accessibility. In the validation, heterogeneity, pleiotropy, and directional analyses, uncorrected *P*-values less than 0.05 were considered significant. All MR analyses were undertaken with the "TwoSampleMR" package in R (28).

Sensitivity analysis considering the aptamer-binding effects

As the blood proteins were measured by SOMAmers and were susceptible to aptamer-binding effects, we looked up the function of blood pQTL variants and their proxies in HaploReg v4.1 (29). Sensitivity analysis was performed after excluding all missense variants and variants in high LD ($r^2 > 0.8$) with missense variants. Subsequently, we performed a transcriptional level MR using blood eQTL to validate the association. eQTL data measured by RNA sequencing are less likely to be confounded by aptamer-binding effects.

Replication and correlation analyses

To understand the consistency of MR estimates within brain and blood tissues, we performed replication MR analyses using replication datasets. Gene and protein names in different datasets were aligned by UniPort ID. We also conducted beta-beta correlation analyses of MR estimates within and across tissues using the Pearson test via "cor.test" function implemented in R. The correlation analyses were first undertaken in all proteins and then limited to proteins at the nominal significance level ($P < 0.05$).

Bayesian colocalization

Bayesian colocalization was performed to further strengthen the evidence of causality by calculating the posterior probability (PP) that the protein and disease share the same causal signal (H4). A posterior probability for H4 (PP.H4) of at least 50% suggests likely to colocalize, and a PP.H4 of at least 80% suggests highly likely to colocalize (7). Colocalization analysis was conducted within a 1-MB window on either side of the sentinel variant by the "coloc" package in R software.

Drug target prioritization

After systematically operating the above analytical pipeline, we prioritized the identified drug targets by their strength of causal evidence, considering the consistency, heterogeneity, pleiotropy, directionality, and colocalization. Notably, targets with conflicting evidence in multi-*cis* or replication analysis, evidence of aptamer-binding effects, or not likely to colocalize were rated as having a low level of causality and were not considered credible targets.

Assessment of safety and druggability

Finally, we expanded our analytical pipeline to the phenome-wide to assess the safety of targets by predicting on-target side-effects. Potential side-effects were extracted from the MRC IEU OpenGWAS Project (28, 30) with European or predominantly European ethnicity. If the same phenotype was available in more than one GWAS, we chose the one with the largest sample size to reduce the multiple testing burden. Similar but not identical phenotypes were retained because the consistent results from similar phenotypes would gain more confidence in the existence of side-effects. The overall level of safety was approximated by the sum PP.H4 of all adverse effects passed the Bonferroni correction. The druggability of each prioritized target was checked according to Finan's criteria (31) and the DrugBank database (32).

Results

Characterizing genetic instruments of protein abundance in brain and blood

After applying the prescribed quality control criteria, 616 brain *cis*-pQTLs for 608 proteins and 840 blood *cis*-pQTLs for 611 proteins were available for MR analysis (Tables S2-3). The instruments across brain pQTL studies showed remarkable consistency, as 92.0% and 71.8% of sentinel *cis*-pQTLs in ROS/MAP were in high LD ($r^2 > 0.8$) with that in the two replication datasets (Table S4). For the blood proteome, the sentinel *cis*-pQTLs of 60.1% and 58.8% proteins in INTERVAL were in high LD ($r^2 > 0.8$) with that in two replication cohorts (Table S5). The F-statistic of all instruments ranged from 30 to 1704 (Table S3 and Table S5).

Mendelian randomization and colocalization in the brain proteome

After Bonferroni correction for multiple testing, our primary MR analysis identified 18 proteins whose abundance in brain was associated with risks of neurogenerative diseases (Figure 2A, Figure 3A, and Table S6). Genetically determined higher levels of brain EPHX2 (OR = 1.42, $P = 2.72\times10^{-13}$), TOM1L2 (OR = 3.85, $P = 2.72\times10^{-5}$), and MAP1S (OR = 2.36, $P = 3.17\times10^{-5}$) were associated with greater risks of AD, while the genetically determined higher levels of ICA1L (OR = 0.38, $P = 1.57\times10^{-5}$), SLC20A2 (OR = 0.45, $P = 4.17\times10^{-5}$) and ACE (OR = 0.55, $P = 5.76\times10^{-5}$) were associated with lower risks of AD. The abundance of brain SCFD1 (OR = 5.42, $P = 1.02\times10^{-14}$) and PSMB3 (OR = 2.24, $P = 5.76\times10^{-5}$) might increase and SARM1 (OR = 0.31, $P = 8.27\times10^{-9}$) and DHRS11 (OR = 0.58, $P = 2.16\times10^{-5}$) might decrease ALS risk. In addition, five proteins in brain would elevate the risk of MS, including TSFM (OR = 4.87, $P = 1.38\times10^{-10}$), GALC (OR = 1.65, $P = 1.01\times10^{-7}$), SHMT1 (OR = 1.94, $P = 1.20\times10^{-5}$), DHRS11 (OR = 2.22, $P = 3.02\times10^{-5}$), and FAM120B (OR = 4.40, $P = 5.10\times10^{-5}$). Genetically predicted high levels of GPNMB (OR = 1.46, $P = 2.48\times10^{-8}$) and SEC23IP (OR = 7.88, $P = 2.45\times10^{-5}$) were associated with an increased PD risk, while high levels of CD38 (OR = 0.32, $P = 6.99\times10^{-14}$) and DGKQ (OR = 0.14, $P = 1.97\times10^{-9}$) were associated with a decreased PD risk. All protein-disease associations showed the correct causal direction in the Steiger filtering analysis (Table S7). Meanwhile, we found that the results in multi-*cis* MR were in accordance with the primary analysis and consistent among multiple MR approaches (Table S8). No pleiotropy was observed, while heterogeneity was detected in three protein-disease pairs (EPHX2-AD, DHRS11-ALS, and GALC-MS). Bayesian colocalization analysis

showed that all protein-disease associations except EPHX2-AD and GALC-MS were likely to be driven by the same causal SNP (Table S9).

Mendelian randomization and colocalization in the blood proteome

After screening the human blood proteome through primary MR analysis, 16 proteins for five diseases passed the Bonferroni correction (Figure 2B, Figure 3B, and Table S10). No reverse causation was observed in either the Steiger filtering or reverse MR analysis (Tables S11-12). Seven proteins for AD were identified in the primary MR, but only four of them showed evidence of colocalization (BIN1, OR = 1.87, $P = 1.46\times10^{-23}$, PP.H4 = 69.6%; GRN, OR = 0.83, $P = 2.99\times10^{-6}$, PP.H4 = 99.5%; CD33, OR = 1.06, $P = 3.69\times10^{-5}$, PP.H4 = 99.8%; RET, OR = 1.18, $P = 7.87\times10^{-5}$, PP.H4 = 74.7%). Notably, we observed high heterogeneity ($P = 1.64\times10^{-5}$) and pleiotropy ($P = 5.54\times10^{-4}$) regarding circulating CD33 levels for AD risk (Table S13). For all FTD subtypes, only the protein WISP1 survived the Bonferroni correction but did not pass the Bayesian colocalization (Table S14). Circulating α-synuclein (encoded by *SNCA*) was highly associated with LBD and PD risks in MR analyses. However, the colocalization results (PP.H4 = 17.2% and 0.0%) suggested the identified association might be a product of LD but not causality (Table S14). Other drug targets both passed MR and colocalization analysis including GPNMB (OR = 1.51, $P = 1.80\times10^{-7}$, PP.H4 = 55.6%) and FCGR2A (OR = 1.06, $P = 4.72\times10^{-5}$, PP.H4 = 92.4%) for PD, and FCRL3 (OR = 0.83, $P = 8.93\times10^{-9}$, PP.H4 = 94.1%), MAPK3 (OR = 0.56, $P = 4.94\times10^{-6}$, PP.H4 = 71.4%), AHSG (OR = 0.88, $P = 2.37\times10^{-5}$, PP.H4 = 96.4%), and LMAN2 (OR = 1.56, $P = 7.19\times10^{-5}$, PP.H4 = 83.4%) for MS.

As the blood pQTL studies measured proteins by aptamer-based approaches, we next investigated whether the MR results were confounded by aptamer-binding effects (Table S15). The instruments for CKM, FCRL3, BAG3, and parts of instruments for CD33 and FCGR2A were known missense variants or in high LD with missense variants, which were susceptible to aptamer-binding effects. We did a sensitivity analysis after excluding missense variants in CD33 and FCGR2A, and both analyses yielded non-significant results. As not all proteins had enough instruments for sensitivity analysis, transcriptional level MR of blood mRNA abundance was conducted for further validation. We found the increased abundance of blood FCRL3 mRNA level could also decrease the MS risk (OR = 0.75, $P = 1.03\times10^{-8}$, PP.H4 = 97.9%,

Table S15). As the transcriptional level results aligned with the protein level, we considered the association between FCRL3 protein abundance and MS risk less likely to be confounded by aptamer-binding effects.

Consistency of results within and across brain and blood

All replication analyses of brain proteins using external replication datasets showed consistent results with the primary analysis. For drug targets identified through MR with blood proteins, AHSG for MS was not replicated, and RET for AD was only partially replicated (Table S16). Additionally, GPNMB for PD was replicated in a second brain region, the parietal lobe cortex (OR = 1.51, $P = 1.80\times10^{-7}$, PP.H4 = 95.0%). Other replication analyses for different brain regions were not conducted due to the lack of eligible instrumental variables.

The correlation analysis showed robust within-tissue consistency. For MR estimates of all brain proteins, the correlation coefficients were 0.84 (P<0.001) and 0.95 (P<0.001) between the discovery dataset and two replication datasets (Figure S2). For MR estimates of all blood proteins, the correlation coefficients were 0.75 (P<0.001) and 0.72 (P<0.001). We also observed greater consistency of MR estimates across studies in proteins whose instruments were in higher LD (Figures S2-4). However, only a weak correction of MR estimates between brain and blood proteins was detected ($r^2 = 0.16$, $P = 0.002$), although the coefficient increased ($r^2 = 0.50$, $P = 0.002$) when the analysis was limited to proteins with at least nominal significance in MR analysis (Figure S4).

Drug target prioritization and phenome-wide Mendelian randomization (phe-MR)

Finally, we prioritized 16 brain-based and seven blood-based proteins as drug targets for neurodegenerative disorders, given the evidence of medium to high levels of causality. Remarkably, high GPNMB abundance in both brain and blood increased the risk of PD (Table 1). We selected 826 phenotypes as potential side-effects from the MRC IEU OpenGWAS Project (28, 30) and performed phenome-wide MR in combination with colocalization analysis among the prioritized drug targets (Table S17). Encouragingly, targeting brain PSMB3, SARM1, DGKQ, and circulating BIN1, RET, MAPK3, and GPNMB protein levels to reduce disease risk did not exhibit any significant adverse side-effect, indicating the general safety of the hypothetical on-target interventions (Table S18). Besides, we found that 12 of 22 prioritized proteins are druggable, and their related approved drugs or candidates in clinical development

are listed in Table S19 (31). The overall causality, safety, and druggability of each prioritized target are illustrated in Figure 4.

Discussion

In this study, we prioritized 22 proteins that had possible causal relationships with neurodegenerative diseases and showed little bias due to confounding, pleiotropy, linkage, or reverse causation. We assessed the target-disease linkage, as well as the safety and druggability of targets, which were key aspects highlighted in the GOT-IT recommendations for drug development (33). Given the enormous cost of measuring thousands of proteins before disease onset in studies with large samples, findings from our integrative analysis would substantially promote the cost-optimization and efficiency in drug development for neurodegenerative disorders.

Our analysis prioritizes five proteins (ACE, ICA1L, MAP1S, SLC20A2, and TOM1L2) in brain and three proteins (BIN1, GRN, and RET) in blood for AD. *ACE* is an established genetic locus contributing to AD risk (14, 34). Our study further indicated that interventions to increase the abundance of protein ACE in brain might decrease the AD risk yet elevate the blood pressure. This finding was supported by a recent network meta-analysis that the ACE inhibitors showed significantly lower efficacy in reducing the risk of dementia than other classes of antihypertensive drugs (35). ICA1L, SLC20A2, and TOM1L2 were not recommended as prioritized drugs due to their potential side-effects indicated by the phe-MR analysis. The effect of brain TOM1L2 on cognition might be dynamic, which needs to be validated in future studies with patients in different stages across the AD continuum. Progranulin (encoded by *GRN*) is a promising target for AD. Previous mouse models had demonstrated the reduced amyloid plaque burden, downregulated beta-secretase 1, and enhanced amyloid phagocytosis of microglia after the intrahippocampal injection of progranulin (36). However, psychiatric side-effects should be considered when targeting circulating progranulin to prevent or treat AD. Medications targeting circulating BIN1 and RET levels to reduce AD risk may be generally safe, while the underlying mechanisms need to be further elucidated in the future.

GPNMB is an attractive drug target for PD, given that the increased protein levels in both blood and brain were associated with the higher lifetime PD risk in our analysis. Targeting GPNMB would be technically feasible due to its druggability, and the medications would be generally safe according to the phe-MR analysis. A recent paper showed that plasma GPNMB levels were elevated in PD patients and

associated with the disease severity (37). In a post-mortem study, GPNMB protein levels were elevated in the substantia nigra in PD patients compared to healthy controls (38). Cell models also indicated that GPNMB might confer PD risk through the interaction with a-synuclein (37). The mechanisms and clinical utility of other protein targets (CD38, DGKQ, and SEC23IP) for PD warrant further exploration by experimental studies.

We also prioritized seven targets (DHRS11, FAM120B, FCRL3, LMAN2, MAPK3, SHMT1, and TSFM) for MS and four targets (DHRS11, PSMB3, SARM1, and SCFD1) for ALS. The safety of these targets is generally acceptable, though there is still a lack of investigations at the protein level by observational and experimental studies. An observational study at the transcriptional level reveled downregulated *FCRL3* expression in blood samples of MS patients compared to healthy controls, consistent with our findings (39). It was suggested that *FCRL3* might inhibit the secretion of inflammatory factors by promoting IL-10 expression in B cells (39). Surprisingly, protein DHRS11 was identified as a drug target for both ALS and MS. As DHRS11 is involved in steroid biosynthesis and most MS cases are steroid responsive (40, 41), our findings could provide novel insights into the therapeutic strategy for ALS.

Compared with previous integrative studies (9, 42, 43), our study highlights the comparison of results between different tissues at the protein level. The consistent results derived from brain and blood data would support the effectiveness of targeting peripheral proteins to prevent or treat brain disorders through non-invasive or minimally invasive approaches. Nonetheless, only one protein–disease linkage (GPNMB-PD) was identified in both tissues in the current study, largely because of the lack of proteins with eligible genetic instruments in both brain and blood. This issue could be addressed with the increased sample size of proteomic studies in the future. Meanwhile, we only observed a significant but weak correlation of MR estimates between brain and blood, indicating that findings from one tissue should not be directly generalized to other tissues. The weak correlation could be explained by the existence of the blood-brain barrier as well as the different protein expression patterns between the brain and blood. Other advantages of this study include the standardized workflow for screening candidate causal targets, as well as the assessment of safety and druggability, which would help promote the development of efficient drugs.

Several limitations should be addressed in this study. First, although MR has competitive advantages over traditional observational studies and trials, the results could only provide evidence for but not prove

causation. Second, since GWAS used in this study were based on lifetime risks of neurodegenerative diseases at the group level, the translation to risk prediction, prevention, and prognosis monitoring at the individual level still needs more investigation. Third, our analytical pipeline was not able to identify every protein implicated in neurodegenerative disorders. As we had set stringent quality control criteria to improve the reliability of identified targets, proteins without eligible instruments were not included in the final analysis. Fourth, MR results derived from a single instrumental variable should be taken with caution, especially for those whose sensitivity and replication analyses were not able to perform. Fifth, our analyses were based on European samples, so the generalization to non-European ancestries needs to be validated in the future.

In conclusion, this study prioritized 22 proteins whose abundance in brain or blood was associated with lifetime risks of neurodegenerative diseases. Some proteins, such as GPNMB, not only demonstrated a causal linkage to neurodegenerative diseases but also showed robust on-target safety and technical feasibility, representing promising targets for current drug discovery. Future experimental studies are warranted to assess the effectiveness and safety of the identified targets and decipher their underlying biological mechanisms.

Acknowledgments and Disclosures

GWAS summary statistics of QTLs and neurodegenerative diseases are available from the peer-reviewed articles or the corresponding authors upon request. Other phenotypes of potential side-effects are available from MRC IEU OpenGWAS Project (https://gwas.mrcieu.ac.uk/) and the MR-Base (https://www.mrbase.org/) platform. The PhenoScanner database is available online (http://www.phenoscanner.medschl.cam.ac.uk/). All data generated from this study are available in the supplementary information or from the corresponding author on reasonable request.

The authors are grateful for all study participants and their families, without whom this research would not have been possible. We thank all original authors of the included studies for their wonderful work. We thank the ROS/MAP study, the BANNER study, the Washington University cohort, the INTERVAL study, the AGES Reykjavik study, the KORA study, the GTEx project, Schwartzentruber and colleagues, Chia and colleagues, the Project MinE, the International FTD-Genetics Consortium, the International Multiple Sclerosis Genetics Consortium, and the International Parkinson's Disease Genomics Consortium for sharing summary data. We thank De-Qiang Li for his valuable contribution to data processing. Additional acknowledgments can be found in the Supplemental Information.

This study was supported by grants from the Science and Technology Innovation 2030 Major Projects (2022ZD0211600), National Natural Science Foundation of China (82071201, 81971032), Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01), Research Start-up Fund of Huashan Hospital (2022QD002), Excellence 2025 Talent Cultivation Program at Fudan University (3030277001), and ZHANGJIANG LAB, Tianqiao and Chrissy Chen Institute, and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University.

