Hypertension

ORIGINAL ARTICLE

Genetic Dissection of Plasma Proteins and Blood Pressure in Small Vessel Disease

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BACKGROUND: White matter hyperintensities (WMH), a hallmark imaging feature of small vessel disease, are strongly associated with neurodegenerative and cardiovascular conditions.

METHODS: We performed bidirectional and mediation Mendelian randomization analyses using summary statistics from GWAS (genome-wide association studies) of 9 large cohorts of plasma proteins (n=997–35 559), blood pressure (n=1 028 980), and WMH (n=21 381). The inverse-variance-weighted method or Wald ratio was applied as the primary Mendelian randomization approach, with false discovery rate correction and independent replication. We further integrated Mendelian randomization with PheWAS (phenome-wide association studies) to prioritize WMH risk factors and assess mediation via systolic blood pressure and diastolic blood pressure.

RESULTS: Eighteen plasma proteins were genetically associated with WMH, 13 of which were replicated. Thirteen antihypertensive target genes were also linked to WMH burden, including *ADRB3*, *AOC1* (amine oxidase copper containing 1), *SHBG* (sex hormone binding blobulin), and *KCNH2* (potassium voltage-gated channel subfamily H member 2), which influenced both systolic blood pressure and diastolic blood pressure. Mendelian randomization-PheWAS highlighted systolic blood pressure and diastolic blood pressure as the top-ranked WMH risk factors among 21 976 traits. Antihypertensive drug targets, including angiotensin II receptor blockers, β-blockers, calcium channel blockers, and diuretics, were significantly associated with WMH burden. Mediation analysis showed that systolic blood pressure partially mediated TFPI's effect (3.04%), and diastolic blood pressure mediated the effects of ACP1 (acid phosphatase 1) (2.74%) and LAMC1 (laminin subunit gamma 1; 4.94%).

CONCLUSIONS: The findings outline protein- and blood pressure-centered mechanisms in small vessel disease, highlighting proteins and antihypertensive targets as biomarkers and therapeutic entry points for precision intervention. ***(Hypertension.* 2025;83:00–00. DOI: 10.1161/HYPERTENSIONAHA.125.25608.)** • **Supplement Material**.

Key Words: antihypertensive agents ■ blood pressure ■ diuretics ■ Mendelian randomization analysis ■ risk factors

Small vessel disease (SVD) encompasses a group of pathological processes affecting the small arteries, arterioles, venules, and capillaries of the brain, and represents a leading cause of stroke, vascular cognitive impairment, and neurodegeneration in aging populations.[1,2] One of the most widely recognized neuroimaging markers of SVD is white matter hyperintensities (WMH), which appear as hyperintense regions on T2-weighted or FLAIR MRI.[2] Histopathologically, WMH reflect cumulative microvascular damage, including demyelination, gliosis, axonal loss, and interstitial edema.[3,4] WMH, and by extension SVD, are highly prevalent among individuals with vascular risk factors such as hypertension and are independently associated with an increased risk of stroke, cognitive decline, dementia, and all-cause mortality.[5–7] Notably, the progression of SVD-related changes is often clinically silent but biologically active over many

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ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

We systematically assessed circulating plasma proteins and antihypertensive drug targets in relation to white matter hyperintensities (WMH). Eighteen proteins were genetically linked to WMH, with 13 replicated. Mendelian randomization with phenome-wide association studies confirmed systolic and diastolic blood pressure as the strongest risk factors. Thirteen antihypertensive target genes and 4 drug classes were implicated, and mediation analysis showed partial effects via blood pressure.

What Is Relevant?

WMH are a hallmark of cerebral small vessel disease, strongly associated with neurodegenerative and cardiovascular disorders. Hypertension is the most important modifiable risk factor, but no drug class has been proven to halt WMH progression. Prior studies lacked replication and mechanistic insight; our findings provide robust cross-cohort genetic evidence for novel protein and drug targets.

Clinical/Pathophysiological Implications?

These results identify plasma proteins and antihypertensive drugs as potential disease-modifying agents, suggesting actionable pathways for WMH prevention and treatment while advancing mechanistic understanding for future targeted therapies.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ACP1	acid phosphatase 1
ADAM12	ADAM metallopeptidase domain 12
ADRB3	adrenoceptor beta 3
AOC1	amine oxidase copper containing 1
ARB	angiotensin II receptor blocker
ARL3	ARF Like GTPase 3
C2	complement C2
CCB	calcium channel blocker
***cis*-pQTL**	*cis*-acting protein quantitative trait locus
DBP	diastolic blood pressure
FYN	FYN proto-oncogene
GALK1	Src family tyrosine kinase, galactokinase 1
GWAS	genome-wide association studies
HAVCR2	hepatitis A virus cellular receptor 2
HEXIM1	HEXIM P-TEFb complex subunit 1
HEXIM2	HEXIM P-TEFb complex subunit 2
ISG15	ISG15 ubiquitin-like modifier
KCNH2	potassium voltage-gated channel subfamily H member 2
LAMC1	laminin subunit gamma 1
MR	Mendelian randomization
NMT1	N-myristoyltransferase 1
PheWAS	phenome-wide association study
PLXNA1	plexin A1
PMM2	phosphomannomutase 2
SBP	systolic blood pressure
SHBG	sex hormone binding blobulin
SNP	single-nucleotide polymorphism
SVD	small vessel disease
TFPI	tissue factor pathway inhibitor
TRDMT1	TRNA aspartic acid methyltransferase 1
UROS	uroporphyrinogen III synthase
WBP2	WW domain binding protein 2
WMH	white matter hyperintensity

years, highlighting the critical need to uncover causal mechanisms and identify modifiable targets for early intervention and disease modification.

