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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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 pathophysologies 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, \( n_{\text{cases}} = 75,024 \), \( n_{\text{controls}} = 397,844 \)) (14), Parkinson’s disease (PD, \( n_{\text{cases}} = 33,674 \), \( n_{\text{controls}} = 449,056 \)) (15), amyotrophic lateral sclerosis (ALS, \( n_{\text{cases}} = 27,205 \), \( n_{\text{controls}} = 110,881 \)) (16), multiple sclerosis (MS, \( n_{\text{cases}} = 14,802 \), \( n_{\text{controls}} = 26,703 \)) (17), frontotemporal dementia (FTD, \( n_{\text{cases}} = 2,154 \), \( n_{\text{controls}} = 4,308 \)) (18), and Lewy body dementia (LBD, \( n_{\text{cases}} = 2,981 \), \( n_{\text{controls}} = 2,173 \)) (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 neurodegenerative 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, \( P = 1.46 \times 10^{-21} \), PP.H4 = 69.6%; GRN, OR = 0.83, \( P = 2.99 \times 10^{-6} \), PP.H4 = 99.5%; CD33, OR =
1.06, \( P = 3.69 \times 10^{-5} \), PP.H4 = 99.8%; RET, OR = 1.18, \( P = 7.87 \times 10^{-5} \), PP.H4 = 74.7%). Notably, we
observed high heterogeneity (\( P = 1.64 \times 10^{-5} \)) and pleiotropy (\( P = 5.54 \times 10^{-4} \)) 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, \( P = 1.80 \times 10^{-7} \), PP.H4 = 55.6%) and FCGR2A (OR = 1.06, \( P = 4.72 \times 10^{-5} \), PP.H4 = 92.4%) for PD,
and FCRL3 (OR = 0.83, \( P = 8.93 \times 10^{-4} \), PP.H4 = 94.1%), MAPK3 (OR = 0.56, \( P = 4.94 \times 10^{-6} \), PP.H4 =
71.4%), AHSG (OR = 0.88, \( P = 2.37 \times 10^{-5} \), PP.H4 = 96.4%), and LMAN2 (OR = 1.56, \( P = 7.19 \times 10^{-5} \),
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, \( P = 1.03 \times 10^{-8} \), 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.

236 Consistency of results within and across brain and blood

237 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, \( P = 1.80 \times 10^{-7} \), PP.H4 = 95.0%). Other replication analyses for different brain regions were not conducted due to the lack of eligible instrumental variables.

243 The correlation analysis showed robust within-tissue consistency. For MR estimates of all brain proteins, the correlation coefficients were 0.84 (\( P \leq 0.001 \)) and 0.95 (\( P \leq 0.001 \)) between the discovery dataset and two replication datasets (Figure S2). For MR estimates of all blood proteins, the correlation coefficients were 0.75 (\( P \leq 0.001 \)) and 0.72 (\( P \leq 0.001 \)). 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).

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

252 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 α-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 revealed
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.

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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.

<table>
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<tr>
<th>Disease</th>
<th>Protein</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>PP.H4</th>
<th>Druggability</th>
<th>On-target adverse side-effects identified by phe-MR analysis</th>
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<tr>
<td>AD</td>
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<td>SBP↑, DBP↑</td>
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<tr>
<td></td>
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<tr>
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<td>CAD↑, MI↑, lean mass↓</td>
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<td>NA (A)</td>
<td>Hemoglobin↓, lean mass↓</td>
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<tr>
<td></td>
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<td>CP↓, WP↑, MI↑, prostate cancer↑</td>
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<tr>
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<td>Tier 1 (I)</td>
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*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. *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, phenotype-wide Mendelian randomization; PP.H4, posterior probability of colocalization; SBP, systolic blood pressure; WP, walking pace.
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 (r^2<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

B

-\log_{10}(\text{p})

chromosome

-\log_{10}(\text{p})

chromosome
### A

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<th>Multi-cis</th>
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### B

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Figure 4

The diagram illustrates the relationships between various proteins and their causality and safety profiles. The proteins are color-coded to indicate their status and are plotted on a graph with axes for causality and safety. The graph includes proteins such as MAPK3, PSMB3, DGKQ, BIN1, RET, GPNMB, SARM1, DHRS11, CD38, LMAN2, SEC23IP, FAM120B, SHMT1, GPNMB, MAP1S, GRN, ACE, SLC20A2, ICA1L, TOM1L2, and others.

The legend indicates bold and druggable proteins, as well as brain proteins and blood proteins. The graph also shows the disease associations of AD, ALS, MS, and PD, with specific proteins highlighted in different colors.
SUPPLEMENTARY INFORMATION

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

Ge et al.

Content

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Figure S4. Correlation analysis of MR estimates between brain and blood.......................9

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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 × 10^-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).

**References for Supplementary Methods**


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.
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.
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.
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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 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.

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
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 Coordination team, Operations Team (led by R. Houghton and C. Moore) and Data Management Team (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-
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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
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GWAS of Alzheimer’s disease by Schwartzentruber et al.

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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...
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**GWAS of amyotrophic lateral sclerosis by the Project MinE**

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**Supplement - Other (Excel tables; movies)**

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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.