The authors report no biomedical financial interests or potential conflicts of interest.

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Figure legends

Figure 1. Flow diagram of the study design.

First, selected independent *cis*-pQTLs from comprehensive pQTL datasets as genetic instruments and filtered the instruments via consistency and specificity tests. Next, we screened the human brain and blood proteomes through MR to identify candidate drug targets. Third, by applying multiple MR approaches, the causal relationships between the identified targets and diseases were further validated. Fourth, we investigated whether the protein and the disease share a common causal variant via Bayesian colocalization. Fifth, replication and correlation analyses were conducted to estimate the consistency of results within and across brain and blood. Sixth, we summarized the evidence of causality and expanded our analysis pipeline to the phenome-wide to evaluate the safety of targets by predicting side-effects. Finally, the druggability of the prioritized protein targets was checked.

Figure 2. Manhattan plots for the primary MR analysis of the brain and blood proteomes.

By screening the human brain and blood proteomes, 19 protein-disease associations in brain (**A**) and 17 protein-disease associations in blood (**B**) were identified. Each point represents a single MR test ordered by chromosomal position of the sentinel *cis*-pQTL on the *X* axis and $-\log_{10} P$ value on the *Y* axis. The red dotted lines represent the Bonferroni multiple testing thresholds (0.05/608 for brain and 0.05/611 for blood). Proteins that survived the Bonferroni threshold are colored by their associated diseases.

Figure 3. Heatmap for the causal relationship assessment of the identified drug targets.

The causal relationships of identified drug targets from brain (**A**) and blood (**B**) with neurodegenerative diseases were further validated by the replication and multi-*cis* analyses, the heterogeneity, pleiotropy, and directional tests, as well as sensitivity analysis regarding aptamer-binding effects. The depths of blue and orange represent the size of *P* values in MR analyses, and the depth of green denotes the posterior probability of colocalization. Targets with consistent evidence in all analyses were rated as a high level of causality, while targets with conflict evidence in either replication or multi-*cis* analysis, evidence of

aptamer-binding effects, or not likely to colocalize were rated as a low level of causality and thus were not considered as credible targets.

Figure 4. Overall assessment of drug targets for neurodegenerative diseases.

This figure illustrates three critical assessment aspects of drug targets: causality (*X*-axis), safety (*Y*-axis), and druggability (in bold). Incredible targets are not depicted in this figure. The evidence of causality was rated according to six analyses and each contributes one point: 1) consistent in multi-*cis* MR 2) no evidence of heterogeneity 3) no evidence of pleiotropy 4) true causal direction 5) replicated in other datasets, and 6) highly likely to colocalize. The evidence of safety was approximated by the sum PP.H4 of all adverse effects passed the Bonferroni correction. A target was rated druggable if identified in any druggable tier according to Finan's criteria or had any related drug in the DrugBank database. Diamonds refer to brain-based proteins and discs represent blood-based proteins. Proteins are colored according to their associated diseases. Notably, the genetic association between protein GPNMB and PD risk was identified in both brain and blood tissues.

Table 1. Prioritized drug targets for neurodegenerative diseases.

Disease	Protein	OR (95% CI)	P value	PP.H4	Druggability[a]	On-target adverse side-effects identified by phe-MR analysis[b]
Brain proteome						
AD	ACE	0.55 (0.41-0.74)	5.76E-05	96.7%	Tier 1 (A/V/I/E)	SBP↑, DBP↑
	ICA1L	0.38 (0.24-0.59)	1.57E-05	98.1%	NA	CAD↑, MI↑, DBP↓
	MAP1S	2.36 (1.58-3.55)	3.17E-05	95.7%	NA	CAD↑, MI↑, lean mass↓
	SLC20A2	0.45 (0.31-0.66)	4.17E-05	93.2%	NA (A)	Hemoglobin↓, lean mass↓
	TOM1L2	3.85 (2.09-7.11)	1.53E-05	88.8%	NA	CP↓, WP↓, MI↑, prostate cancer↑
ALS	DHRS11	0.58 (0.45-0.74)	2.16E-05	56.6%	NA (E)	MS↑
	PSMB3	2.24 (1.51-3.33)	5.76E-05	97.0%	Tier 3 (E)	None
	SARM1	0.31 (0.20-0.48)	8.27E-08	100.0%	NA	None
	SCFD1	5.42 (3.53-8.32)	1.02E-14	98.3%	NA	Lung function↓
MS	DHRS11	2.22 (1.52-3.22)	3.02E-05	71.5%	NA (E)	ALS↑
	FAM120B	4.40 (2.15-9.03)	5.10E-05	95.8%	NA	SBP↓, DBP↓
	SHMT1	1.94 (1.44-2.61)	1.20E-05	98.0%	NA (A/V/N/I/E)	Triglycerides↑, HDL cholesterol↓
	TSFM	4.87 (3.00-7.89)	1.38E-10	96.0%	NA	25(OH)D↓, hemoglobin↓
PD	CD38	0.32 (0.24-0.42)	6.99E-14	100.0%	Tier 1 (A/I)	Lung function↓
	DGKQ	0.14 (0.07-0.26)	1.97E-09	87.9%	NA (A/V/N)	None
	GPNMB	1.46 (1.28-1.67)	2.48E-08	98.4%	Tier 1 (I)	Grip strength↓
	SEC23IP	7.88 (3.02-20.56)	2.45E-05	98.5%	NA	SBP↑
Blood proteome						
AD	BIN1	1.87 (1.66-2.12)	1.46E-23	69.6%	NA	None
	GRN	0.83 (0.77-0.90)	2.99E-06	99.5%	Tier 3	Worry↑, mood swings↑,
	RET	1.18 (1.09-1.28)	7.87E-05	74.7%	Tier 1 (A/I/E)	None
MS	FCRL3	0.83 (0.79-0.89)	8.93E-09	94.1%	Tier 3	Hypothyroidism↑
	LMAN2	1.56 (1.25-1.95)	7.19E-05	83.4%	NA	Sleep duration↓, red blood cell↓
	MAPK3	0.56 (0.44-0.72)	4.94E-06	71.4%	Tier 1 (A/I/E)	None
PD	GPNMB	1.51 (1.30-1.77)	1.80E-07	55.6%	Tier 1 (I)	None

[a]The druggability was checked according to Finan's criteria (druggable tiers) and the DrugBank database (drug relations). Briefly, tier 1 included targets with approved drugs or drugs in clinical trials. Tier 2 contained targets with drug-like binding partners or those in high identity with approved drug targets. Tier 3 was composed of targets encoding extracellular proteins and members of major drug target families. Approved drugs (A) are officially accepted for commercialization, while vet-approved drugs (V) are only accepted to be used in animals. Nutraceuticals (N) have demonstrable nutritional effects and are regulated and processed at a pharmaceutical grade. Investigational drugs (I) have entered clinical trials and are being researched for a determinate condition. Experimental drugs (E) are experimentally proven but have not reached clinical trials. [b]On-target adverse side-effects that survive the correction for multiple testing ($P<0.05/824$) with evidence of colocalization (PP.H4≥50%) are displayed here. Abbreviations: ALS, amyotrophic lateral sclerosis; CAD, coronary artery disease; CP, cognitive performance; DBP, diastolic blood pressure; HDL, high-density lipoprotein; MI, myocardial infarction; MS, multiple sclerosis; NA, not available; phe-MR, phenome-wide Mendelian randomization; PP.H4, posterior probability of colocalization; SBP, systolic blood pressure; WP, walking pace.

Figure 1

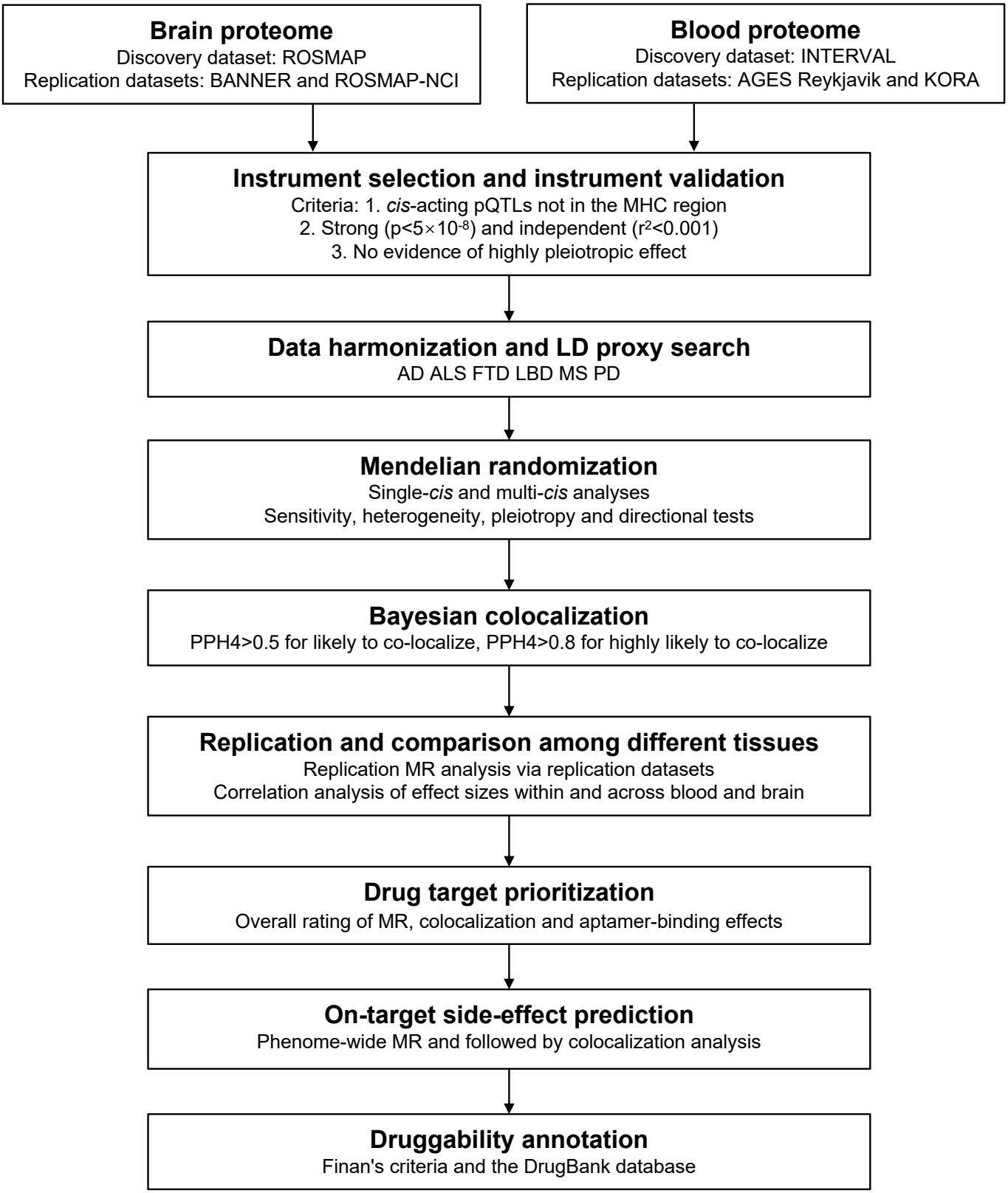

Brain proteome
Discovery dataset: ROSMAP
Replication datasets: BANNER and ROSMAP-NCI
Blood proteome
Discovery dataset: INTERVAL
Replication datasets: AGES Reykjavik and KORA
Instrument selection and instrument validation
Criteria: 1. cis-acting pQTLs not in the MHC region
2. Strong (p<5×10-8) and independent (r2<0.001)
3. No evidence of highly pleiotropic effect
Data harmonization and LD proxy search
AD ALS FTD LBD MS PD
Mendelian randomization
Single-cis and multi-cis analyses
Sensitivity, heterogeneity, pleiotropy and directional tests
Bayesian colocalization
PPH4>0.5 for likely to co-localize, PPH4>0.8 for highly likely to co-localize
Replication and comparison among different tissues
Replication MR analysis via replication datasets
Correlation analysis of effect sizes within and across blood and brain
Drug target prioritization
Overall rating of MR, colocalization and aptamer-binding effects
On-target side-effect prediction
Phenome-wide MR and followed by colocalization analysis
Druggability annotation
Finan's criteria and the DrugBank database

Figure 2

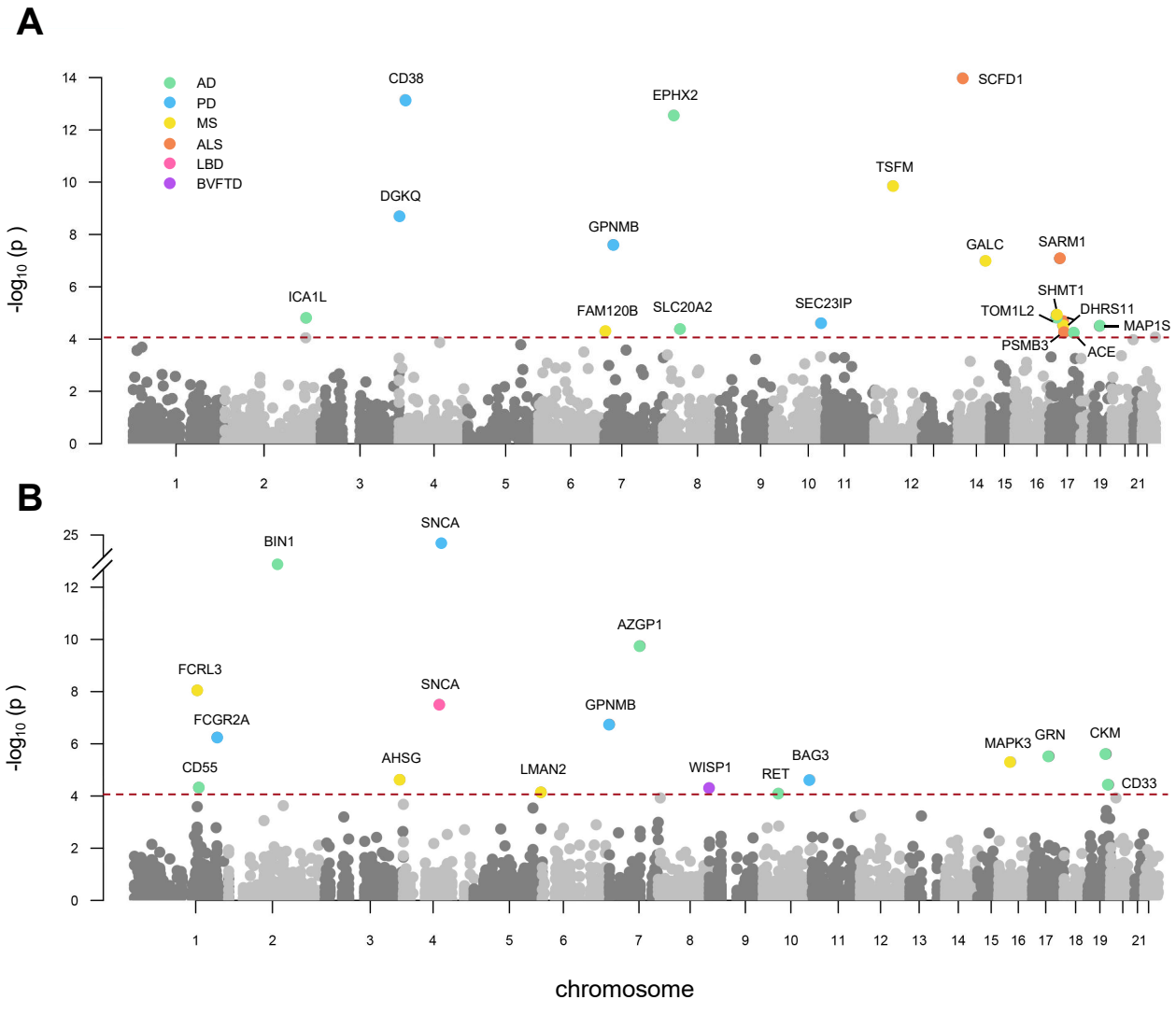

A
AD
PD
MS
ALS
LBD
BVFTD
CD38
EPHX2
SCFD1
TSFM
DGKQ
GPNMB
GALC
SARM1
ICA1L
FAM120B
SLC20A2
SEC23IP
SHMT1
TOM1L2
DHRS11
MAP1S
PSMB3
ACE
-log10 (p)
B
BIN1
SNCA
AZGP1
FCRL3
SNCA
GPNMB
FCGR2A
MAPK3
GRN
CKM
CD55
AHSG
LMAN2
WISP1
RET
BAG3
CD33
chromosome

Figure 3

A

Disease	Protein	Discovery	Replication	Multi-*cis*	Heterogeneity	Pleiotropy	Colocalization	Rating
AD	ACE	5.8E-05	1.5E-07	5.3E-11	3.9E-01		96.7%	Medium
	EPHX2	2.7E-13	2.7E-13	9.7E-05	8.3E-06	9.0E-01	0.0%	Low
	ICA1L	1.6E-05					98.1%	Medium
	MAP1S	3.2E-05	3.2E-05	3.5E-08	9.9E-01		95.7%	Medium
	SLC20A2	4.2E-05					93.2%	Medium
	TOM1L2	1.5E-05	3.2E-05	1.2E-08	9.0E-01		88.8%	Medium
ALS	DHRS11	2.2E-05	2.0E-02	3.5E-05	4.2E-02	8.8E-01	56.6%	Medium
	PSMB3	5.8E-05					97.0%	Medium
	SARM1	8.3E-08	2.5E-06	1.7E-10	5.2E-01		100.0%	Medium
	SCFD1	1.0E-14		2.6E-34	9.7E-01	9.7E-01	98.3%	Medium
MS	DHRS11	3.0E-05	3.1E-05	9.6E-09	2.2E-01	9.1E-01	71.5%	Medium
	FAM120B	5.1E-05		5.1E-05			95.8%	Medium
	GALC	1.0E-07	1.1E-07	3.5E-04	3.7E-05	5.6E-01	4.7%	Low
	SHMT1	1.2E-05	1.2E-05	3.1E-06	7.6E-02	8.3E-01	98.0%	High
	TSFM	1.4E-10	6.4E-11	2.9E-24	7.0E-01	5.8E-01	96.0%	High
PD	CD38	7.0E-14	3.5E-04	2.0E-21	4.5E-01		100.0%	Medium
	DGKQ	2.0E-09					87.9%	Medium
	GPNMB	2.5E-08	1.2E-08	5.9E-14	4.9E-01		98.4%	Medium
	SEC23IP	2.5E-05	1.8E-05				98.5%	Medium