Among the known risk factors, elevated blood pressure, especially systolic blood pressure (SBP), is the most consistently associated and modifiable contributor to SVD progression, particularly WMH burden.[8,9] However, despite the widespread clinical use of antihypertensive agents, no specific drug class has been conclusively shown to halt or reverse SVD-associated white matter injury, and the molecular mechanisms linking blood pressure control to SVD pathophysiology remain insufficiently understood.

Recent advances in large-scale plasma proteomics have enabled high-throughput quantification of thousands of circulating proteins, offering powerful opportunities to elucidate molecular drivers of complex vascular and neurodegenerative phenotypes.[10] When combined with Mendelian randomization (MR), a method that leverages genetic variants as proxies for modifiable exposures such as protein levels, these data sets facilitate robust causal inference while minimizing confounding.[11,12] The incorporation of PheWAS

(phenome-wide association studies) into this framework further expands its utility by enabling systematic evaluation of protein effects across a broad spectrum of clinical traits, thereby improving therapeutic target prioritization and safety profiling.[13] Several proteins, such as TIMD4, FLT4, HEXIM1 (HEXIM P-TEFb complex subunit 1), and KLHL24, have been preliminarily linked to WMH burden using MR-based approaches.[14,15] Nevertheless, prior studies often lacked adequate replication, mechanistic clarity, or cross-cohort validation, limiting their translational relevance.

In the present study, we conducted a comprehensive MR analysis across 9 large-scale plasma proteomic data sets to identify circulating proteins with putative causal effects on WMH burden, serving as an imaging biomarker of SVD, and to investigate the role of blood pressure as both a driver and mediator of this relationship (Figure 1). We report 3 clinically relevant findings. First, we identified 13 plasma proteins that demonstrated robust, replicable causal associations with SVD imaging burden. Second, by integrating MR with PheWAS, we confirmed blood pressure as the top-ranked modifiable determinant of WMH severity and reassessed the therapeutic implications of gene targets from major antihypertensive drug classes. Third, we revealed that the effect of several proteins on WMH may be partially mediated by blood pressure, suggesting a mechanistic bridge between molecular and hemodynamic factors in SVD pathogenesis. Collectively, our findings outline a vascular protein-based framework for understanding the molecular pathophysiology of SVD and highlight actionable targets for early therapeutic intervention aimed at mitigating cerebrovascular injury and vascular cognitive decline.

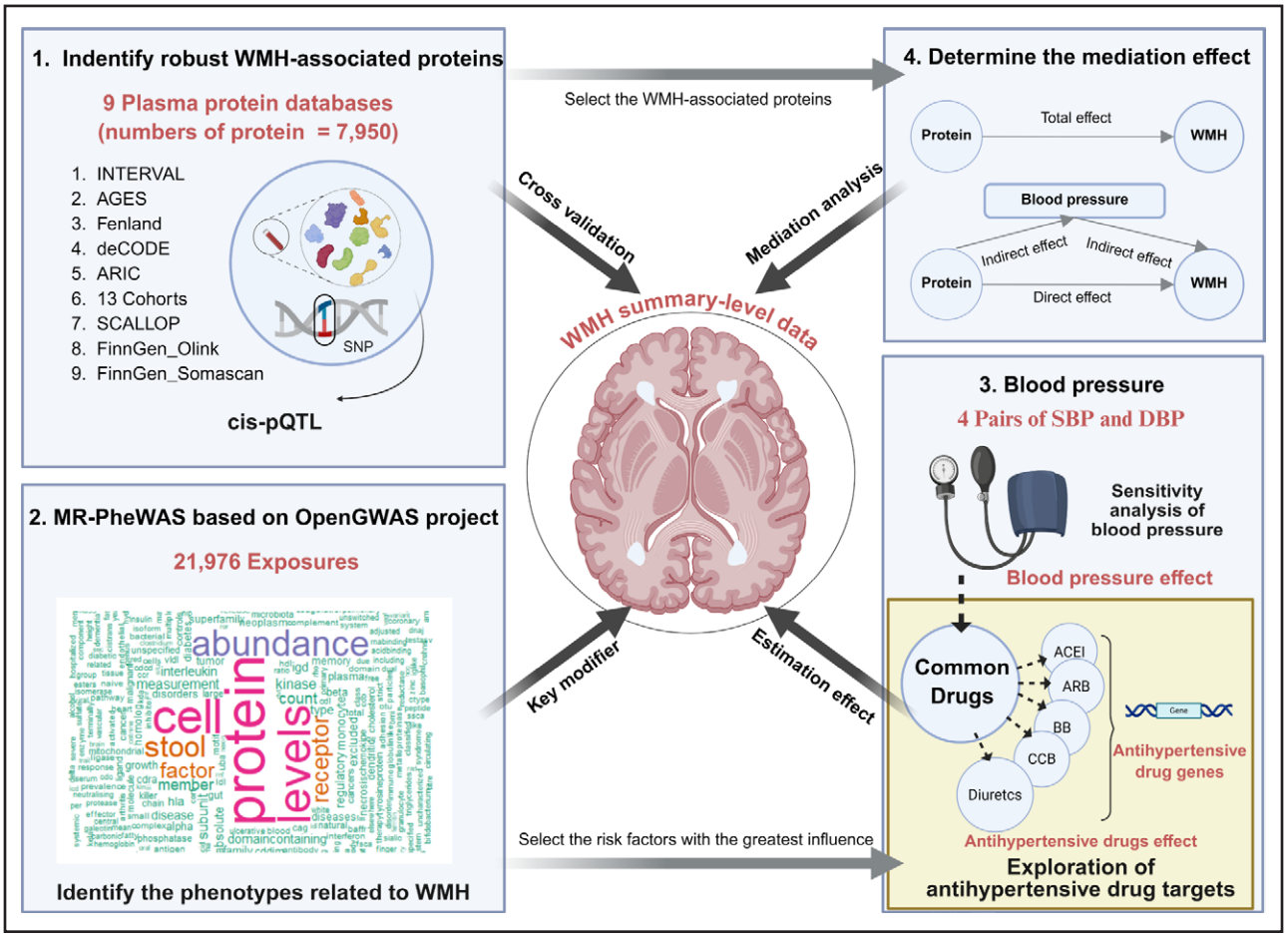

Figure 1. Study overview and workflow.
This study followed a 4-step design. We first conducted *cis*-acting protein quantitative trait locus (*cis*-pQTL) Mendelian randomization (MR) analyses across 9 plasma protein databases to identify proteins associated with white matter hyperintensities (WMH) using cross-validation across multiple large-scale cohorts. We then performed MR-PheWAS (phenome-wide association study; n=21 976) to evaluate the role of blood pressure in WMH. Next, we investigated the effects of blood pressure and assessed whether known antihypertensive drug targets are associated with WMH, aiming to identify potential opportunities for drug repurposing. Finally, we applied a 2-step mediation analysis to determine whether blood pressure mediates the effects of WMH-associated potential proteins on WMH burden. The image used is from the BioRender platform, and the copyright proof ID is PP288OSO3I. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BB, beta blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure; and SNP, single-nucleotide polymorphism.

METHODS

Data Availability

All data and materials have been made publicly available at the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/) and the GWAS Catalog database (https://www.ebi.ac.uk/gwas/). This study was based on publicly available summary-level data from GWAS (genome-wide association studies). Ethics approvals for each original study are detailed in the respective publications. Comprehensive information on all data sets used is provided in Table 1 and Tables S1 and S2. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology Using MR guidelines.[16]

Human Plasma *cis*-Protein Quantitative Trait Locis Data

Plasma proteomic summary statistics were obtained from 9 large-scale European cohorts, using either Olink or SomaScan platforms for protein quantification.[17–25] Protein-coding genes were annotated accordingly. To identify *cis*-acting protein quantitative trait loci (*cis*-pQTLs), we extracted all independent single-nucleotide polymorphisms (SNPs) located within ±1 MB of the corresponding gene and significantly associated with protein levels ($P<5\times10^{-8}$). SNPs were then clumped based on linkage disequilibrium ($R^2<0.001$) and filtered for a minor allele frequency ≥0.01. Furthermore, we re-extracted variants using a±0.5 Mb window, limited to MR associations that remained significant after correction, while keeping all other conditions unchanged.

Summary-Level Data Used in MR-PheWAS Analysis

We conducted an MR-PheWAS to systematically evaluate the causal effects of modifiable risk factors on WMH burden, using 21 976 traits from the IEU OpenGWAS project.[26] Exposures were excluded if they were entirely derived from the UK Biobank, restricted to a single gender, or based on non-European ancestry. This approach enabled an unbiased, large-scale assessment of potential contributors to WMH across a wide range of phenotypes.

Blood Pressure and WMH Summary-Level Data

We compiled the latest large-scale summary-level data from 1 028 980 individuals of European ancestry to evaluate exposure-outcome effects.[27] To assess the robustness of blood pressure-related findings, 3 additional GWAS data sets on systolic and DBP from the IEU OpenGWAS project were included

Table 1. Characteristics of Genome-Wide Association Studies of Phenotypes Included in This Study

Phenotype	Database	Platform	PMID	Population	Sample size	Accession ID
Plasma protein	13 COEA	Olink	33067605	European	21 758	
	AGES	Somascan	30072576	European	5457	
	ARIC	Somascan	35501419	European American	7213	
	deCODE	Somascan	34857953	European	35 559	
	Fenland	Somascan	34648354	European	10 708	
	INTERVAL	Somascan	29875488	European	3301	
	FinnGen	Olink	30111768	European	6861	
	SCALLOP	Olink	37563310	European	14 824	
	FinnGen	Somascan	28240269	European	997	
SBP			30224653	European	757 601	IEU OpenGWAS: ieu-b-38
			33230300	European	810 865	IEU OpenGWAS: ebi-a-GCST90000059
			33230300	European	810 865	IEU OpenGWAS: ebi-a-GCST90000062
			38689001	European	1028,980	GWAS Catalog: GCST90310294
DBP			30224653	European	757 601	IEU OpenGWAS: ieu-b-39
			33230300	European	810 865	IEU OpenGWAS: ebi-a-GCST90000063
			33230300	European	810 865	IEU OpenGWAS: ebi-a-GCST90000066
			38689001	European	1028,980	GWAS Catalog: GCST90310295
WMH	UK Biobank		33875891	European	21 381	GWAS Catalog: GCST90003862

Data are numbers of participants. 13COEA indicates 13 cohorts of EUR; DBP, diastolic blood pressure; PMID, Pubmed Unique Identifier; SBP, systolic blood pressure; and WMH, white matter hyperintensities.

as sensitivity analyses.[28,29] WMH burden was quantified in 21 381 individuals of British ancestry from the UK Biobank.[30] WMH volume was derived as an imaging phenotype from T2 FLAIR MRI scans using the Brain Intensity AbNormality Classification Algorithm pipeline.