B

AD	AZGP1	1.8E-10					0.1%	Low
	BIN1	1.5E-23		5.2E-38	3.4E-01		69.6%	Medium
	CD33	3.7E-05	4.9E-06	7.2E-14	1.6E-05	5.5E-04	99.8%	Low
	CD55	5.6E-07	2.6E-05	1.7E-17	4.5E-16	4.6E-01	0.0%	Low
	CKM	2.5E-06	2.0E-07				0.0%	Low
	GRN	3.0E-06		2.7E-12	8.5E-01	5.8E-01	99.5%	Medium
	RET	7.9E-05	9.8E-05	8.8E-08	7.3E-02	5.5E-01	74.7%	Medium
BVFTD	WISP1	4.8E-05	1.5E-02	2.7E-14	6.8E-01	1.1E-01	33.3%	Low
LBD	SNCA	3.1E-08	1.0E-07	3.1E-14	8.5E-01	9.9E-01	17.2%	Low
MS	AHSG	2.4E-05	3.6E-01	5.7E-07	6.9E-03	8.0E-01	96.4%	Low
	FCRL3	8.9E-09	5.2E-08	6.5E-32	1.4E-04	9.8E-01	94.1%	Medium
	LMAN2	7.2E-05		1.2E-09	5.2E-01		83.4%	Medium
	MAPK3	4.9E-06					71.4%	Medium
PD	BAG3	2.4E-05					1.1%	Low
	FCGR2A	4.7E-05	2.5E-04	2.1E-22	1.6E-02	8.2E-01	92.4%	Low
	GPNMB	1.8E-07	2.2E-07	1.3E-25	7.3E-01	4.9E-01	55.6%	Medium
	SNCA	6.3E-25	5.9E-29	9.7E-53	9.1E-01	8.0E-01	0.0%	Low

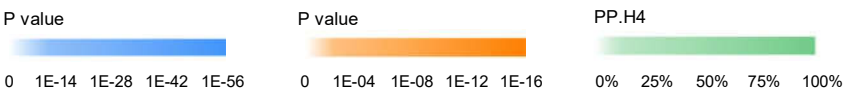
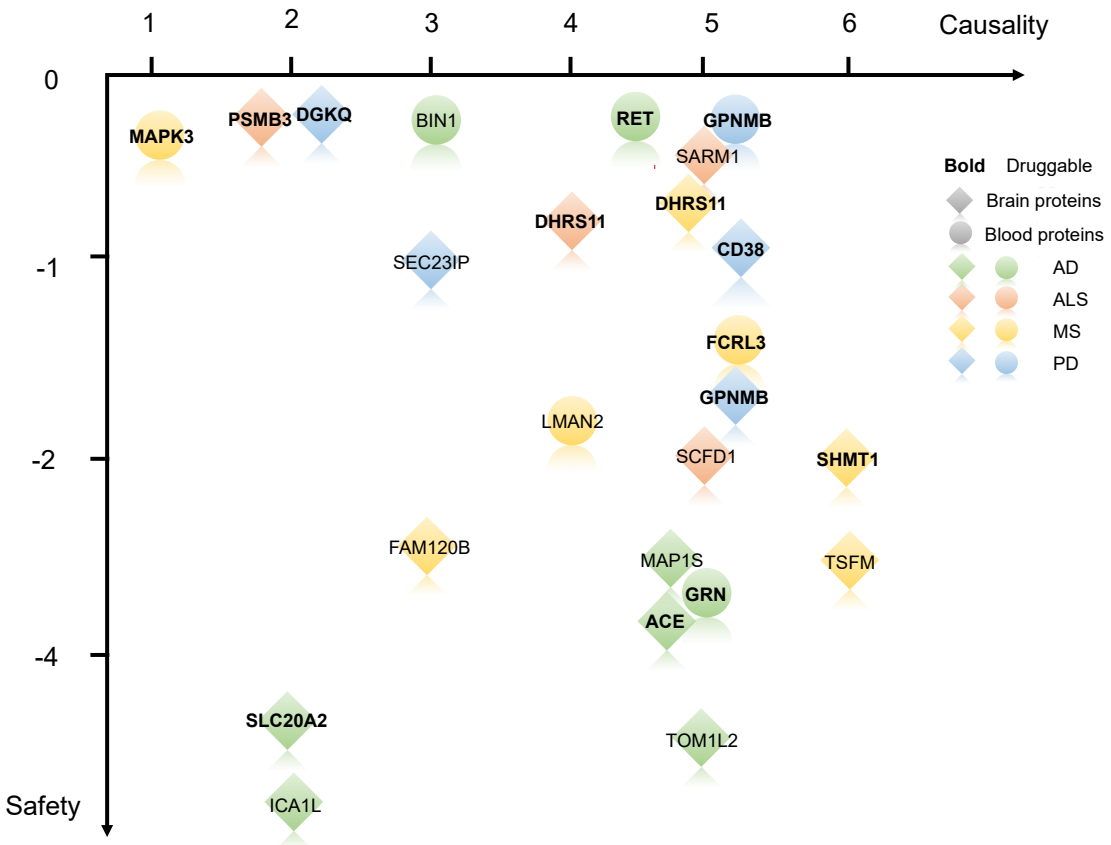


Figure 4


1
2
3
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5
6
Causality
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-1
-2
-4
Safety
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PSMB3
DGKQ
BIN1
RET
GPNMB
SARM1
DHRS11
DHRS11
CD38
SEC23IP
FCRL3
GPNMB
LMAN2
SCFD1
SHMT1
FAM120B
MAP1S
TSFM
GRN
ACE
SLC20A2
TOM1L2
ICA1L
Bold Druggable
Brain proteins
Blood proteins
AD
ALS
MS
PD

SUPPLEMENTARY INFORMATION

Prioritization of Drug Targets for Neurodegenerative Diseases by Integrating Genetic and Proteomic Data From Brain and Blood

Ge *et al.*

Content

Supplementary Methods

Human brain and blood-derived pQTL data

The discovery brain pQTL data were generated from post-mortem samples of the dorsolateral prefrontal cortex (dPFC) donated by 376 individuals in ROS/MAP (1). The proteomic profiles included 8,356 proteins labeled by isobaric tandem mass tag (TMT) peptide and analyzed by liquid chromatography coupled to mass spectrometry (LC-MS) (2, 3). As the full discovery dataset included cognitively impaired participants, we used the same dataset restricted to 144 cognitively normal individuals for replication (4). Another brain pQTL data derived from 149 donors from the Banner Sun Health Research Institute were used for cross-study replication (5). The proteomic data in the Banner study were profiled using similar approaches to ROS/MAP (4). Besides, the Washington University cohort has identified brain pQTLs in the parietal lobe cortex recently, and the pQTL data were used for the replication analysis of different brain regions in this study (6).

The discovery blood pQTL data originated from the INTERVAL study, which was nested in an RCT of varying blood donation intervals and comprised around 50,000 generally healthy participants (7). The proteomic profiles of the INTERVAL study were generated from 3,301 blood donors and included 3,622 plasma proteins measured by SOMAscan. We leveraged pQTL data from two independent SOMAmer–based blood proteomic datasets (AGES Reykjavik, n = 3,200 and KORA, n = 997) for cross-study replication (8, 9). The INTERVAL study was utilized for the primary analysis owing to its large sample size and availability of the complete summary data. Additionally, blood expression quantitative trait loci (eQTLs) from the Genotype-Tissue Expression (GTEx) project were used for target validation considering the aptamer-binding effects (10). Further details of all QTL studies are listed in Table S1.

Principal assumptions of MR

The MR approach builds upon principal assumptions (Figure S1). The three fundamental assumptions of MR analysis are: 1) the instruments must be truly associated with the exposure, 2) the instruments should not be associated with confounders, and 3) the instruments affect the outcome only through the exposure (11). To satisfy assumption 1, we selected instruments only strongly ($P < 5 \times 10\text{-}8$) associated with the protein abundance and later conducted a sensitivity analysis considering the aptamer-binding effect. For assumption 2, we checked the instrument specificity and excluded all variants (and their proxies) associated with more than five proteins

before performing MR analysis. Additionally, we only selected cis-acting pQTLs for analysis to reduce the horizontal pleiotropy (violation of assumption 3) and further tested the existence of horizontal pleiotropy by Egger intercept. Although the second and third assumptions could not be fully validated in MR practice, our endeavors would minimize the bias due to violations of the above assumptions.

Hypotheses of Bayesian colocalization

Bayesian colocalization was performed to strengthen the evidence of causality by calculating the posterior probability (PP) that the protein and disease share the same causal signal (H4). It is opposed to other hypotheses: 1) no causal signal (H0), 2) only one causal signal for either the protein or the disease (H1/H2), and 3) two distinct causal signals were identified in the region (H3). A posterior probability for H4 (PP.H4) of at least 50% (i.e., the highest among all five hypotheses) suggests likely to colocalize, and a PP.H4 of at least 80% suggests highly likely to colocalize (12).

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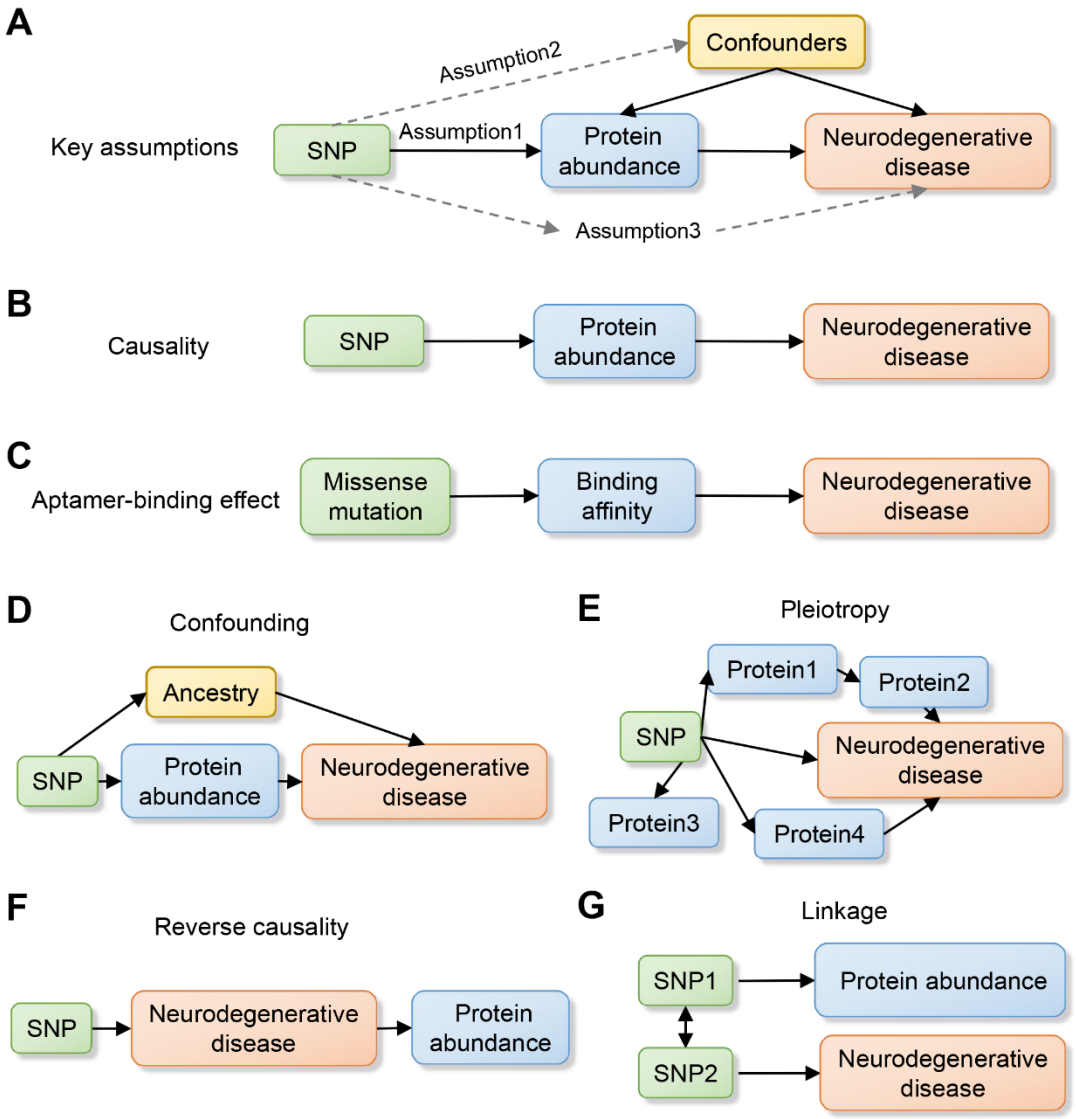
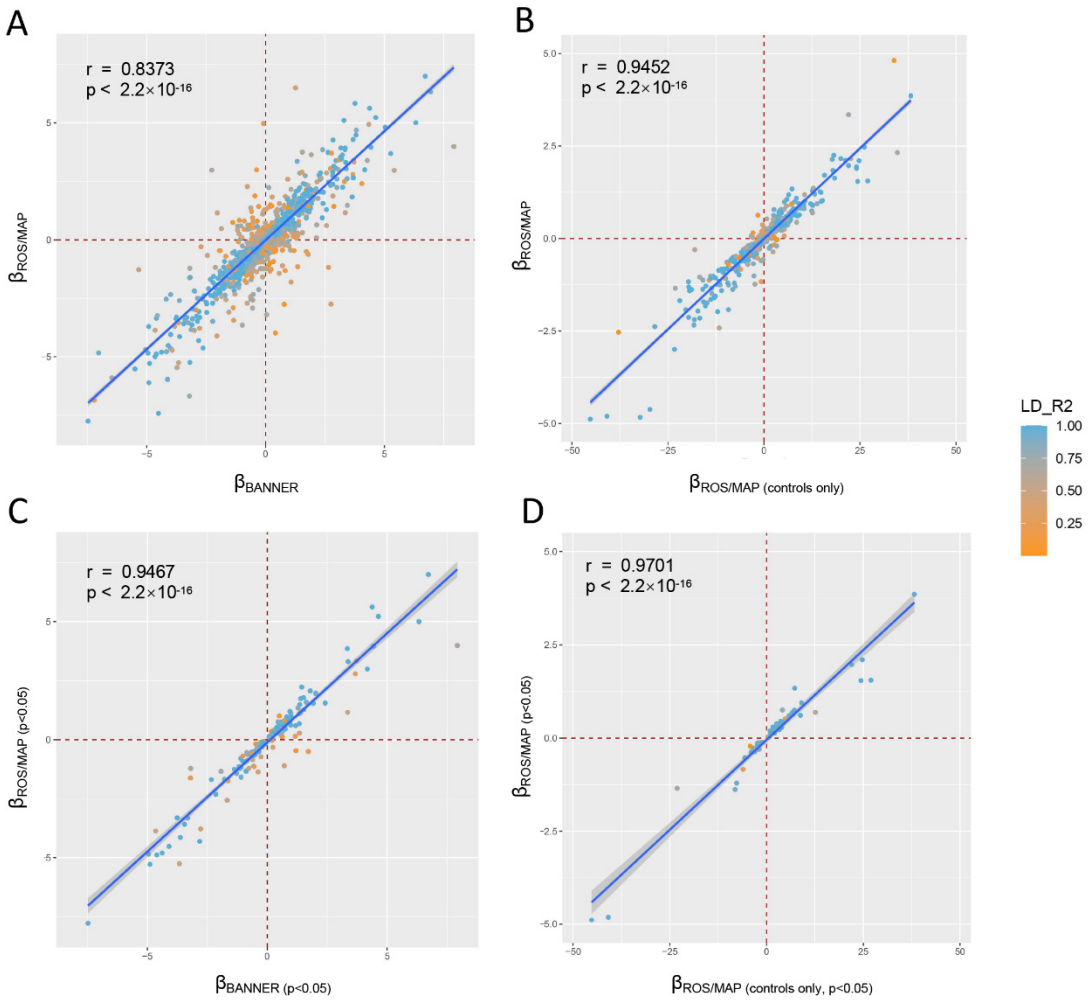
Figure S1. MR assumptions and possible explanations for the observed associations between pQTL and neurodegenerative diseases



The three basic assumptions of MR analysis are: 1) the instruments must be truly associated with the exposure, 2) the instruments should not be associated with confounders, and 3) the instruments affect the outcome only through the exposure **(A)**. If the risk of a neurodegenerative disease is affected by the abundance of a protein only through the instrument, it is known as causality **(B)**. Aptamer-binding effects indicate that the protein-altering variants (PAVs) in aptamer-based proteomic studies may yield artifactual pQTLs by influencing the molecular structure of the protein and then the binding affinity instead of the protein abundance. In this case, the causal association identified by MR analysis based on the PAVs might be attributed to different protein isoforms but not the protein abundance **(C)**. Violation of assumption 2 often occurs when there are confounders

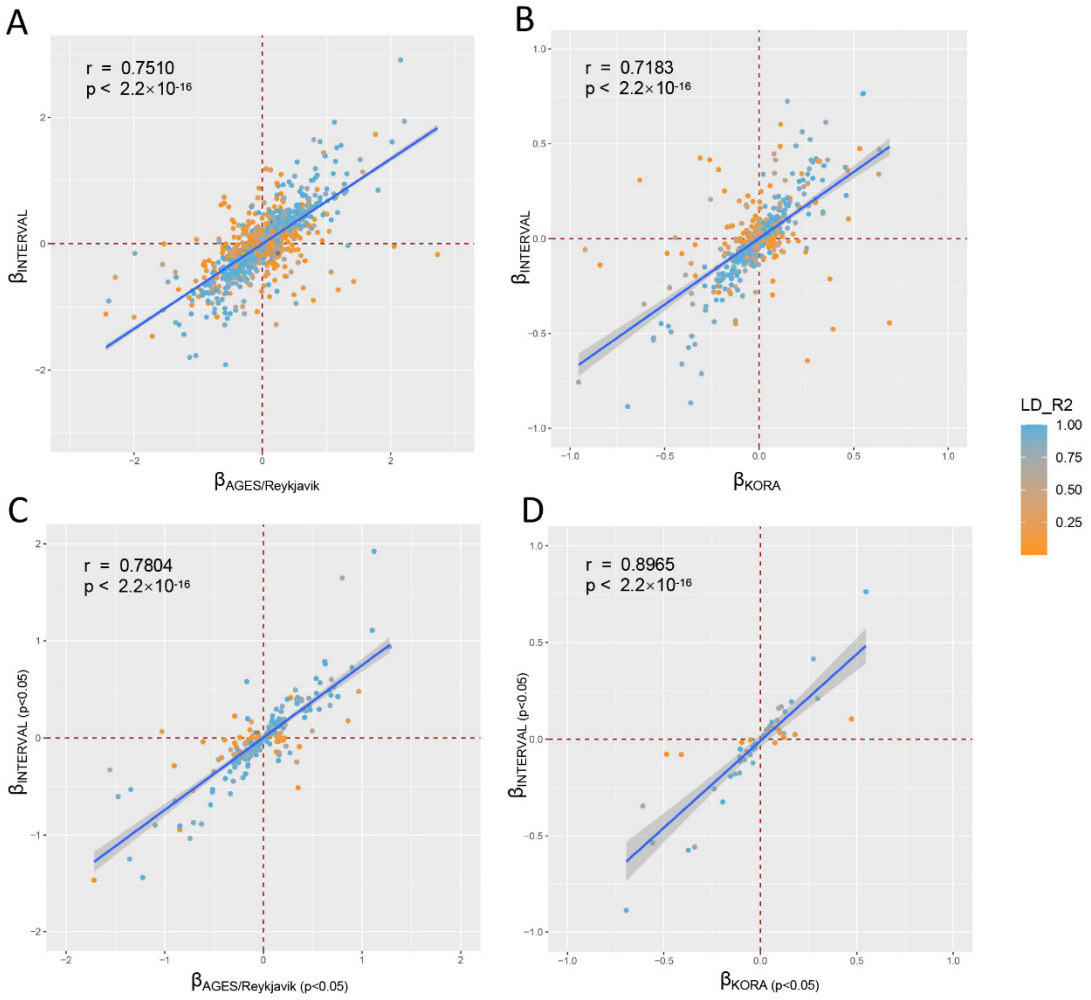
(e.g., ancestry) of the associations between instruments and outcome **(D)**. Instruments associated with large amounts of proteins are more likely to affect the disease risk through indirect pathways, which was a manifestation of horizontal pleiotropy **(E)**. Reverse causality may occur when the instrument has a stronger association with the outcome than the exposure **(F)**. In some cases, SNP associated with the protein is in linkage disequilibrium with another SNP that independently influences the neurodegenerative disease **(G)**.

Figure S2. Correlation analysis of MR estimates within brain proteomes



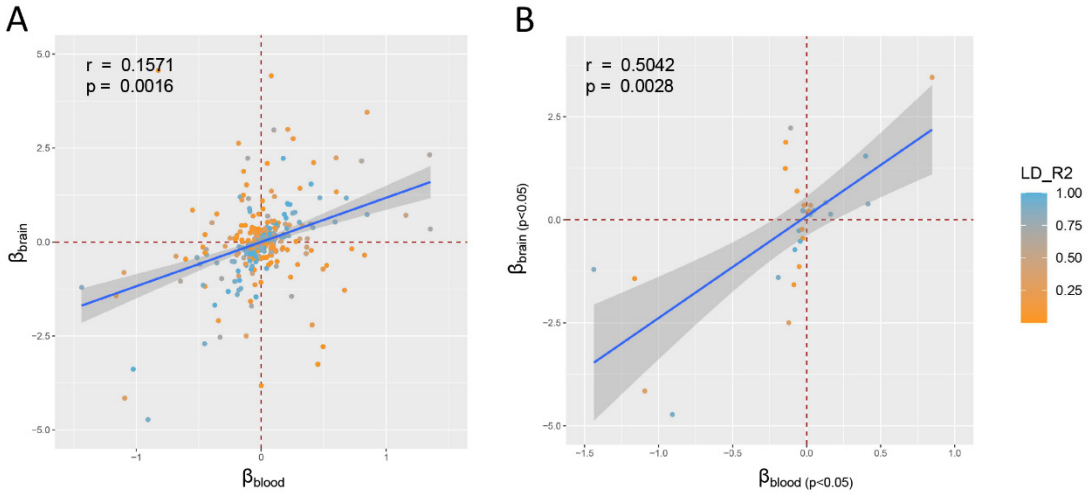
The correlation analyses of MR estimates indicated remarkable consistency within brain pQTL datasets. The correlation coefficient was 0.84 (P<0.001) between ROS/MAP and BANNER (**A**), and 0.95 (P<0.001) between the discovery dataset and same the dataset limited in the normal cognition (**B**). Restricting the analyses to proteins with at least nominal significance yielded similar correlation coefficients (**C** and **D**). Proteins with instruments in higher LD showed greater consistency of MR estimates across studies.

Figure S3. Correlation analysis of MR estimates within blood proteomes



Strong consistency was also identified in the correlation analyses of MR estimates within blood pQTL datasets. The correlation coefficient was 0.75 (P<0.001) and 0.72 (P<0.001) between INTERVAL and two replication datasets (**A** and **B**). Restricting the analyses to proteins with at least nominal significance would lead to stronger correlations (**C** and **D**). Proteins with instruments in higher LD showed greater consistency of MR estimates across studies.

Figure S4. Correlation analysis of MR estimates between brain and blood



Only a weak correction of MR estimates between brain and blood proteins was detected (correlation coefficient=0.16, *P*=0.002) (**A**), although the coefficient increased (correlation coefficient=0.50, *P*=0.002) when the correlation analysis was limited in proteins with at least nominal significance in MR analysis (**B**). Instruments of brain and blood proteins were generally in low LD.

Supplementary Acknowledgements

The Religious Orders Study and Memory and Aging Project (ROSMAP) Study

The results published here are in whole or in part based on data obtained from the AD Knowledge Portal (https://adknowledgeportal.org). Study data were provided through the Accelerating Medicine Partnership for AD (U01AG046161 and U01AG061357) based on samples provided by the Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago. Data collection was supported through funding by NIA grants P30AG10161, R01AG15819, R01AG17917, R01AG30146, R01AG36836, U01AG32984, U01AG46152, the Illinois Department of Public Health, and the Translational Genomics Research Institute.

The Banner Sun Health Research Institute (Banner) Study

The results published here are in whole or in part based on data obtained from the AD Knowledge Portal (https://adknowledgeportal.org/). These data were provided by Dr. Levey from Emory University. A portion of these data were generated from samples collected through the Sun Health Research Institute Brain and Body Donation Program of Sun City, Arizona. The Brain and Body Donation Program is supported by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinson¹s Disease and Related Disorders), the National Institute on Aging (P30 AG19610 Arizona Alzheimer¹s Disease Core Center), the Arizona Department of Health Services (contract 211002, Arizona Alzheimer¹s Research Center), the Arizona Biomedical Research Commission (contracts 4001, 0011, 05-901 and 1001 to the Arizona Parkinson's Disease Consortium) and the Michael J. Fox Foundation for Parkinson's Research.

The Washington University cohort

We thank the authors for sharing summary data. The summary statistics (pQTL) data are available by emailing niagads@pennmedicine.upenn.edu. Individual-level data are accessible through formal data request. Both summary statistics and individual-level data have been uploaded to the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site repository at https://www.niagads.org/datasets/ng00102 for multiple tissues from the Knight ADRC dataset for discovery. This work was supported by grants from the National Institutes of Health (NIH) (R01AG044546 (C.C.), P01AG003991 (C.C. and J.C.M.), RF1AG053303 (C.C.), RF1AG058501

(C.C.), U01AG058922 (C.C.), R01NS118146 (B.A.B.) and R01AG057777 (O.H.)) and the Alzheimer Association (NIRG-11-200110 (C.C.), BAND14-338165 (C.C.), AARG-16-441560 (C.C.) and BFG-15-362540 (C.C.)). This work was supported by access to equipment made possible by the Hope Center for Neurological Disorders and the Departments of Neurology and Psychiatry at Washington University School of Medicine. The recruitment and clinical characterization of research participants at Washington University were supported by NIH P50AG05681 (J.C.M.), P01AG03991 (J.C.M.) and P01AG026276 (J.C.M.).

The INTERVAL study

Participant-level genotype and protein data, and full summary association results from the genetic analysis, are available through the European Genotype Archive (accession number EGAS00001002555). Summary association results are also publicly available at http://www.phpc.cam.ac.uk/ceu/proteins/, through PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk) and from the NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/downloads/summary-statistics). We thank INTERVAL study participants; staff at recruiting NHSBT blood donation centres; and the INTERVAL Study Co-ordination team, Operations Team (led by R. Houghton and C. Moore) and Data Management T eam (led by M. Walker). This research was supported as follows. The Cardiovascular Epidemiology Unit at the University of Cambridge: UK MRC (G0800270), BHF (SP/09/002), UK NIHR Cambridge Biomedical Research Centre, ERC (268834), and European Commission Framework Programme 7 (HEALTH-F2-2012-279233); B.B.S.: Cambridge School of Clinical Medicine MB-PhD programme and MRC/Sackler Prize PhD Studentship (MR/K50127X/1); J.E.P.: a BHF Cambridge Centre of Excellence Research Fellowship [RE/13/6/30180] and a UK Research Innovation Fellowship (MR/S004068/1). P.S.: a Rutherford Fund Fellowship (MR/S003746/1); D.S.P. and D.S.: the Wellcome Trust (105602/Z/14/Z); N.S.: the Wellcome Trust (WT098051 and WT091310), the EU FP7 (EPIGENESYS 257082 and BLUEPRINT HEALTH-F5-2011-282510); J.A.T: the Wellcome Trust (091157) and JDRF (9-2011-253); K.S.: the Biomedical Research Program at Weill Cornell Medicine in Qatar via the Qatar Foundation; J.D.: BHF Professor, European Research Council Senior Investigator, and NIHR Senior Investigator; the INTERVAL study: NHSBT (11-01-GEN) and the NIHR-BTRU in Donor Health and Genomics (NIHR BTRU-

2014-10024) at the University of Cambridge in partnership with NHSBT. Data analysis was partly supported by the Cambridge Substantive Site of Health Data Research UK. This study was partially funded by Merck Sharp & Dohme Corp. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health of England, or NHSBT.

The AGES Reykjavik study

Sentinel blood pQTL data are available in the supplementary materials of the pQTL study (doi: 10.1126/science.aaq1327). Data from the AGES Reykjavik study are available through collaboration (AGES_data_request@hjarta.is) under a data usage agreement with the IHA. We thank the staff at SomaLogic (CO) for performing the assays to measure protein levels, and P. MacNamara and G. Joyce of the Genomics Institute of the Novartis Research Foundation (GNF) for their leadership in supporting this work. We thank J. Loureiro, V. Swaroop, S. Abubucker, and F. Mapa of NIBR Cambridge for their contributions in support of the mass spectrometry workflow. We thank K. Bjarnadóttir, S. Gunnarsdóttir, and A. Hauksdóttir at the Icelandic Heart Association (IHA) for all specimen handling. The work was supported by Novartis Institute for Biomedical Research (NIBR), IHA, and in part by the intramural research program at the National Institute of Aging (N01-AG-12100 and HHSN271201200022C), the Althingi (the Icelandic Parliament), and the Icelandic Centre for Research (RANNIS) grant 141101-051.

The Cooperative Health Research in the Region of Augsburg (KORA) study

Blood pQTL data are available in the supplementary materials of the pQTL study (doi: 10.1038/ncomms14357) and accessible online on an integrated web-server at http://proteomics.gwas.eu. Data for KORA are available upon request from KORA-gen (http://epi.helmholtz-muenchen.de/kora-gen). Requests are submitted online and are subject to approval by the KORA board. This work was supported by ‘Biomedical Research Program’ funds at Weill Cornell Medicine in Qatar, a program funded by the Qatar Foundation. The statements made herein are solely the responsibility of the authors. M. Arnold was supported by the Helmholtz cross-program topic ‘Metabolic Dysfunction’. D. Mook-Kanamori was supported by Dutch Science Organization (ZonMW-VENI Grant 916.14.023). The KORA study was initiated and financed by the Helmholtz Zentrum Mu ¨nchen—German Research Center for Environmental Health, which is

funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-Maximilians-Universita ¨t, as part of LMUinnovativ. The KORA-Study Group consists of A. Peters (speaker), J.Heinrich, R.Holle, R.Leidl, C.Meisinger, K.Strauch and their co-workers, who are responsible for the design and conduct of the KORA studies. We gratefully acknowledge the contribution of all members of field staff conducting the KORA F4 study. We thank the staff from HMC dermatology department and WCM-Q clinical research core for their contribution to QMDiab. We thank Brian Sellers from SomaLogic for support with measuring the QMDiab samples at WCM-Q. We acknowledge free access to summary statistics provided by the GWAS consortia listed in Supplementary Data 4. We thank Jenine Davidson for the design of Figure 1a. Most of all, we thank all study participants of KORA and QMDiab for their invaluable contributions to this study.

The Genotype-Tissue Expression (GTEx) project

GTEx can be accessed at https://gtexportal.org/home/datasets (GTEx Analysis V6) or in BESD format through https://cnsgenomics.com/software/smr/#eQTLsummarydata. The Genotype-Tissue Expression (GTEx) project was supported by the Common Fund of the Office of the Director of the National Institutes of Health (http://commonfund.nih.gov/GTEx). Additional funds were provided by the National Cancer Institute (NCI), National Human Genome Research Institute (NHGRI), National Heart, Lung, and Blood Institute (NHLBI), National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), and National Institute of Neurological Disorders and Stroke (NINDS). Donors were enrolled at Biospecimen Source Sites funded by Leidos Biomedical, Inc. (Leidos) subcontracts to the National Disease Research Interchange (10XS170) and Roswell Park Cancer Institute (10XS171). The Laboratory, Data Analysis, and Coordinating Center (LDACC) was funded through a contract (HHSN268201000029C) to The Broad Institute, Inc. Biorepository operations were funded through a Leidos subcontract to the V an Andel Institute (10ST1035). Additional data repository and project management were provided by Leidos (HHSN261200800001E). The Brain Bank was supported by a supplement to University of Miami grant DA006227. J.R.D. is supported by a Lucille P. Markey Biomedical Research Stanford Graduate Fellowship. J.R.D., Z.Z., and N.A.T. acknowledge the Stanford Genome Training Program

(SGTP; NIH/NHGRI T32HG000044). Z.Z. is also supported by the National Science Foundation (NSF) GRFP (DGE-114747). L.F. is supported by the Stanford Center for Computational, Evolutionary, and Human Genomics (CEHG). D.G.M. is supported by a “la Caixa”-Severo Ochoa pre-doctoral fellowship. D.M. is supported by NIH grants U54DK105566 and R01GM104371. B.J.S is supported by NIH training grant T32GM007057. E.K.T is supported by a Hewlett-Packard Stanford Graduate Fellowship and a doctoral scholarship from the Natural Science and Engineering Council of Canada. T.S. is supported by a National Science Foundation Graduate Research Fellowship (DGE-1656518). A.B. is supported by the Searle Scholars Program and NIH grant R01MH109905. A.B., C.D.Bu. and S.B.M are supported by NIH grant R01HG008150 (NHGRI; Non-Coding Variants Program). S.B.M. and C.D.Bu. are supported by NHGRI grants U01HG007436 and U01HG009080. A.B., C.D.Bu., E.T.D., S.E.C., T.L, and S.B.M. are supported by NIH grants R01MH101814 (NIH Common Fund; GTEx Program). C.D.Br., Y.P., B.J., G.G., and B.E.E. are supported by NIH grant R01MH101822. B.E.E. is supported by NIH grants R00HG006265, R01MH101822 and U01 HG007900 and a Sloan Faculty Fellowship. G.L., A.B.N, J.J.P., A.S., Y -H.Z., and F.A.W. are supported by NIH grants R01MH101819, R01HG009125, and R21HG007840. T.L. and P.M. are supported by NIH grant R01MH106842. T.L. is supported by the NIH grant UM1HG008901. T.L. and S.E.C. are supported by NIH contract HHSN2682010000029C. B.J. is supported by NIH grant 2T32HG003284-11. C.B.P. and C.S. are supported by NIH grant R01MH101782. D.F.C. is supported by NIH grant R01MH101810. E.R.G and N.J.C are supported by NIH grants R01MH101820 and R01MH090937A. We thank A. Nellore and C. Wilks for assistance with TCGA data, K. Small for discussions, J. T. Leek for suggestions on the manuscript, N. L. Cyr for drawing the body map in Fig. 1a, and A. Kundaje and O. Ursu for input on Hi-C analysis.