Selection of the Genetic Instrumental Variables

For nonprotein phenotypes, SNPs that reached genome-wide significance at $P<5\times10^{-8}$ were selected as instrumental variables. Independent SNPs were identified using a strict linkage disequilibrium threshold ($R^2<0.001$) within a 10 MB window. Exposure and outcome data were harmonized to ensure allele alignment, and palindromic SNPs were excluded. Horizontal pleiotropy was assessed using the MR-PRESSO test, and outlier SNPs ($P<0.05$) were discarded. The remaining set of SNPs was used for MR analysis. Instrument strength was evaluated using *F*-statistics, with $F>10$ indicating strong instruments,[31] more details are provided in the Supplementary Methods.

Statistical Analysis

MR Analysis

The present study used a 2-sample MR design. The inverse-variance-weighted method was used as the primary analysis when multiple instrumental variables were available, while the Wald ratio was applied for single-SNP exposures.[32] Additional MR methods were used for sensitivity analyses to assess the robustness of the findings; further details are provided in the Supplementary Methods.

WMH-Associated Potential Protein Identifying

First, we evaluated the causal association between plasma protein levels and WMH burden. *Cis*-pQTLs from 9 independent data sets were used as exposures, with WMH volume as the outcome. Each data set was analyzed separately and used for cross-validation to ensure robustness. Associations were corrected for multiple testing using the false discovery rate ($P<0.05$), yielding a set of plasma proteins with putative causal effects on WMH.

MR-PheWAS Analysis on WMH

Second, we performed an MR-PheWAS using all available traits from the IEU OpenGWAS data set (https://api.opengwas.io/) to systematically identify modifiable risk factors associated with WMH burden. To identify key modifiable contributors, we ranked exposures based on the minimum *P* values and frequency of significant associations. Notably, SBP and diastolic blood pressure (DBP) consistently exhibited the strongest associations with WMH across the entire phenome-wide scan, supporting their prioritization for further investigation.

Blood Pressure Drug Targets on WMH

Third, we further assessed the causal effects of SBP and DBP on WMH burden and explored the relevance of established antihypertensive drug targets. Genetic instruments for 125 target genes corresponding to commonly prescribed antihypertensive drug classes, including ACE (angiotensin-converting enzyme) inhibitors, ARBs (angiotensin receptor blockers), β-blockers, calcium channel blockers (CCBs), and diuretics, were identified via DrugBank (Table S3). MR was then performed to evaluate the associations between genetically proxied inhibition of these targets and WMH, with statistical significance defined as $P<0.05$.

Mediation Analysis Among Protein, Blood Pressure, and WMH

Furthermore, we performed bidirectional MR to evaluate the relationships between WMH-associated plasma proteins and blood pressure traits, with WMH fixed as the outcome. For mediation analysis, significant associations ($P<0.05$) were required across all 3 components: exposure, mediator, and outcome. Indirect effects and their proportions were estimated using a 2-step MR framework. The mediated (indirect) effect was derived using the product-of-coefficients method, with standard errors estimated via the delta method based on MR-derived estimates. The Sobel test was used to evaluate the proportion of the mediation effect. The proportion of effect mediated was calculated by dividing the indirect effect by the total effect.

Sensitivity Analysis

In the MR analytical pipeline, outlier SNPs were identified and removed using the MR-PRESSO method. Heterogeneity across instruments was assessed with Cochrane's *Q* statistic, and horizontal pleiotropy was evaluated using the MR-Egger intercept. As a supplementary sensitivity test, we repeated the MR analyses of plasma proteins on WMH using a narrower ±0.5 Mb window for defining *cis*-pQTLs, allowing us to assess the consistency of results relative to those obtained under the primary ±1 Mb window. To confirm the directionality of the observed associations among plasma proteins, blood pressure, and WMH, reverse MR analyses were conducted. Given that most blood pressure GWAS data sets were derived from multicohort studies including UK Biobank participants, partial sample overlap may introduce bias in conventional 2-sample MR estimates. To mitigate this, we applied the MRlap approach, which leverages cross-trait LD-score regression to quantify sample overlap and correct instrument bias and inflation due to overlap. Final causal estimates were derived from MRlap-adjusted inverse-variance-weighted models and benchmarked against standard MR estimates for robustness. Additional GWAS data sets for DBP and SBP were used to replicate key findings. All MR analyses were performed using the TwoSampleMR (version 0.6.8) and MRlap (version 0.0.6) packages in R software (version 4.4.2).

RESULTS

Genetically Predicted Plasma Proteins Associated With Imaging Markers of SVD

We identified between 60 and 1729 *cis*-pQTLs per protein across 9 independent European plasma proteomic data sets. After quality control and harmonization, MR analysis revealed 25 significant associations between plasma proteins and the burden of WMH, a canonical imaging marker of SVD, under false discovery rate correction (Figure 2A). Instrument characteristics are detailed in Tables S4 and S5.

From these, 18 plasma proteins demonstrated genetically predicted effects on WMH volume (Table S6).