GWAS of Alzheimer’s disease by Schwartzentruber et al.

The summary statistics from the meta-analysis are available through the National Human Genome Research Institute-European Bioinformatics Institute GWAS catalog under accession nos. GCST90012877 and GCST90012878 (https://www. ebi.ac.uk/gwas/downloads/summary-statistics). This work was funded by Open Targets (OTAR037). We thank J. Barrett for guidance during the initiation of the project and K. Alasoo for early access to the eQTL Catalogue. We thank A. Ruiz for

support in using the summary results from the GR@ACE study. We thank the participants and investigators of the FinnGen study and UK Biobank. R.J.M.F. is supported by grants from the UK Multiple Sclerosis Society (MS 50), the Adelson Medical Research Foundation and a core support grant from the Wellcome Trust and Medical Research Council (MRC) to the Wellcome-MRC Cambridge Stem Cell Institute (no. 203151/Z/16/Z). A.M.H.Y. is supported by a Wellcome Trust PhD for Clinicians fellowship.

GWAS of Lewy body dementia by Chia et al.

Individual-level sequence data for the resource genomes have been deposited at dbGaP (accession no. phs001963.v1.p1 NIA DementiaSeq). The GWAS summary statistics have been deposited in the GWAS catalog: https://www.ebi.ac.uk/gwas/home. We thank contributors who collected samples used in this study, as well as patients and families, whose help and participation made this work possible. We would like to thank Ms. Cynthia Crews for her technical assistance with DNA extractions. This research was supported in part by the Intramural Research Program of the National Institutes of Health (National Institute on Aging, National Institute of Neurological Disorders and Stroke; project numbers: 1ZIAAG000935 [PI Bryan J. Traynor, MD PhD], 1ZIANS003154 [PI Sonja W. Scholz, MD PhD], 1ZIANS0030033 and 1ZIANS003034 [David S. Goldstein, MD PhD]). Drs. Sidransky, Lopez and Tayebi were supported by the Intramural Research Program of the National Human Genome Research Institute. We would like to thank members of the International Parkinson's Disease Genomics Consortium for providing genotyping data from 100 random Parkinson's disease cases; these data are publicly available on dbGaP (phs00918.v1.p1). Dr. Besser gratefully acknowledges support from the National Institutes of Health (NIA K01AG063895). The American Genome Center is supported by the Department of Defense award: HU0001-18-20038 and in part by an NHLBI grant: IAA-A-HL-007.001. The opinions and assertions expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense, or the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. or the U.S. Government. The American Genome Center receives administrative and programmatic support from the Henry Jackson M. Foundation for the Advancement of Military Medicine. This paper represents independent research partly funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South

London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health. The study used samples from the Sant Pau Initiative on Neurodegeneration (SPIN) cohort (Sant Pau Hospital, Barcelona, Spain). We gratefully acknowledge the Knight ADRC grant P50 AG05681 (PI J.C. Morris), and its affiliated program project grant Healthy Aging and Senile Dementia P01 AG03991 (PI J.C. Morris) and its affiliated program project grant Healthy Aging and Senile Dementia P01 AG03991 (PI J.C. Morris). Dr. Kaufmann and Dr. Palma acknowledge support from the NIH (NINDS R01NS107596, U54NS065736, and the Michael J. Fox Foundation (MJFF grant 11355). Dr. Calvo acknowledges that this study was performed under the Department of Excellence grant of the Italian Ministry of Education, University and Research to the "Rita Levi Montalcini" Department of Neuroscience, University of Torino, Italy. Dr. Huw R. Morris reports that the Progressive Supranuclear Palsy-Corticobasal Syndrome-Multiple System Atrophy (PROSPECT) study is supported by grants from the PSP Association UK, CBD Solutions, the MSA Trust, and the NIHR UCLH Biomedical Research Centre. We would like to thank the University of Toronto Brain Bank for providing DNA specimens, and we thank the Canadian Consortium on Neurodegeneration in Aging. We acknowledge the Oxford Brain Bank, supported by the Medical Research Council, Brains for Dementia Research (Alzheimer's Society and Alzheimer's Research UK), Autistica UK, and the National Institute for Health Research Oxford Biomedical Research Centre. Dr. St. George-Hyslop gratefully acknowledges support from the Canadian Institutes of Research (Foundation Grant and Canadian Consortium on Neurodegeneration in Aging Grant), Wellcome Trust Collaborative Award 203249/Z/16/Z, ALS Canada Project Grant and ALS Society of Canada/Brain Canada 499553, Alzheimer Research UK, Alzheimer Society UK, and US Alzheimer Society Zenith Grant ZEN-18-529769 (PHStGH). Dr. Kevin Morgan gratefully acknowledges support by the Alzheimer's Research UK (ARUK) Consortium. We are grateful to the Rush Alzheimer's Disease Center for providing brain tissue and DNA samples, which was supported by the grants P30 AG10161, R01 AG15819, R01 AG17917, U01 AG46152, U01 AG61356. We thank the Dublin Brain Bank, Oregon Health & Science University Brain Bank (with support of the ADC grant 5 P30 AG008017), Duke University School of Medicine ADRC Brain Bank and Biorepository, Virginia Commonwealth University Brain Bank, Georgetown University Brain Bank, Manchester University Brain Bank, NIH NeuroBioBank, the New York Brain Bank at Columbia University, and the

Department of Pathology and Laboratory Medicine at the University of Kansas School of Medicine for contributing tissue specimens. We are grateful to Dr. Bernardino Ghetti from the Department of Pathology and Laboratory Medicine at Indiana University for providing tissue samples. The biospecimens from the University of California, Irvine ADRC used in this project were supported by the NIH/NIA grant P50 AG016573. Samples from the National Centralized Repository for Alzheimer's Diseases and Related Dementias (NCRAD), which receives government support under a cooperative agreement grant (U24 AG021886) awarded by the National Institute on Aging (NIA), were used in this study. The National Alzheimer's Coordinating Center (NACC) database is funded by the NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA-funded 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), P30 AG062677 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI Robert Vassar, PhD), 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 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, 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), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD). Data used in the preparation of this article were obtained from the AMP PD Knowledge Platform. For up-to-date information on the study, https://www.amp-pd.org. AMP PD – a public-private partnership – is managed by the FNIH and funded by Celgene, GSK, the Michael J. Fox Foundation for Parkinson's Research, the National Institute of Neurological Disorders and Stroke, Pfizer, Sanofi, and Verily. Clinical data and biosamples used in preparation of this article were obtained from the Fox Investigation for New Discovery of Biomarkers (BioFIND), the Harvard Biomarker Study (HBS), the Parkinson's Progression Markers Initiative (PPMI), and the Parkinson's Disease Biomarkers

Program (PDBP). BioFIND is sponsored by The Michael J. Fox Foundation for Parkinson's Research (MJFF) with support from the National Institute of Neurological Disorders and Stroke (NINDS). The BioFIND Investigators have not participated in reviewing the data analysis or content of the manuscript. For up-to-date information on the study, visit michaeljfox.org/biofind. The Harvard Biomarker Study (HBS) is a collaboration of HBS investigators (a full list of HBS investigators can be found at https://www.bwhparkinsoncenter.org/biobank) and funded through philanthropy and NIH and Non-NIH funding sources. The HBS Investigators have not participated in reviewing the data analysis or content of the manuscript. Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmiinfo.org/data). For up-to-date information on the study, visit www.ppmi-info.org. PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbvie, Allergan, Avid Radiopharmaceuticals, Biogen, BioLegend, Bristol-Myers-Squibb, Celgene, Jenali, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi Genzyme, Servier, Takeda, Teva, ucb, Verily, Voyager Therapeutics, Golub Capital. The PPMI investigators have not participated in reviewing the data analysis or content of the manuscript. For up-to-date information on the study, visit www.ppmiinfo.org. Parkinson's Disease Biomarker Program (PDBP) consortium is supported by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institutes of Health. A full list of PDBP investigators can be found at https://pdbp.ninds.nih.gov/policy. The PDBP Investigators have not participated in reviewing the data analysis or content of the manuscript. We would like to thank the South West Dementia Brain Bank (SWDBB) for providing DNA samples for this study. The SWDBB is part of the Brains for Dementia Research Programme, jointly funded by Alzheimer's Research UK and Alzheimer's Society, and is supported by BRACE (Bristol Research into Alzheimer's and Care of the Elderly) and the Medical Research Council. We are grateful to the Banner Sun Health Research Institute Brain and Body Donation Program of Sun City, Arizona, for the provision of human brain tissue (PI: Thomas G. Beach, MD). The Brain and Body Donation Program is supported by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinson's Disease and Related Disorders), the National Institute on Aging (P30 AG19610 Arizona Alzheimer's Disease Core Center), the Arizona Department of Health Services (contract

211002, Arizona Alzheimer's Research Center), the Arizona Biomedical Research Commission (contracts 4001, 0011, 05-901 and 1001 to the Arizona Parkinson's Disease Consortium) and the Michael J. Fox Foundation for Parkinson's Research. This study was supported in part by an Alzheimer's Disease Core Center grant (P30 AG013854) from the National Institute on Aging to Northwestern University, Chicago, Illinois. We gratefully acknowledge the assistance of the Neuropathology Core. The Alzheimer's Disease Genetics Consortium supported the collection of samples used in this study through the National Institute on Aging (NIA) grants U01 AG032984 and RC2 AG036528 and data were prepared by the National Institute on Aging Alzheimer's Disease Data Storage Site (NIAGADS) at the University of Pennsylvania (U24-AG041689). This study used samples from the NINDS Repository at Coriell (https://catalog.coriell.org), as well as clinical data. Samples and data from patients included in this study were provided by the Biobank Valdecilla (PD13/0010/0024), integrated into the Spanish National Biobank Network, and they were processed following standard operating procedures with the appropriate approval of the Ethics and Scientific Committees. Data included in this manuscript has been generated with support of the grans PI16/01861 – Accion Estrategica en Salud integrated in the Spanish National I+D+P+I Plan and financed by Instituto de Salud Carlos III (ISCIII) – Subdireccion General de Evaluacion and the Fondo Europeo de Desarrollo Regional (FEDER – "Una Manera de Hacer Europa"). We thank the Mayo Clinic Brain Bank for contributing DNA samples and data from patients with Lewy body dementia, which is supported by U54 NS110435 (PI Dennis W. Dickson, MD), U01 NS100620 (PI Kejal Kantarci, MD) and The Mangurian Foundation Lewy Body Dementia Program. Sample collection and characterization is also supported by the Mayo Clinic Functional Genomics of LBD Program, NINDS R01 NS78086 (PI Owen Ross, PhD), Mayo Clinic Center for Individualized Medicine, and The Little Family Foundation. Mayo Clinic is an American Parkinson Disease Association (APDA) Mayo Clinic Information and Referral Center, an APDA Center for Advanced Research and the Mayo Clinic Lewy Body Dementia Association (LBDA) Research Center of Excellence. Dr. Zbigniew Wszolek is partially supported by the Mayo Clinic Center for Regenerative Medicine, the gifts from The Sol Goldman Charitable Trust, and the Donald G. and Jodi P. Heeringa Family, the Haworth Family Professorship in Neurodegenerative Diseases fund, and The Albertson Parkinson's Research Foundation. We thank the Paris NeuroCEB Brain Bank (C. Duyckaerts) for contributing DNA samples. We would like to thank the Baltimore Longitudinal

Study of Aging for providing DNA samples (www.blsa.nih.gov). Tissue samples were provided by the Johns Hopkins Morris K. Udall Center of Excellence for Parkinson's Disease Research (NIH P50 NS38377 [PI Ted M. Dawson]; U01NS097049 [PD Ted M. Dawson]) and the Johns Hopkins Alzheimer Disease Research Center (NIH P50 AG05146). This study used tissue samples and data provided by the Michigan Brain Bank, the Michigan Alzheimer's Disease Center (P30 AG053760), and the Protein Folding Disorders Program. We are indebted to the IDIBAPS Biobank (Barcelona, Spain) for sample and data procurement. Dr. Trojanowski gratefully acknowledges support by the grant # P30 AG10124 and U19 AG06241801A1. Tissue for this study was provided by the Newcastle Brain Tissue Resource, which is funded in part by a grant from the UK Medical Research Council (G0400074), by NIHR Biomedical Research Centre Newcastle awarded to the Newcastle upon Tyne NHS Foundation Trust and Newcastle University, and as part of the Brains for Dementia Research Programme jointly funded by Alzheimer's Research UK and Alzheimer's Society. Samples from the NIND BioSend, which receives government support under a cooperative agreement grant (U24 NS095871) awarded by the National Institute of Neurological Disorders and Stroke (NINDS), were used in this study. We thank contributors who collected samples used in this study, as well as patients and their families, whose help and participation made this work possible. This study was supported in part by the Dementia with Lewy Bodies Consortium (grant #: U01 NS100610). This study acknowledges the National Institute of Neurological Disorders and Stroke (NINDS) supported Parkinson's Disease Biomarkers Program Investigators (https://pdbp.ninds.nih.gov/sites/default/files/assets/ PDBP_investigator_list.pdf). A full list of PDBP investigators can be found at https://pdbp.ninds.nih.gov/policy. Data and biospecimens used in the preparation of this manuscript were obtained from the Parkinson's Disease Biomarkers Program (PDBP) Consortium, part of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health. Investigators include: Roger Albin, Roy Alcalay, Alberto Ascherio, Thomas Beach, Sarah Berman, Bradley Boeve, F. DuBois Bowman, Shu Chen, Alice Chen-Plotkin, William Dauer, Ted Dawson, Paula Desplats, Richard Dewey, Ray Dorsey, Jori Fleisher, Kirk Frey, Douglas Galasko, James Galvin, Dwight German, Lawrence Honig, Xuemei Huang, David Irwin, Kejal Kantarci, Anumantha Kanthasamy, Daniel Kaufer, James Leverenz, Carol Lippa, Irene Litvan, Oscar Lopez, Jian Ma, Lara Mangravite, Karen Marder, Laurie Ozelius, Vladislav Petyuk, Judith Potashkin, Liana Rosenthal, Rachel Saunders-Pullman, Clemens Scherzer, Michael Schwarzschild,

Tanya Simuni, Andrew Singleton, David Standaert, Debby Tsuang, David Vaillancourt, David Walt, Andrew West, Cyrus Zabetian, Jing Zhang, and Wenquan Zou. The PDBP Investigators have not participated in reviewing the data analysis or content of the manuscript. Dr. Leverenz acknowledges funding from the National Institutes of Health (grant #: P30 AG063762), GE Health Care for imaging studies of participants enrolled in the Dementia with Lewy Bodies Consortium (UO1 NS100610), the Lewy Body Dementia Association for the Cleveland Clinic Research Center of Excellence, the Jane and Lee Seidman Fund, and the Douglas Herthel DVM Memorial Fund. We thank members of the North American Brain Expression Consortium (NABEC) for providing DNA samples derived from brain tissue. Brain tissue for the NABEC cohort was obtained from the Baltimore Longitudinal Study on Aging at the Johns Hopkins School of Medicine, and from the NICHD Brain and Tissue Bank for Developmental Disorders at the University of Maryland, the Banner Sun Health Research Institute Brain and Body Donation Program, and the University of Kentucky Alzheimer's Disease Center Brain Bank. The NABEC study was supported, in part, by the Intramural Research Program of the National Institutes of Health (National Institute on Aging, National Institute of Neurological Disorders and Stroke; project numbers 1ZIANS003154, Z01-AG000949-02, Z01-ES101986, and UK ADC NIA P30-AG0-28383. We would like to thank the United Kingdom Brain Expression Consortium (UKBEC) for providing DNA samples. Tissue samples and associated clinical and neuropathological data were supplied by the Parkinson's UK Brain Bank, funded by Parkinson's UK, a charity registered in England and Wales (258197) and in Scotland (SC037554). The authors would like to thank Parkinson's UK for their continued support as well as the donors and family for their invaluable donation of brain tissue to the Parkinson's UK Tissue Bank. This work was supported by a grant from the Luxembourg National Research Fund (Fonds National de Recherche, FNR) within the National Centre of Excellence in Research on Parkinson's disease (NCER-PD) and by an Excellence Award for Research (PEARL) or R.K. We would like to thank Estelle Sandt, Integrated Biobank Luxembourg (IBBL), and Lars Geffers, Luxembourg Centre for Systems Biomedicine (LCSB) of the University of Luxembourg, for excellent project management and the whole NCER-PD Consortium (Aguayo, Gloria; Allen, Dominic; Ammerlann, Wim; Aurich, Maike; Baldini, Federico; Balling, Rudi; Banda, Peter; Beaumont, Katy; Becker, Regina; Berg, Daniela; Betsou, Fay; Binck, Sylvia; Bisdorff, Alexandre; Bobbili, Dheeraj; Brockmann, Kathrin; Calmes, Jessica; Castillo, Lorieza; Diederich, Nico;

Dondelinger, Rene; Esteves, Daniela; Ferrand, JeanYves; Fleming, Ronan; Gantenbein, Manon; Gasser, Thomas; Gawron, Piotr; Geffers, Lars; Giarmana, Virginie; Glaab, Enrico; Gomes, Clarissa P.C.; Goncharenko, Nikolai; Graas, Jérôme; Graziano, Mariela; Groues, Valentin; Grünewald, Anne; Gu, Wei; Hammot, Gaël; Hanff, AnneMarie; Hansen, Linda; Hansen, Maxime; Haraldsdöttir, Hulda; Heirendt, Laurent; Herbrink, Sylvia; Hertel, Johannes; Herzinger, Sascha; Heymann, Michael; Hiller, Karsten; Hipp, Geraldine; Hu, Michele; Huiart, Laetitia; Hundt, Alexander; Jacoby, Nadine; Jarosław, Jacek; Jaroz, Yohan; Kolber, Pierre; Krüger, Rejko; Kutzera, Joachim; Landoulsi, Zied; Larue, Catherine; Lentz, Roseline; Liepelt, Inga; Liszka, Robert; Longhino, Laura; Lorentz, Victoria; Mackay, Clare; Maetzler, Walter; Marcus, Katrin; Marques, Guilherme; Martens, Jan; Mathay, Conny; Matyjaszczyk, Piotr; May, Patrick; Meisch, Francoise; Menster, Myriam; Minelli, Maura, Mittelbronn, Michel; Mollenhauer, Brit; Mommaerts, Kathleen; Moreno, Carlos; Mühlschlegel, Friedrich; Nati, Romain; Nehrbass, Ulf; Nickels, Sarah; Nicolai, Beatrice; Nicolay, Jean-Paul; Noronha, Alberto; Oertel, Wolfgang; Ostaszewski, Marek; Pachchek, Sinthuja; Pauly, Claire; Pavelka, Lukas; Perquin, Magali; Reiter, Dorothea; Rosety, Isabel; Rump, Kirsten; Sandt, Estelle; Satagopam, Venkata; Schlesser, Marc; Schmitz, Sabine; Schmitz, Susanne; Schneider, Reinhard; Schwamborn, Jens; Schweicher, Alexandra; Stallinger, Christian; Simons, Janine; Stute, Lara; Thiele, Ines; Thinnes, Cyrille; Trefois, Christophe; Trezzi, JeanPierre; Vaillant, Michel; Vasco, Daniel; Vyas, Maharshi; Wade-Martins, Richard; Wilmes, Paul). Finally, we would like to thank all participants of the Luxembourg Parkinson's Study within the NCER-PD. This work was in part supported by the NIA grants U01AG049508 (PI Alison Goate, DPhil) and U01AG052411 (PI Alison Goate, DPhil). This work was supported in part by the Italian Ministry of Health (Ministero della Salute, Ricerca Sanitaria Finalizzata, grant RF-201602362405), the European Commission's Health Seventh Framework Programme (FP7/20072013 under grant agreement 259867), the Italian Ministry of Education, University and Research (Progetti di Ricerca di Rilevante Interesse Nazionale, PRIN, grant 2017SNW5MB), the Joint Programme – Neurodegenerative Disease Research (Strength and Brain-Mend projects), granted by the Italian Ministry of Education, University and Research. This study was performed under the Department of Excellence grant of the Italian Ministry of Education, University and Research to the Rita Levi Montalcini Department of Neuroscience, University of Torino, Italy. Tissue samples were supplied by The London Neurodegenerative Diseases Brain Bank, which receives funding from the MRC (grant

MR/L016397/1) and as part of the Brains for Dementia Research programme, jointly funded by Alzheimer's Research UK and Alzheimer's Society. DNA samples were generated by funding from the Alzheimer's Society (422; AS-URB-18-013; PI Angela Hodges, PhD). We thank the Paris Neuro-CEB Brain Bank (C. Duyckaerts, S. Lesage) for contributing DNA samples. We are grateful to the DNA and Cell bank at the ICM institute for DNA sample preparation (S. Lesage). The biospecimens from the Sunnybrook Dementia Study (https://clinicaltrials.gov/ct2/show/NCT01800214) used in this project was supported by grants from the Canadian Institutes of Health Research (Foundation Grant FDN 159910 [PI S.E. Black] and Operating Grant MOP13129 [PIs Sandra E. Black, MD, Mario Masellis, MD, PhD]) and an Early Researcher Award from the Ministry of Research, Innovation and Science (MRIS; Ontario; PI Mario Masellis, MD, PhD). Dr. Marder reports that this publication was supported by the National Institutes of Health through grant number UL1TR001873 and U01NS100600. The Harvard Biomarkers Study (https://www.bwhparkinsoncenter.org) is a collaborative initiative of Brigham and Women's Hospital and Massachusetts General Hospital, co-directed by Dr. Clemens Scherzer and Dr. Bradley T. Hyman. The HBS Investigators have not participated in reviewing the current manuscript. The HBS Study Investigators are: Harvard Biomarkers Study. Co-Directors: Brigham and Women's Hospital: Clemens R. Scherzer, Massachusetts General Hospital: Bradley T. Hyman; Investigators and Study Coordinators: Brigham and Women's Hospital: Yuliya Kuras, Karbi Choudhury, Michael T. Hayes, Aleksandar Videnovic, Nutan Sharma, Vikram Khurana, Claudio Meleo De Gusmao, Reisa Sperling; Massachusetts General Hospital: John H. Growdon, Michael A. Schwarzschild, Albert Y. Hung, Alice W. Flaherty, Deborah Blacker, Anne-Marie Wills, Steven E. Arnold, Ann L. Hunt, Nicte I. Mejia, Anand Viswanathan, Stephen N. Gomperts, Mark W. Albers, Maria Allora-Palli, David Hsu, Alexandra Kimball, Scott McGinnis, John Becker, Randy Buckner, Thomas Byrne, Maura Copeland, Bradford Dickerson, Matthew Frosch, Theresa Gomez-Isla, Steven Greenberg, Julius Hedden, Elizabeth Hedley-Whyte, Keith Johnson, Raymond Kelleher, Aaron Koenig, Maria MarquisSayagues, Gad Marshall, Sergi Martinez-Ramirez, Donald McLaren, Olivia Okereke, Elena Ratti, Christopher William, Koene Van Dij, Shuko Takeda, Anat Stemmer-Rachaminov, Jessica Kloppenburg, Catherine Munro, Rachel Schmid, Sarah Wigman, Sara Wlodarcsyk; Data Coordination: Brigham and Women's Hospital: Thomas Yi; Biobank Management Staff: Brigham and Women's Hospital: Idil Tuncali. We thank all study participants

and their families for their invaluable contributions. HBS is made possible by generous support from the Harvard NeuroDiscovery Center, with additional contributions from the American Parkinson Disease Association, Michael J Fox Foundation, NINDS U01NS082157, and the Massachusetts Alzheimer's Disease Research Center NIA P50AG005134. Dr. Scherzer gratefully acknowledges support from NINDS/NIA R01NS115144 and NINDS U01NS10063. Data governance was provided by the METADAC data access committee, funded by ESRC, Wellcome, and MRC. (2015-2018: Grant Number MR/N01104X/1 2018-2020: Grant Number ES/S008349/1). This work made use of data and samples generated by the 1958 Birth Cohort (NCDS), which is managed by the Centre for Longitudinal Studies at the UCL Institute of Education, funded by the Economic and Social Research Council (grant number ES/M001660/1). Access to these resources was enabled via the Wellcome Trust & MRC: 58FORWARDS grant [108439/Z/15/Z] (The 1958 Birth Cohort: Fostering new Opportunities for Research via Wider Access to Reliable Data and Samples). Before 2015, biomedical resources were maintained under the Wellcome Trust and Medical Research Council 58READIE Project (grant numbers WT095219MA and G1001799). This study also used genotype and clinical data from the Wellcome Trust Case Control Consortium, and the HyperGenes Consortium. The InCHIANTI study baseline (was supported as a "targeted project" (ICS110.1/RF97.71) by the Italian Ministry of Health and in part by the United States National Institute on Aging (contracts 263 MD 9164 and 263 MD 821336), the InCHIANTI follow-up 1 (2001-2003) was funded by the United States National Institute on Aging (contracts N.1-AG-1-1 and N.1-AG-1 2111), and the InCHIANTI follow-ups 2 and 3 studies (2004-2010) were financed by the United States National Institute on Aging (contract N01-AG-5-0002). This study also used genotype and clinical data from the Wellcome Trust Case Control Consortium, and the HyperGenes Consortium. Trans-Omics in Precision Medicine (TOPMed) program imputation panel (version TOPMed-r2) is supported by the National Heart, Lung and Blood Institute (NHLB); see www.nhlbiwgs.org. TOPMed study investigators contributed data to the reference panel, which can be accessed through the Michigan Imputation Server; see https://imputationserver.sph.umich.edu. The panel was constructed and implemented by the TOPMed Informatics Research Center at the University of Michigan (3R01HL-117626-02S1; contract HHSN2682018000021). The TOPMed Data Coordinating Center (3R01HL-12039302S1; contract HHSN2682018000011) provided additional data management, sample identify checks, and overall program coordination and support.

We gratefully acknowledge the studies and participants who provided biological samples and data for TOPMed. The Molecular data for the Trans-Omics in Precision Medicine (TOPMed) program was supported by the National Heart, Lung and Blood Institute (NHLBI). Genome sequencing for "NHLBI TOPMed: Atherosclerosis Risk in Communities (ARIC)" (phs001211.v2.p2) was performed at the Broad Institute of MIT and Harvard (3R01HL092577-06S1) and at the Baylor Human Genome Sequencing Center (3U54HG003273-12S2, HHSN268201500015C). Genome sequencing for "NHLBI TOPMed: Cleveland Clinic Atrial Fibrillation (CCAF) Study" (phs001189.v1.p1) was performed at the Broad Institute of MIT and Harvard (3R01HL092577-06S1). Genome sequencing for "NHLBI TOPMed: Trans-Omics for Precision Medicine (TOPMed) Whole Genome Sequencing Project: Cardiovascular Health Study (phs001368.v1.p1) was performed at the Baylor Human Genome Sequencing Center (3U54HG003273-12S2, HHSN268201500015C). Genome sequencing for "NHLBI TOPMed: Partners HealthCare Biobank" (phs001024.v3.p1) was performed at the Broad Institute of MIT and Harvard (3R01HL092577-06S1). Genome sequencing for "NHLBI TOPMed: Whole Genome Sequencing of Venous Thromboembolism (WGS of VTE)" (phs001402.v1.p1) was performed at the Baylor Human Genome Sequencing Center (3U54HG003273-12S2, HHSN268201500015C). Genome sequencing for "NHLBI TOPMed: Novel Risk Factors for the Development of Atrial Fibrillation in Women" (phs001040.v3.p1) was performed at the Broad Institute of MIT and Harvard (3R01HL092577-06S1). Genome sequencing for "NHLBI TOPMed: The Genetics and Epidemiology of Asthma in Barbados" (phs001143.v2.p1) was performed by Illumina Genomic Services (3R01HL104608-04S1). Genome sequencing for "NHLBI TOPMed: The Vanderbilt Genetic Basis of Atrial Fibrillation" (phs001032.v4.p2) was performed at the Broad Institute of MIT and Harvard (3R01HL092577-06S1). Genome sequencing for "NHLBI TOPMed: Heart and Vascular Health Study (HVH)" (phs000993.v3.p2) was performed at the Broad Institute of MIT and Harvard (3R01HL092577-06S1) and at the Baylor Human Genome Sequencing Center (3U54HG003273-12S2, HHSN268201500015C). Genome sequencing for "NHLBI TOPMed: Genetic Epidemiology of COPD (COPDGene)" (phs000951.v3.p3) was performed at the University of Washington Northwest Genomics Center (3R01HL089856-08S1) and at the Broad Institute of MIT and Harvard (HHSN268201500014C). Genome sequencing for "NHLBI TOPMed: The Vanderbilt Atrial Fibrillation Ablation Registry" (phs000997.v3.p2) was performed at the Broad

Institute of MIT and Harvard (3U54HG003067-12S2, 3U54HG00306713S1). Genome sequencing for “NHLBI TOPMed: The Jackson Heart Study" (phs000964.v3.p1) was performed at the University of Washington Northwest Genomics Center (HHSN268201100037C). Genome sequencing for “NHLBI TOPMed: Genetics of Cardiometabolic Health in the Amish" (phs000956.v3.p1) was performed at the Broad Institute of MIT and Harvard (3R01HL121007-01S1). Genome sequencing for “NHLBI TOPMed: Massachusetts General Hospital Atrial Fibrillation (MGH AF) Study" (phs001062.v3.p2) was performed at the Broad Institute of MIT and Harvard (3R01HL092577-06S1, 3U54HG00306712S2, 3U54HG003067-13S1, 3UM1HG008895-01S2). Genome sequencing for “NHLBI TOPMed: The Framingham Heart Study" (phs000974.v3.p2) was performed at the Broad Institute of MIT and Harvard (3U54HG003067-12S2). Core support including centralized genomic read mapping and genotype calling, along with variant quality metrics and filtering were provided by the TOPMed Informatics Research Center (3R01HL-117626-02S1; contract HHSN268201800002I). Core support including phenotype harmonization, data management, sample-identity QC, and general program coordination were provided by the TOPMed Data Coordinating Center (R01HL-120393; U01HL-120393; contract HHSN268201800001I). We gratefully acknowledge the studies and participants who provided biological samples and data for TOPMed. The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institute of Health, Department of Health and Human Services, under contract numbers (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I, and HHSN268201700005I). The authors thank the staff and participants of the ARIC study for their important contributions. The research reported in this article was supported by grants from the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute grants R01 HL090620 and R01 HL111314, the NIH National Center for Research Resources for Case Western Reserve University and Cleveland Clinic Clinical and Translational Science Award (CTSA) UL1-RR024989, the Department of Cardiovascular Medicine philanthropic research fund, Heart and Vascular Institute, Cleveland Clinic, the Fondation Leducq grant 07-CVD 03, and The Atrial Fibrillation Innovation Center, State of Ohio. This research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01-HC85079, N01-HC-85080, N01HC-85081, N01-HC-85082, N01-HC-85083, N01-HC-85084, N01-HC-85085, N01-HC-85086, N01-HC-35129, N01-HC-15103,

N01-HC-55222, N01-HC-75150, N01-HC-45133, and N01- HC-85239; grant numbers U01 HL080295 and U01 HL130014 from the National Heart, Lung, and Blood Institute, and R01 AG023629 from the National Institute on Aging, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at https://chs-nhlbi.org/pi. This manuscript was not prepared in collaboration with CHS investigators and does not necessarily reflect the opinions or views of CHS, or the NHLBI. We thank the Broad Institute for generating high-quality sequence data supported by the NHLBI grant 3R01HL092577-06S1 to Dr. Patrick Ellinor. Funded in part by grants from the National Institutes of Health, National Heart, Lung and Blood Institute (HL66216 and HL83141) and the National Human Genome Research Institute (HG04735). The Women's Genome Health Study (WGHS) is supported by HL 043851 and HL099355 from the National Heart, Lung, and Blood Institute and CA 047988 from the National Cancer Institute, the Donald W. Reynolds Foundation with collaborative scientific support and funding for genotyping provided by Amgen. AF endpoint confirmation was supported by HL-093613 and a grant from the Harris Family Foundation and Watkin's Foundation. The Genetics and Epidemiology of Asthma in Barbados is supported by National Institutes of Health (NIH) National Heart, Lung, Blood Institute TOPMed (R01 HL104608-S1) and: R01 AI20059, K23 HL076322, and RC2 HL101651. The research reported in this article was supported by grants from the American Heart Association to Dr. Darbar (EIA 0940116N), and grants from the National Institutes of Health (NIH) to Dr. Darbar (HL092217), and Dr. Roden (U19 HL65962, and UL1 RR024975). This project was also supported by CTSA award (UL1TR000445) from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences of the NIH. The research reported in this article was supported by grants HL068986, HL085251, HL095080, and HL073410 from the National Heart, Lung, and Blood Institute. This manuscript was not prepared in collaboration with Heart and Vascular Health (HVH) Study investigators and does not necessarily reflect the opinions or views of the HVH Study or the NHLBI. This research used data generated by the COPDGene study, which was supported by NIH grants U01 HL089856 and U01 HL089897. The COPDGene project is also supported by the COPD Foundation through contributions made by an Industry Advisory Board comprised of Pfizer, AstraZeneca, Boehringer Ingelheim, Novartis, and Sunovion.