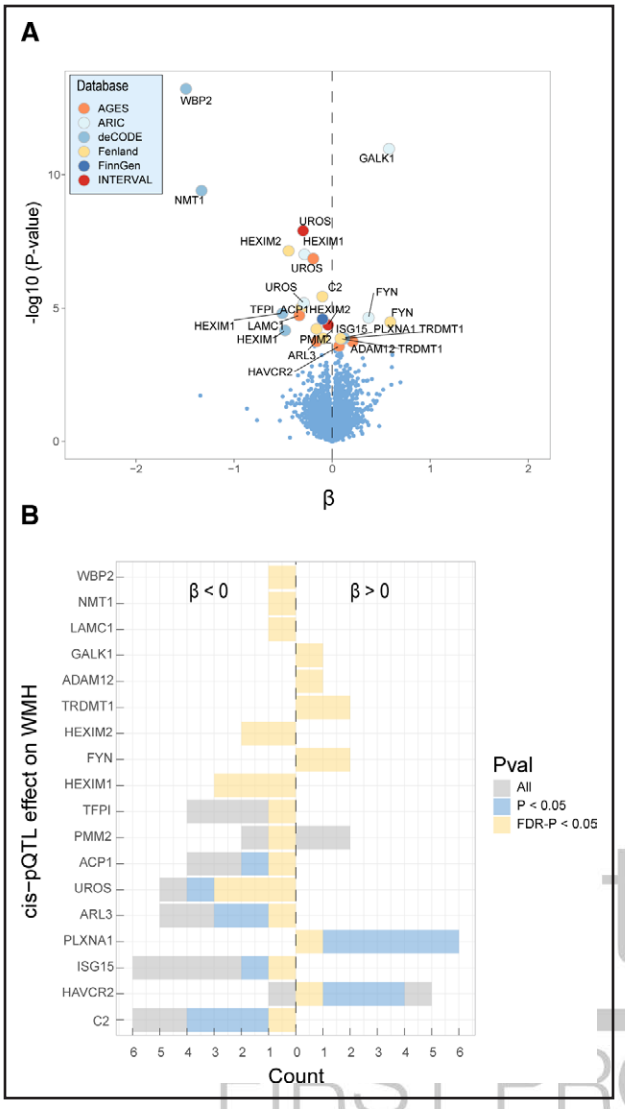

Figure 2. Identification of robust white matter hyperintensities (WMH)-associated potential proteins and robustness analysis.

A, The volcano plot displays Mendelian randomization (MR) results for 7950 plasma proteins in relation to WMH, highlighting proteins with false discovery rate (FDR)-adjusted $P<0.05$. The *x* axis indicates β values, and the *y* axis shows −log10 (*P* values). **B**, A pyramid-style cumulative histogram illustrates the replication of protein-WMH associations across databases, with the *x* axis representing the number of replicated associations and the *y* axis showing the corresponding protein-WMH pairs. *cis*-pQTL indicates *cis*-acting protein quantitative trait locus.

Higher predicted levels of UROS (uroporphyrinogen III synthase), LAMC1 (laminin subunit gamma 1), ARL3 (ARF like GTPase 3), HEXIM1 and HEXIM2 (HEXIM P-TEFb complex subunit 2), WBP2 (WW domain binding protein 2), NMT1 (N-myristoyltransferase 1), C2 (complement C2), ACP1 (acid phosphatase 1), TFPI (tissue factor pathway inhibitor), PMM2 (phosphomannomutase 2), and ISG15 (ISG15 ubiquitin-like modifier) were associated with lower WMH burden. In contrast, elevated genetically proxied expression of ADAM12 (ADAM metallopeptidase domain 12), HAVCR2 (hepatitis A virus cellular receptor 2), PLXNA1 (plexin A1), TRDMT1 (TRNA aspartic acid methyltransferase 1), FYN (FYN proto-oncogene), and GALK1 (Src family tyrosine kinase, galactokinase 1) was associated with increased WMH volume. With a±0.5 Mb *cis*-window, C2 in Fenland lost significance, and other associations remained consistent (Table S7).

To ensure replicability, we conducted cross-data set validation for all 18 proteins, excluding those available in only one cohort (LAMC1, ADAM12, GALK1, WBP2, and NMT1; Figures 2B and 3; Table S8). Thirteen proteins, including UROS, ARL3, HAVCR2, HEXIM1/2, PLXNA1, TRDMT1, C2, FYN, TFPI, PMM2, ISG15, and ACP1, showed consistent associations across independent data sets. For instance, genetically predicted UROS levels were consistently associated with reduced WMH burden across AGES, ARIC, deCODE, and INTERVAL, but not in Fenland. PMM2 demonstrated a protective effect only in the Fenland cohort.

There was no significant heterogeneity across data sets for WMH-associated proteins. However, reverse MR analysis suggested potential bidirectional effects for HEXIM1/2, WBP2, and FYN, warranting cautious interpretation. The remaining 14 proteins showed unidirectional effects with no evidence of reverse causality (Table S9).

MR-PheWAS Identifies Blood Pressure as the Dominant Modifiable Risk Factor for SVD

To comprehensively identify upstream determinants of WMH and SVD, we performed an MR-PheWAS using 21 976 exposures from the IEU OpenGWAS database. A total of 1825 traits were nominally associated with WMH burden; 161 remained significant after false discovery rate correction (Table S10). Among the top 30 traits (*P* values ranging from 1.42×10^{-13} to 1.49×10^{-6}), 10 were directly related to blood pressure, including SBP, DBP, hypertension diagnoses, and use of antihypertensive agents (Figure 4A). These findings underscore elevated blood pressure as the most prominent modifiable determinant of SVD imaging burden and emphasize the potential therapeutic significance of antihypertensive drug targets.

Causal Effects of Blood Pressure and Antihypertensive Drug Targets on SVD

Using the largest available blood pressure GWAS data set, we performed primary MR analyses linking genetically predicted blood pressure traits to WMH volume. Both SBP (β, 0.019 [95% CI, 0.013–0.024]; $P=8.21\times10^{-12}$) and DBP (β, 0.030 [95% CI, 0.022–0.039]; $P=7.86\times10^{-12}$) were significantly associated with increased WMH burden, with no evidence of horizontal pleiotropy. These associations remained