Centralized read mapping and genotype calling, along with variant quality metrics and filtering were provided by the TOPMed Informatics Research Center (3R01HL-117626-02S1; contract HHSN2682018000002I). Phenotype harmonization, data management, sample-identity QC, and general study coordination were provided by the TOPMed Data Coordinating Center (3R01HL-120393-02S1; contract HHSN2682018000001I). We gratefully acknowledge the studies and participants who provided biological samples and data for TOPMed. This study is part of the Centers for Common Disease Genomics (CCDG) program, a large-scale genome sequencing effort to identify rare risk and protective alleles that contribute to a range of common disease phenotypes. The CCDG program is funded by the National Human Genome Research Institute (NHGRI) and the National Heart, Lung, and Blood Institute (NHLBI). Sequencing was completed at the Human Genome Sequencing Center at Baylor College of Medicine under NHGRI grant UM1 HG008898. The research reported in this article was supported by grants from the American Heart Association to Dr. Shoemaker (11CRP742009), Dr. Darbar (EIA 0940116N), and grants from the National Institutes of Health (NIH) to Dr. Darbar (R01 HL092217), and Dr. Roden (U19 HL65962, and UL1 RR024975). The project was also supported by a CTSA award (UL1 TR00045) from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the NIH. The Jackson Heart Study (JHS) is supported and conducted in collaboration with Jackson State University (HHSN2682018000013I), Tougaloo College (HHSN2682018000014I), the Mississippi State Department of Health (HHSN2682018000015I/HHSN26800001) and the University of Mississippi Medical Center (HHSN2682018000010I, HHSN2682018000011I and HHSN2682018000012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute for Minority Health and Health Disparities (NIMHD). The authors also wish to thank the staff and participants of the JHS. The Amish studies upon which these data are based were supported by NIH grants R01 AG18728, U01 HL072515, R01 HL088119, R01 HL121007, and P30 DK072488. See publication: PMID: 18440328. The research reported in this article was supported by NIH grants K23HL071632, K23HL114724, R21DA027021, R01HL092577, R01HL092577S1, R01HL104156, K24HL105780, and U01HL65962. The research has also been supported by an Established Investigator Award from the American Heart Association (13EIA14220013) and by support from the Fondation Leducq (14CVD01). This manuscript was not

prepared in collaboration with MGH AF Study investigators and does not necessarily reflect the opinions or views of the MGH AF Study investigators or the NHLBI. The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University (Contract No. N01-HC-25195, HHSN268201500001I and 75N92019D00031). This manuscript was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University, or NHLBI. R.H.R was supported through the award of a Leonard Wolfson Doctoral Training Fellowship in Neurodegeneration. Raffaele Ferrari was supported by the Alzheimer's Society (grant number 284). This work was supported by the UK Dementia Research Institute which receives its funding from DRI Ltd, funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK. Dr. Hardy gratefully acknowledges support from the Wellcome Trust (award number 202903/Z/16/Z), the Dolby Family Fund, National Institute for Health Research University College London Hospital Biomedical Research Centre, the BRCNIHR Biomedical Centre at University College London Hospital NHS Foundation Trust and University College London. Dr. Tienari gratefully acknowledges grant support from the Helsinki University Hospital, Finnish Academy (grant No. 134150) and Sigrid Juselius Foundation. Dr. Myllykangas gratefully acknowledges grant support from the Helsinki University Hospital and Finnish Academy (grant No. 294817). This work was supported by the Scripps Research Translational Institute, an NIH-NCATS Clinical and Translational Science Award (CTSA; 5 UL1 RR025774). This study used the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, Maryland, USA (http://biowulf.nih.gov).

GWAS of amyotrophic lateral sclerosis by the Project MinE

The GWAS summary statistics generated in this study are publicly available in the NHGRI-EBI GWAS Catalog at https://www.ebi.ac.uk/gwas/ (accession IDs GCST90027163 and GCST90027164 for cross-ancestry and European ancestry meta-analyses, respectively) and through the Project MinE website (https://www. projectmine.com/research/download-data/). W.v.R. is supported by funding provided by the Dutch Research Council (NWO) [VENI scheme grant 09150161810018] and Prinses Beatrix Spierfonds (neuromuscular fellowship grant W.F19-03). J.J.F.A.v.V. is funded by Projectnumber W.OR20-08 (The "Repeatome" as a basis for new

treatments of ALS) of the Prinses Beatrix Spierfonds. K.P.K. is supported by funding provided by the Dutch Research Council (NWO) [VIDI grant 91719350]. G.S. was supported by a PhD studentship from the Alzheimer's Society. E.H. and J.M. were supported by Medical Research Council (MRC) grant K013807 (awarded to J.M). mQTL SMR data analysis was undertaken using high-performance computing supported by a Medical Research Council (MRC) Clinical Infrastructure award M008924 (awarded to J.M.). French ALS patients of the Pitié-Salpêtrière hospital (Paris) have been collected with ARSla funding support. D.B. and T.R.G. received funding from Biogen and UK Medical Research Council (MRC Epidemiology Unit, MC_UU_00011/1 and MC_UU_00011/4) for this project. G.D.S. works in the Medical Research Council Integrative Epidemiology Unit at the University of Bristol MC_UU_00011/1. D.B., E. Tsai and H.R. are employees of Biogen. J.P.R. is funded by the Canadian Institutes of Health Research (FRN 159279). A.A.K is supported by The Motor Neurone Disease Association (MNDA) and NIHR Maudsley Biomedical Research Centre. R.J.P. is supported by the Gravitation program of the Dutch Ministry of Education, Culture, and Science and the Netherlands Organization for Scientific Research (NWO; BRAINSCAPES). Project MinE Belgium was supported by a grant from IWT (n° 140935), the ALS Liga België, the National Lottery of Belgium and the KU Leuven Opening the Future Fund (awarded to P.V.D.). P.V.D holds a senior clinical investigatorship of FWO-Vlaanderen and is supported by the E. von Behring Chair for Neuromuscular and Neurodegenerative Disorders, the ALS Liga België and the KU Leuven funds "Een Hart voor ALS", "Laeversfonds voor ALS Onderzoek" and the "Valéry Perrier Race against ALS Fund". Several authors of this publication are members of the European Reference Network for Rare Neuromuscular Diseases (ERN-NMD). The authors are pleased to acknowledge the contribution of "Live now" Charity Foundation and Moscow ALS palliative care service for supporting patients with ALS and their families. G.A.R is supported by the Canadian Institutes of Health. Research Australia including its Ice Bucket Challenge Grant. This work was supported in part by the Intramural Research Programs of the NIH, National Institute on Aging (Z01-AG000949-02). We acknowledge funding from the National Health and Medical Research Council (NHMRC) (1078901, 1083187, 1113400, 1095215, 1121962, 1173790, Enabling Grant #402703). S.T.N. is supported by funding through the FightMND Mid-Career Fellowship. The Older Australian Twins Study (OATS, used for controls) acknowledges funding from the NHMRC/Australian Research Council Strategic Award (401162) and NHMRC (1405325, 1024224,

1025243, 1045325, 1085606, 568969, 1093083). OATS was facilitated through access to Twins Research Australia, a national resource supported by a NHMRC Centre of Research Excellence Grant (1079102). The Sydney Memory and Ageing Study (Sydney MAS, used for controls) has been funded by three NHMRC Program Grants (350833, 568969, and 1093083). We also acknowledge the OATS and Sydney MAS research teams: https://cheba.unsw.edu.au/research-projects/sydney-memory-and-ageing-study; https://cheba.unsw.edu.au/project/older-australian-twins-study. D.C.W. is supported by a Research Fellowship [APP1155413] from the National Health and Medical Research Council of Australia (NHMRC). The QSkin Study is supported by Grants [APP1185416, APP1073898, APP1063061] from the National Health and Medical Research Council of Australia (NHMRC). Several authors of this publication are members of the Netherlands Neuromuscular Center (NL-NMD) and the European Reference Network for rare neuromuscular diseases EURO-NMD. PJS is supported as an NIHR Senior Investigator and by the Sheffield NIHR Biomedical Research Centre. This is in part an EU Joint Programme - Neurodegenerative Disease Research (JPND) project. The project is supported through the following funding organisations under the aegis of JPND - www.jpnd.eu (United Kingdom, Medical Research Council (MR/L501529/1; MR/R024804/1) and Economic and Social Research Council (ES/L008238/1)) and through the Motor Neurone Disease Association. This study represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. A.A-C is supported by an NIHR Senior Investigator Award. Samples used in this research were in part obtained from the UK National DNA Bank for MND Research, funded by the MND Association and the Wellcome Trust. We would like to thank people with MND and their families for their participation in this project. We acknowledge sample management undertaken by Biobanking Solutions funded by the Medical Research Council at the Centre for Integrated Genomic Medical Research, University of Manchester. L.H.v.d.B. reports grants from The Netherlands Organization for Health Research and Development (Vici scheme), grants from The European Community's Health Seventh Framework Programme (grant agreement n° 259867 (EuroMOTOR)), grants from The Netherlands Organization for Health Research and Development) the STRENGTH project, funded through the EU Joint Programme – Neurodegenerative Disease Research, JPND). This project has received funding from the European Research Council (ERC) under the European

Union's Horizon 2020 research and innovation programme (grant agreement n° 772376 – EScORIAL). The collaboration project is co-funded by the PPP Allowance made available by Health~Holland, Top Sector Life Sciences & Health, to stimulate public-private partnerships. This study was supported by the ALS Foundation Netherlands.

GWAS of frontotemporal dementia and its subtypes by the International Multiple Sclerosis Genetics Consortium (IMSGC)

The summary statistics were requested from IMSGC (https://imsgc.net/?page_id=31). We thank the Biorepository Facility and the Center for Genome Technology laboratory personnel (specifically S. West, S. Clarke, D. Martinez, and P. Whitehead) within the John P. Hussman Institute for Human Genomics at the University of Miami for centralized DNA handling and genotyping for this project. The IMSGC acknowledges W. Edgerly and L. Edgerly, J. Carlos and E. Carlos, M. Crowninshield, and W. Fowler and C. Fowler, whose enduring commitments were critical in creation of the Consortium. We thank the volunteers from the Oxford Biobank (www.oxfordbiobank.org.uk) and the Oxford National Institute for Health Research (NIHR) Bioresource for their participation. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health, German Ministry for Education and Research, German Competence Network MS (BMBF KKNMS). This investigation was supported in part by grants from the National MS Society (NMSS) to A.J.I. on behalf of the International MS Genetics Consortium (RG 4198-A-1 and AP-3758-A-16). Other grants include a Harry Weaver Neuroscience Scholar Award from the NMSS to P.L.D. (JF2138A1) as well as NIH grants RC2 GM093080 and R01AG036836. This work was also supported by a postdoctoral fellowship from the National Multiple Sclerosis Society (FG 1938-A-1) and a Career Independence Award from the National Multiple Sclerosis Society (TA 3056-A-2) to N.A.P. and National Multiple Sclerosis Society award AP3758-A-16. N.A.P. has been supported by Harvard NeuroDiscovery Center and an Intel Parallel Computing Center award, the U.S. National Multiple Sclerosis Society (grants RG 4680-A-1), and the NIH/NINDS (grant R01NS096212). T.A. was supported by the German Federal Ministry of Education and Research (BMBF) through the Integrated Network IntegraMent, under the auspices of the e:Med Programme (01ZX1614J), Swedish Medical Research Council; Swedish Research Council for Health, Working Life and Welfare, Knut and Alice Wallenberg Foundation, AFA insurance, Swedish Brain

Foundation, and the Swedish Association for Persons with Neurological Disabilities. This study makes use of data generated as part of the Wellcome Trust Case Control Consortium 2 project (085475/B/08/Z and 085475/Z/08/Z), including data from the British 1958 Birth Cohort DNA collection (funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02) and the UK National Blood Service controls (funded by the Wellcome Trust). The study was supported by the Cambridge NIHR Biomedical Research Centre, UK Medical Research Council (G1100125), and the UK MS society (861/07); NIH/NINDS: R01 NS049477, NIH/NIAID: R01 AI059829, NIH/NIEHS: R01 ES0495103; Research Council of Norway grant 196776 and 240102; NINDS/NIH R01NS088155; Oslo MS association and the Norwegian MS Registry and Biobank and the Norwegian Bone Marrow Registry; Research Council KU Leuven, Research Foundation Flanders; AFM, AFM-Généthon, CIC, ARSEP, ANR-10-INBS-01 and ANR-10-IAIHU-06; Research Council KU Leuven, Research Foundation Flanders; Inserm ATIP-Avenir Fellowship and Connect-Talents Award; German Ministry for Education and Research, German Competence Network MS (BMBF KKNMS); and Dutch MS Research Foundation. TwinsUK is funded by the Wellcome Trust, Medical Research Council, European Union, the NIHR-funded BioResource, Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London. The recall process was supported by the NIHR Oxford Biomedical Research Centre Programme; Italian Foundation of Multiple Sclerosis (FISM grants, Special Project "Immunochip" 2011/R/1, 2015/R/10); NMSS (RG 4680A1/1); and the MultipleMS EU project. We acknowledge the Lundbeck Foundation and Benzon Foundation for support (THP). This research was supported by grants from the Danish Multiple Sclerosis Society, the Danish Council for Strategic Research [grant 2142-08-0039], Novartis, Biogen (Denmark) A/S, the Sofus Carl Emil Friis og Hustru Olga Doris Friis Foundation, and the Foundation for Research in Neurology. The Observatoire Français de la Sclérose en Plaques (OFSEP) is supported by a grant provided by the French government and handled by the Agence Nationale de la Recherche, within the framework of the Investments for the Future program, under the reference ANR-10-COHO-002, by the Eugène Devic EDMUS Foundation against multiple sclerosis, and by the ARSEP Foundation.

GWAS of Parkinson's disease by the International Parkinson's Disease Genomics Consortium

(IPDGC)

GWAS summary statistics for the post-Chang 23andMe dataset and 23andMe summary statistics included in the studies of Chang and colleagues and Nalls and colleagues will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Interested investigators should visit http://research.23andme.com/dataset-access to submit a request. An immediately accessible version of the summary statistics is available online, excluding Nalls and colleagues, 23andMe post-Chang and colleagues and Web-Based Study of Parkinson's Disease but including all analysed SNPs (https://bit.ly/2ofzGrk). After approval from 23andMe, the full summary statistics including all analysed SNPs and samples in this GWAS meta-analysis will be accessible to approved researchers. Underlying participant level International Parkinson's Disease Genomics Consortium data are available to potential collaborators, please contact ipdgc.contact@gmail.com. We would like to thank all of the subjects who donated their time and biological samples to be a part of this study. This work was supported in part by the Intramural Research Programs of the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), and the National Institute of Environmental Health Sciences both part of the National Institutes of Health, Department of Health and Human Services; project numbers 1ZIANS003154, Z01-AG000949-02 and Z01-ES101986. In addition this work was supported by the Department of Defense (award W81XWH-09-2-0128), and The Michael J Fox Foundation for Parkinson's Research. John Hardy's contribution was in part supported by MR/N026004/1. This work was supported by National Institutes of Health grants R01NS037167, R01CA141668, P50NS071674, American Parkinson Disease Association (APDA); Barnes Jewish Hospital Foundation; Greater St Louis Chapter of the APDA. The KORA (Cooperative Research in the Region of Augsburg) research platform was started and financed by the Forschungszentrum für Umwelt und Gesundheit, which is funded by the German Federal Ministry of Education, Science, Research, and Technology and by the State of Bavaria. This study was also funded by the German Federal Ministry of Education and Research (BMBF) under the funding code 031A430A, the EU Joint Programme - Neurodegenerative Diseases Research (JPND) project under the aegis of JPND -www.jpnd.eu- through Germany, BMBF, funding code 01ED1406 and iMed - the Helmholtz Initiative on Personalized Medicine. This study is funded by the German National Foundation grant (DFG SH599/6-1) (grant to M.S), Michael J

Fox Foundation, and MSA Coalition, USA (to M.S). The French GWAS work was supported by the French National Agency of Research (ANR-08-MNP-012). This study was also funded by France-Parkinson Association, Fondation de France, the French program “Investissements d’avenir” funding (ANR-10-IAIHU-06) and a grant from Assistance Publique-Hôpitaux de Paris (PHRC, AOR08010) for the French clinical data. This study was also sponsored by the Landspitali University Hospital Research Fund (grant to SSv); Icelandic Research Council (grant to SSv); and European Community Framework Programme 7, People Programme, and IAPP on novel genetic and phenotypic markers of Parkinson’s disease and Essential Tremor (MarkMD), contract number PIAP-GA-2008-230596 MarkMD (to HP and JHu). Institutional research funding IUT20-46 was received of the Estonian Ministry of Education and Research (SK). Finnish exome sequencing study was partly funded by Sigrid Juselius Foundation. This study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, Md. (http://biowulf.nih.gov), and DNA panels, samples, and clinical data from the National Institute of Neurological Disorders and Stroke Human Genetics Resource Center DNA and Cell Line Repository. People who contributed samples are acknowledged in descriptions of every panel on the repository website. We thank the French Parkinson’s Disease Genetics Study Group and the Drug Interaction with genes (DIGPD) study group: Y Agid, M Anheim, F Artaud, A-M Bonnet, C Bonnet, F Bourdain, J-P Brandel, C BrefelCourbon, M Borg, A Brice, E Broussolle, F Cormier-Dequaire, J-C Corvol, P Damier, B Debilly, B Degos, P Derkinderen, A Destée, A Dürr, F Durif, A Elbaz, D Grabli, A Hartmann, S Klebe, P. Krack, J Kraemmer, S Leder, S Lesage, R Levy, E Lohmann, L Lacomblez, G Mangone, L-L Mariani, A-R Marques, M Martinez, V Mesnage, J Muellner, F Ory-Magne, F Pico, V PlantéBordeneuve, P Pollak, O Rascol, K Tahiri, F Tison, C Tranchant, E Roze, M Tir, M Vérin, F Viallet, M Vidailhet, A You. We also thank the members of the French 3C Consortium: A Alpérovitch, C Berr, C Tzourio, and P Amouyel for allowing us to use part of the 3C cohort, and D Zelenika for support in generating the genome-wide molecular data. We thank P Tienari (Molecular Neurology Programme, Biomedicum, University of Helsinki), T Peuralinna (Department of Neurology, Helsinki University Central Hospital), L Myllykangas (Folkhalsan Institute of Genetics and Department of Pathology, University of Helsinki), and R Sulkava (Department of Public Health and General Practice Division of Geriatrics, University of Eastern Finland) for the Finnish controls (Vantaa85+ GWAS data). We used genome-wide