A

Protein	Database	Nsnp	P-value	FDR_P	β (95% CI)
UROS	AGES	1	<0.001	<0.001	−0.193 (−0.265, −0.121)
UROS	ARIC	1	<0.001	0.003	−0.289 (−0.414, −0.163)
UROS	deCODE	4	0.004	0.386	−0.203 (−0.341, −0.066)
UROS	Fenland	2	0.146	0.844	−0.169 (−0.397, 0.059)
UROS	INTERVAL	1	<0.001	<0.001	−0.297 (−0.399, −0.195)
ARL3	AGES	2	<0.001	0.039	−0.159 (−0.243, −0.076)
ARL3	ARIC	3	0.042	0.707	−0.058 (−0.114, −0.002)
ARL3	deCODE	2	0.234	0.924	−0.155 (−0.411, 0.100)
ARL3	Fenland	3	0.040	0.582	−0.088 (−0.171, −0.004)
ARL3	FinnGen_Somascan	1	0.268	0.905	−0.044 (−0.122, 0.034)
HAVCR2	AGES	2	<0.001	0.046	0.070 (0.032, 0.107)
HAVCR2	ARIC	1	<0.001	0.163	0.063 (0.025, 0.100)
HAVCR2	deCODE	17	0.351	0.978	0.029 (−0.032, 0.089)
HAVCR2	Fenland	3	<0.001	0.065	0.059 (0.027, 0.091)
HAVCR2	FinnGen_Olink	1	0.598	0.967	−0.029 (−0.135, 0.078)
HAVCR2	FinnGen_Somascan	1	<0.001	0.107	0.061 (0.026, 0.096)
HEXIM1	ARIC	1	<0.001	<0.001	−0.282 (−0.386, −0.179)
HEXIM1	deCODE	1	<0.001	0.030	−0.481 (−0.717, −0.244)
HEXIM1	Fenland	1	<0.001	0.005	−0.316 (−0.456, −0.176)
HEXIM2	deCODE	1	<0.001	0.009	−0.508 (−0.738, −0.277)
HEXIM2	Fenland	1	<0.001	<0.001	−0.445 (−0.606, −0.283)
PLXNA1	AGES	1	0.005	0.272	0.158 (0.047, 0.268)
PLXNA1	ARIC	1	0.007	0.368	0.066 (0.018, 0.113)
PLXNA1	deCODE	7	<0.001	0.039	0.120 (0.059, 0.182)
PLXNA1	Fenland	1	0.006	0.282	0.139 (0.040, 0.239)
PLXNA1	INTERVAL	1	0.009	0.332	0.111 (0.028, 0.195)
PLXNA1	FinnGen_Somascan	1	0.006	0.300	0.092 (0.026, 0.158)
TRDMT1	deCODE	3	<0.001	0.039	0.122 (0.059, 0.184)
TRDMT1	Fenland	3	<0.001	0.033	0.086 (0.042, 0.131)
GALK1	ARIC	1	<0.001	<0.001	0.580 (0.412, 0.747)

B

Protein	Database	Nsnp	P-value	FDR_P	β (95% CI)
C2	AGES	3	0.183	0.840	−0.026 (−0.037, 0.194)
C2	ARIC	4	0.055	0.731	−0.050 (−0.101, 0.001)
C2	deCODE	6	0.015	0.545	−0.062 (−0.112, −0.012)
C2	Fenland	13	<0.001	0.003	−0.100 (−0.142, −0.058)
C2	FinnGen_Olink	1	0.003	0.260	−0.096 (−0.160, −0.033)
C2	FinnGen_Somascan	1	0.003	0.286	−0.091 (−0.151, −0.031)
ISG15	AGES	1	0.001	0.127	−0.122 (−0.197, −0.047)
ISG15	deCODE	6	0.482	0.978	−0.029 (−0.110, 0.052)
ISG15	Fenland	1	<0.001	0.033	−0.092 (−0.140, −0.045)
ISG15[a]	INTERVAL	1	0.352	0.929	−0.055 (−0.172, 0.061)
ISG15[b]	INTERVAL	1	0.352	0.929	−0.036 (−0.110, 0.039)
ISG15	FinnGen_Somascan	1	0.369	0.911	−0.027 (−0.086, 0.032)
ACP1	ARIC	4	0.095	0.840	−0.044 (−0.095, 0.008)
ACP1	deCODE	12	0.129	0.846	−0.029 (−0.067, 0.009)
ACP1	Fenland	4	0.004	0.277	−0.041 (−0.070, −0.013)
ACP1	INTERVAL	2	<0.001	0.013	−0.042 (−0.062, −0.022)
TFPI	ARIC	1	0.343	0.939	−0.056 (−0.173, 0.060)
TFPI	deCODE	1	0.218	0.918	−0.150 (−0.390, 0.089)
TFPI	Fenland	1	0.343	0.956	−0.084 (−0.258, 0.090)
TFPI	FinnGen_Olink	1	<0.001	0.016	−0.098 (−0.144, −0.053)
PMM2	ARIC	1	0.522	0.966	0.030 (−0.063, 0.123)
PMM2	deCODE	9	0.264	0.950	−0.045 (−0.125, 0.034)
PMM2	Fenland	2	<0.001	0.020	−0.160 (−0.238, −0.082)
PMM2	FinnGen_Somascan	1	0.108	0.780	0.114 (−0.025, 0.253)
FYN	ARIC	1	<0.001	0.008	0.371 (0.199, 0.543)
FYN	Fenland	1	<0.001	0.014	0.593 (0.313, 0.873)
LAMC1	AGES	1	<0.001	0.008	−0.335 (−0.489, −0.182)
WBP2	deCODE	1	<0.001	<0.001	−1.491 (−1.880, −1.102)
NMT1	deCODE	1	<0.001	<0.001	−1.332 (−1.750, −0.915)
ADAM12	AGES	1	<0.001	0.039	0.209 (0.100, 0.319)

Figure 3. Forest plot depicting white matter hyperintensities (WMH)-associated potential proteins across all data sets.
A and **B**, Show the effect estimates of 18 plasma proteins on WMH across different databases. ISG15[a]=ISG15_14148; ISG15[b]=ISG15_14151. The CI lines for GALK1 (Src family tyrosine kinase, galactokinase 1), NMT1 (N-myristoyltransferase 1), and WBP2 (WW domain binding protein 2) are not visible due to their extremely small β values and narrow 95% CIs.

consistent across 3 independent GWAS data sets and were robust to correction for sample overlap using the MRlap method (Table S11). No reverse causal effects of WMH on blood pressure were observed (P>0.05; Table S12).

We next evaluated whether genetically proxied modulation of antihypertensive drug targets influences WMH burden. MR analysis showed that genetically predicted SBP effects of calcium channel blockers CCBs (β, 0.020 [95% CI, 0.007–0.033]) and diuretics (β, 0.013 [95% CI, 0.001–0.024]) were associated with increased SVD imaging burden. For DBP, targets of ARBs (β, 0.049 [95% CI, 0.004–0.094]), β-blocker (β, 0.033 [95% CI, 0.008–0.057]), CCB (β, 0.032 [95% CI, 0.015–0.048]), and diuretics (β, 0.025 [95% CI, 0.010–0.040]) showed significant associations, whereas no such effect was seen for ACE inhibitors (Table 2 and Table S13).

Further gene-level MR analysis identified 9 SBP-associated and 8 DBP-associated drug targets (Tables S14 and S15). Of note, increased genetically predicted expression of *ADRB3* (adrenoceptor beta 3) was linked to lower SBP and DBP, while expression of *KCNH2* (potassium voltage-gated channel subfamily H member 2), *AOC1* (amine oxidase copper containing 1), and *SHBG* (sex hormone binding blobulin) was positively associated with both traits.

Blood Pressure Mediates the Impact of Specific Proteins on SVD Burden

To identify proteins acting upstream of blood pressure in SVD pathogenesis, we conducted 2-step MR mediation analyses using 13 of the previously identified proteins. Forward MR indicated that genetically predicted levels of TFPI, TRDMT1, and ISG15 were associated with lower SBP, while TRDMT1, ACP1, and LAMC1 were inversely associated with DBP (Table S16). Reverse MR showed no bidirectional effects, supporting directionality (Table S17).

Mediation analysis revealed that SBP partially mediated the effect of TFPI on SVD (3.04% of total effect; P=0.01), while DBP mediated the effects of ACP1 (2.74%; P=0.01) and LAMC1 (4.94%; P<0.01; Figure S1; Table S18). Mediation analysis was not performed for TRDMT1 due to inconsistent directionality of effects. These results suggest that blood pressure may function as a key mechanistic conduit linking protein expression to small vessel damage in the brain.

DISCUSSION

SVD is a major contributor to stroke and vascular cognitive impairment, yet effective preventive or disease-modifying strategies remain elusive.[33] WMH, the most

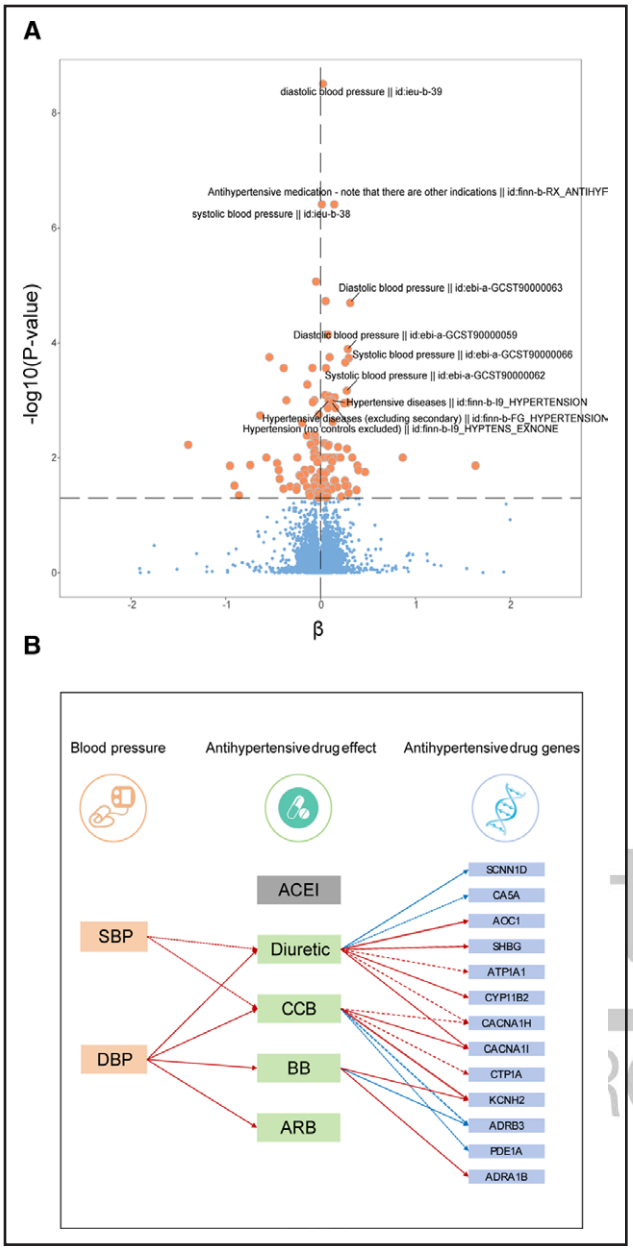

Figure 4. Mendelian randomization (MR)-PheWAS (phenome-wide association studies) results of white matter hyperintensities (WMH) risk factors and effects of common antihypertensive drug targets on WMH.