association data generated by the Wellcome Trust Case-Control Consortium 2 (WTCCC2) from UK patients with Parkinson's disease and UK control individuals from the 1958 Birth Cohort and National Blood Service. Genotyping of UK replication cases on ImmunoChip was part of the WTCCC2 project, which was funded by the Wellcome Trust (083948/Z/07/Z). UK population control data was made available through WTCCC1. This study was supported by the Medical Research Council and Wellcome Trust disease centre (grant WT089698/Z/09/Z to NW, JHa, and ASc). As with previous IPDGC efforts, this study makes use of data generated by the Wellcome Trust Case-Control Consortium. A full list of the investigators who contributed to the generation of the data is available from www.wtccc.org.uk. Funding for the project was provided by the Wellcome Trust under award 076113, 085475 and 090355. This study was also supported by Parkinson's UK (grants 8047 and J-0804) and the Medical Research Council (G0700943 and G1100643). Sequencing and genotyping done in McGill University was supported by grants from the Michael J Fox Foundation, the Canadian Consortium on Neurodegeneration in Aging (CCNA), the Canada First Research Excellence Fund, awarded to McGill University for the Healthy Brains for Healthy Lives (HBHL) program. The access to part of the participants in the McGill cohort has been made possible thanks to the Quebec Parkinson's Network (http://rpq-qpn.ca/en/). Ziv GanOr is supported by the FRQS Chercheurs-boursiers Award, granted by the Fonds de recherche du Québec – Santé (FRQS) and Parkinson's Quebec. We thank Jeffrey Barrett and Jason Downing for assistance with the design of the ImmunoChip and NeuroX arrays. DNA extraction work that was done in the UK was undertaken at University College London Hospitals, University College London, who received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding. This study was supported in part by the Wellcome Trust/Medical Research Council Joint Call in Neurodegeneration award (WT089698) to the Parkinson's Disease Consortium (UKPDC), whose members are from the UCL Institute of Neurology, University of Sheffield, and the Medical Research Council Protein Phosphorylation Unit at the University of Dundee. We thank the Quebec Parkinson's Network (http://rpq-qpn.org) and its members. This work was supported by the Medical Research Council grant MR/N026004/1. The Braineac project was supported by the MRC through the MRC Sudden Death Brain Bank Grant (MR/G0901254) to J.H. P.A.L. was supported by the MRC (grants MR/N026004/1 and MR/L010933/1) and Michael J. Fox Foundation for Parkinson's Research. D.T. was supported by

the King Faisal Specialist Hospital and Research Centre, Saudi Arabia, and the Michael J. Fox Foundation for Parkinson's Research and MRC grant (MR/N026004/1). Lasse Pihlstrøm is supported by the Norwegian Health Association and Michael J. Fox Foundation. Mathias Toft is supported by the Research Council of Norway and the South-Eastern Norway Regional Health Authority. We thank Ole Andreassen and the DemGene consortium, Norway for genotyping of the Oslo cohort. Mike A. Nalls' participation is supported by a consulting contract between Data Tecnica International and the National Institute on Aging, NIH, Bethesda, MD, USA, as a possible conflict of interest Dr. Nalls also consults for SK Therapeutics Inc, Lysosomal Therapeutics Inc, the Michael J. Fox Foundation and Vivid Genomics among others. Joshua M. Shulman was supported by Huffington Foundation, the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, and a Career Award for Medical Scientists from the Burroughs Wellcome Fund. The Baylor College of Medicine and University of Maryland replication cohorts were made possible in part due to assistance from Amanda Stillwell, Christina Griffin, Katrina Schrader, and Weidong Le with sample collection, preparation, and handling. Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. PPMI – a public-private partnership – is funded by The Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbvie, Allergan, Avid Radiopharmaceuticals, Biogen, BioLegend, Bristol-Myers Squibb, Denali, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Roche, Sanofi, Servier, Takeda, Teva, and UCB. . The SGPD's contribution was supported by the Australian Research Council (ARC) (DP160102400) and the Australian National Health and Medical Research Council (NHMRC) (1078037,1078901, 1103418, 1107258, 1127440, 1113400). Support also came from ForeFront, a large collaborative research group dedicated to the study of neurodegenerative diseases and funded by the NHMRC (Program Grant 1132524, Dementia Research Team Grant 1095127, NeuroSleep Centre of Research Excellence 1060992) and ARC (Centre of Excellence in Cognition and its Disorders Memory Program CE10001021). Simon Lewis was supported by an NHMRC-ARC Dementia Fellowship (1110414) and Glenda Halliday was supported by an NHMRC Fellowship (1079679). The Queensland Parkinson's Project (QPP) was supported by a grant from the Australian National Health and Medical Research Council (1084560) to George Mellick. The New Zealand Brain

Research Institute (NZBRI) cohort was funded by a University of Otago Research Grant, together with financial support from the Jim and Mary Carney Charitable Trust (Whangarei, New Zealand). We thank Allison Miller for processing and handling of NZBRI samples. Additional support was given by The Mater Foundation.

GWAS of frontotemporal dementia and its subtypes by the International FTD-Genetics Consortium (IFGC)

The International FTD-Genetics Consortium (IFGC) shares the summary results data to allow other researchers to explore variants and/or loci for hypothesis driven work (https://ifgcsite.wordpress.com/data-access/). Intramural funding from the National Institute of Neurological Disorders and Stroke (NINDS) and National Institute on Aging (NIA), the Wellcome/MRC Centre on Parkinson's disease, Alzheimer's Research UK (ARUK, Grant ARUK-PG2012-18), and by the offi ce of the Dean of the School of Medicine, Department of Internal Medicine, at Texas Tech University Health Sciences Center. We thank Mike Hubank and Kerra Pearce at the Genomic core facility at the Institute of Child Health (ICH), UCL, for assisting RF in doing Illumina genotyping experiments (FTD-GWAS genotyping). The work done by the North American Brain Expression Consortium (NABEC) was supported in part by the Intramural Research Program of the National Institute on Aging, National Institutes of Health, part of the US Department of Health and Human Services (project number ZIA AG000932-04), and by a Research Grant from the Department of Defense (W81XWH-09-2-0128). Work done by the UK Brain Expression Consortium (UKBEC) was supported by the MRC through the MRC Sudden Death Brain Bank (CS), by a Project Grant (G0901254 to JH and MW), and by a Fellowship award (G0802462 to MR). DT was supported by the King Faisal Specialist Hospital and Research Centre, Saudi Arabia. Computing facilities used at King's College London were supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. We thank AROS Applied Biotechnology AS company laboratories and Aff ymetrix for their valuable input. JBJK was supported by the National Health and Medical Resarch Council (NHMRC), Australia (project grants 510217 and 1005769). CDS was supported by NHMRC (project grants 630428 and 1005769). PRS was supported by NHMRC (project grants 510217 and 1005769) and acknowledges that DNA samples were prepared

by Genetic Repositories Australia, supported by NHMRC Enabling Grant 401184. GMH was supported by NHMRC Research Fellowship 630434, Project Grant 1029538, and Program Grant 1037746. JRH was supported by the Australian Research Council Federation Fellowship, NHMRC Project Grant 1029538 and NHMRC Program Grant 1037746. OP was supported by NHMRC Career Development Fellowship 1022684, Project Grant 1003139. IH, AR, and MB acknowledge the patients and controls who participated in this project and the Trinitat Port-Carbó (deceased) and her extended family who are supporting Fundació ACE research programmes. CC was supported by Grant P30-NS069329-01 and acknowledges that the recruitment and clinical characterisation of research participants at Washington University were supported by NIH P50 AG05681, P01 AG03991, and P01 AG026276. LB and GB were supported by the Ricerca Corrente, Italian Ministry of Health. RG was supported by Fondazione CARIPLO 2009-2633, Ricerca Corrente, Italian Ministry of Health. GF was supported by Fondazione CARIPLO 2009–2633. ES was supported by the Italian Ministry of Health. CF was supported by Fondazione Cariplo. MS was supported from the Italian Ministry of Health (Ricerca Corrente). MLW was supported by Government funding of clinical research within NHS Sweden (ALF). KN was supported by Thure Carlsson Foundation. CN was supported by Swedish Alzheimer Fund. IRAM and GYRH were supported by CIHR (grant 74580) PARF (grant C06-01). JG was supported by the NINDS intramural research funds for FTD research. CMM was supported by Medical Research Council UK, Brains for Dementia Research, Alzheimer's Society, Alzheimer's Research UK, National Institutes for Health Research, Department of Health, and Yvonne Mairy Bequest, and acknowledges that tissue samples made available for this study were provided by the Newcastle Brain Tissue Resource, which was funded in part by grants G0400074 and G1100540 from the UK MRC, the Alzheimer's Research Trust and Alzheimer's Society through the Brains for Dementia Research Initiative and an NIHR Biomedical Research Centre Grant in Ageing and Health, and NIHR Biomedical Research Unit in Lewy Body Disorders. CMM was supported by the UK Department of Health and Medical Research Council and the Research was supported by the National Institute for Health Research Newcastle Biomedical Research Centre based at Newcastle Hospitals Foundation Trust and Newcastle University and acknowledges that the views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. JA was supported by MRC, Dunhill Medical Trust, and Alzheimer's Research UK. TDG was supported by Wellcome Trust Senior Clinical Fellow. IGM

was supported by NIHR Biomedical Research Centre and Unit on Ageing Grants and acknowledges the National Institute for Health Research Newcastle Biomedical Research Centre based at Newcastle Hospitals Foundation Trust and Newcastle University. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. AJT was supported by Medical Research Council, Alzheimer's Society, Alzheimer's Research UK, and the National Institutes for Health Research. EJ was supported by NIHR and Newcastle Biomedical Research Centre. PP, CR, SOC, and EA were supported partially by FIMA (Foundation for Applied Medical Research). PP acknowledges Manuel Seijo-Martínez (Department of Neurology, Hospital do Salnés, Pontevedra, Spain) and Ramon Rene, Jordi Gascon, and Jaume Campdelacreu (Department of Neurology, Hospital de Bellvitge, Barcelona, Spain) for providing FTD DNA samples. RP, JDS, PA, AK, and AD were supported by the German Federal Ministry of Education and Research (BMBF; grant number FKZ 01GI1007A— German FTLD consortium). IR was supported by Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) of Italy. PStG-H was supported by the Canadian Institutes of Health Research, Wellcome Trust, Ontario Research Fund. FT was supported by the Italian Ministry of Health (ricerca corrente) and MIUR grant RBAP11FRE9. GR and GG were supported by the Italian Ministry of Health (ricerca corrente). JBR was supported by Cambridge NIHR Biomedical Research Centre and Wellcome Trust (088324). JU, JC, and SM were supported by the MRC Prion Unit core funding and acknowledge MRC UK, UCLH Biomedical Research Centre, and Queen Square Dementia BRU. SM thanks John Beck, Tracy Campbell, Gary Adamson, Ron Druyeh, Jessica Lowe, and Mark Poulter. AD thanks Benedikt Bader, Manuela Neumann, Sigrun Roeber, Thomas Arzberger, and Hans Kretzschmar (deceased). VMVD and JQT were supported by grants AG032953, AG017586 and AG010124. MG was supported by Grants AG032953, AG017586, AG010124, and NS044266. VMVD thanks EunRan Suh for assistance with sample handling and Elisabeth McCarty-Wood for help in selection of patients. JQT thanks Terry Schuck, John Robinson, and Kevin Raible for assistance with neuropathological assessment of patients. CVB and the Antwerp site were in part funded by the MetLife Foundation Award for Medical Research (to CVB), the Belgian Science Policy Offi ce Interuniversity Attraction Poles programme; the Foundation for Alzheimer Research (SAO-FRA); the Medical Foundation Queen Elisabeth; the Flemish Government Methusalem Excellence award (to CVB); the Research Foundation Flanders (FWO); and the University of Antwerp Research Fund.

JvdZ holds a postdoctoral fellowship of the FWO. CVB and the Antwerp site authors thanks neurologists S Engelborghs, P P De Deyn, A Sieben, and Rik Vandenberghe and neuropathologist J J Martin for the clinical and pathological diagnoses. Isabelle Leber and Alexis Brice were supported by the programme Investissements d'avenir ANR-10-IAIHU-06 and acknowledges the contribution of The French Research Network on FTLD/FTLD-ALS for the contribution in samples collection. BN, SS, SB, and IP were supported by Prin 2010-prot.2010PWNJXK; Cassa di Rispario di Firenze e Cassa di Risparmio di Pistoia e Pescia. JEN was supported by the Novo Nordisk Foundation, Denmark. MR was supported by the German National Genome Network (NGFN) and the German Ministry for Education and Research Grant Number 01GS0465. JDR, MNR, NCF, and JDW were supported by an MRC programme grant, the NIHR Queen Square Dementia Biomedical Research Unit and the Leonard Wolfson Experimental Neurology Centre. MGS was supported by MRC grant n G0301152, Cambridge Biomedical Research Centre, and thanks K Westmore for extracting DNA. HM was supported by the Motor Neuron Disease Association (Grant 6057). RR was supported by P50 AG016574, R01 NS080882, R01 NS065782, P50 NS72187, and the Consortium for Frontotemporal Dementia. DWD was supported by P50NS072187, P50AG016574, State of Florida Alzheimer Disease Initiative, and CurePSP Inc. NRGR, JEP, RCP, DK, and BFB were supported by P50 AG016574. KAJ was supported by R01 AG037491. WWS was supported by NIH AG023501, AG019724, Consortium for Frontotemporal Dementia Research. BLM was supported by P50AG023501, P01AG019724, Consortium for FTD Research. HR was supported by AG032306. JCvS was supported by Stichting Dioraphte Foundation (11 02 03 00), Nuts Ohra Foundation (0801-69), Hersenstichting Nederland (BG 2010-02), and Alzheimer Nederland. CG and HHC acknowledge families, patients, clinicians including Inger Nennesmo and Vesna Jelic, Laura Fratiglioni for control samples and Jenny Björkström, Håkan Thonberg, Charlotte Forsell, Anna-Karin Lindström, and Lena Lilius for sample handling. CG was supported by Swedish Brain Power (SBP), the Strategic Research Programme in Neuroscience at Karolinska Institutet (StratNeuro), the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, Swedish Alzheimer Foundation, Swedish Research Council, Karolinska Institutet PhDstudent funding, King Gustaf V, and Queen Victoria's Free Mason Foundation. FP, AR, VD, and FL acknowledge Labex DISTALZ. RF acknowledges the help and support of June Howard at the Texas Tech University Health Sciences Center Office of Sponsored

Programs for tremendous help in managing Material Transfer Agreement at TTUHSC.

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KEY RESOURCES TA

Resource Type	Specific Reagent or Resource	Source or Reference
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.
Antibody	NA	NA
Bacterial or Viral Strain	NA	NA
Biological Sample	NA	NA
Cell Line	NA	NA
Chemical Compound or Drug	NA	NA
Commercial Assay Or Kit	NA	NA
Deposited Data; Public Database	Phenome-wide GWAS summary data	MRC IEU OpenGWAS Project
Deposited Data; Public Database	Blood pQTL database	PhenoScanner
Deposited Data; Public Database	Dorsolateral prefrontal cortex pQTL	ROSMAP;10.1038/s41588-020-00773-z
Deposited Data; Public Database	Dorsolateral prefrontal cortex pQTL (controls only)	ROSMAP;10.1016/j.ajhg.2021.01.012
Deposited Data; Public Database	Dorsolateral prefrontal cortex pQTL	BANNER;10.1016/j.ajhg.2021.01.012
Deposited Data; Public Database	Parietal lobe cortex pQTL	WU;10.1038/s41593-021-00886-6
Deposited Data; Public Database	Plasma pQTL	INTERVAL;10.1038/s41586-018-0175-2
Deposited Data; Public Database	Plasma pQTL	KORA;10.1038/ncomms14357
Deposited Data; Public Database	Serum pQTL	AGES Reykjavik;10.1126/science.aaq1327
Deposited Data; Public Database	Whole blood eQTL	GTEx;10.1038/nature24277
Deposited Data; Public Database	Alzheimer’s disease GWAS summary statistics	UKB, ADGC, CHARGE, EADI;10.1038/s41588-
Deposited Data; Public Database	Amyotrophic lateral sclerosis GWAS summary statistics	Project MinE;10.1038/s41588-021-00973-1
Deposited Data; Public Database	Frontotemporal dementia GWAS summary statistics	IFGC;10.1016/S1474-4422(14)70065-1

Deposited Data; Public Database	Lewy body dementia GWAS summary statistics	NA;10.1038/s41588-021-00785-3
Deposited Data; Public Database	Multiple sclerosis GWAS summary statistics	IMSGC;10.1126/science.aav7188
Deposited Data; Public Database	Parkinson’s disease GWAS summary statistics	IPDGC;10.1016/S1474-4422(19)30320-5
Genetic Reagent	NA	NA
Organism/Strain	NA	NA
Peptide, Recombinant Protein	NA	NA
Recombinant DNA	NA	NA
Sequence-Based Reagent	NA	NA
Software; Algorithm	R software v4.0.2.	Bell Laboratories
Transfected Construct	NA	NA
Other	NA	NA

ABLE

Identifiers	Additional Information
Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
NA	
NA	
NA	
NA	
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NA	
https://gwas.mrcieu.ac.uk/	
http://www.phenoscanner.medschl.cam.ac.uk/	
https://adknowledgeportal.org/	
https://adknowledgeportal.org/	
https://adknowledgeportal.org/	
NA	
http://www.phpc.cam.ac.uk/ceu/proteins/	
NA	
NA	
https://cnsgenomics.com/software/smr/#eQTLsummarydata	
https://www.ebi.ac.uk/gwas/studies/GCST90012877	
https://www.projectmine.com/research/download-data/	
https://ifgcsite.wordpress.com/data-access/	

https://www.ebi.ac.uk/gwas/studies/GCST90001390	
https://imsgc.net/?page_id=31	
https://bit.ly/2ofzGrk	
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Neurodegenerative diseases are among the most prevalent and devastating neurological disorders, but few effective prevention and treatment strategies are available. Through integrating genetic and proteomic data, Ge et al. systematically screened and validated the causal relationships between proteomes and risks of neurodegenerative diseases and assessed the safety and druggability of targets. They prioritized 22 potential targets associated with lifetime risks of neurodegenerative diseases. These findings will facilitate the development of novel drugs for neurodegenerative diseases.