A, The volcano plot presents MR results for 21 976 phenotypes in relation to WMH. After false discovery rate (FDR) correction (P<0.05, indicated by the horizontal black line), 10 blood pressure-related risk factors showing significant associations are labeled. **B**, Shows the MR results for 5 common antihypertensive drug targets and currently known antihypertensive target genes in relation to WMH. Solid lines represent the effects of diastolic blood pressure (DBP) on WMH, dashed lines represent the effects of systolic blood pressure (SBP), and double lines indicate that both DBP and SBP influence WMH. Red indicates a positive effect, while blue indicates a negative effect. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BB, beta blocker; and CCB, calcium channel blocker.

prominent neuroimaging feature of SVD, reflect chronic small vessel damage and serve as a clinically accessible surrogate for disease burden.[1,34] In this study, we leveraged large-scale genomic and proteomic data sets to systematically dissect the molecular underpinnings of WMH, focusing on the causal roles of plasma proteins, blood pressure, and their interplay. Through an integrated MR framework, we identified 18 WMH-associated plasma proteins and 13 gene targets of antihypertensive drugs with potential therapeutic relevance. Notably, mediation analysis revealed that blood pressure acts as a partial conduit linking several circulating proteins to WMH burden, uncovering mechanistic pathways that may be leveraged for early intervention.

Eighteen proteins were identified with significant causal associations with WMH, which can be categorized into 10 functional groups. We observed negative associations of TFPI and C2 with WMH, indicating potential protective effects mediated through local hemostatic balance.[35] The MR association between C2 and WMH was sensitive to the *cis*-window definition, remaining significant with the ±1 Mb window (13 SNPs) but disappearing with the ±0.5 Mb window (3 SNPs), likely due to limited variant coverage. Nevertheless, this association was replicated in independent cohorts, and the established role of C2 in the complement system provides a biologically plausible mechanistic link. In angiogenesis and endothelial–basement membrane remodeling, LAMC1 and PLXNA1 were identified. LAMC1, a key component of the basement membrane, is essential for endothelial cell adhesion, migration, and blood-brain barrier integrity. It has been shown to inversely correlate with HMGB1, a pro-atherogenic mediator implicated in cardiovascular disease,[36] aligning with our findings. In addition, several other proteins were linked to immune regulation (ISG15, HAVCR2), extracellular matrix metabolism (ADAM12), transcriptional regulation (HEXIM1/2, WBP2), protein modification and lipidation (NMT1, ARL3), signal transduction (FYN), metabolic enzymes (UROS, PMM2, GALK1), epigenetic regulation (TRDMT1), and phosphatases (ACP1). Collectively, these proteins may contribute to SVD pathogenesis through effects on immune inflammation, extracellular matrix stability, energy and glucose metabolism, transcriptional regulation, and epigenetic modifications.[37–39] Chronic neuroinflammation, endothelial dysfunction, cellular stress, and aberrant glycosylation are well-established mechanisms underlying WMH and SVD, and our findings provide novel molecular evidence supporting these processes. In sum, the identification of these 18 proteins underscores the complexity of molecular pathways involved in SVD, including coagulation-fibrinolysis imbalance, immune activation, angiogenesis, basement membrane disruption, and metabolic or epigenetic dysregulation. These proteins show promise as potential peripheral biomarkers and therapeutic targets,

Table 2. Mendelian randomization Results for the Association Between Blood Pressure-Related Therapeutic Target Proteins and White Matter Hyperintensities

Exposure	Method	Nsnp	β (95% CI)	*P* value	Ple_*P*	Het_*P*
Antihypertensive drugs effect (SBP)						
ACE inhibitor	IVW	3	−0.006 (−0.043 to 0.032)	7.73×10^{-1}	0.520	0.453
ARB	IVW	6	0.009 (−0.020 to 0.039)	5.24×10^{-1}	0.725	0.204
BB	IVW	19	0.016 (0.000 to 0.033)	5.33×10^{-2}	0.933	0.003
CCB	IVW	43	0.020 (0.007 to 0.033)	2.39×10^{-3}	0.062	0.000
Diuretics	IVW	66	0.013 (0.001, 0.024)	2.68×10^{-2}	0.507	0.000
Antihypertensive drugs effect (DBP)						
ACE inhibitor	IVW	4	−0.004 (−0.057 to 0.050)	8.99×10^{-1}	0.910	0.925
ARB	IVW	5	0.049 (0.004 to 0.094)	3.43×10^{-2}	0.686	0.555
BB	IVW	26	0.033 (0.008 to 0.057)	8.24×10^{-3}	0.937	0.002
CCB	IVW	48	0.032 (0.015 to 0.048)	1.70×10^{-4}	0.050	0.000
Diuretics	IVW	63	0.025 (0.010 to 0.040)	1.37×10^{-3}	0.723	0.000
Antihypertensive drug genes (SBP)						
ADRB3	Wald ratio	1	−0.150 (−0.238 to −0.062)	7.98×10^{-4}	NA	NA
CACNA1H	IVW	2	0.112 (0.037 to 0.186)	3.21×10^{-3}	0.286	NA
CTP1A	Wald ratio	1	0.103 (0.004 to 0.201)	4.07×10^{-2}	NA	NA
KCNH2	IVW	2	0.060 (0.017 to 0.103)	6.52×10^{-3}	0.559	NA
PDE1A	Wald ratio	1	−0.083 (−0.164 to −0.001)	4.61×10^{-2}	NA	NA
AOC1	IVW	2	0.060 (0.017 to 0.103)	6.52×10^{-3}	0.559	NA
ATP1A1	Wald ratio	1	0.154 (0.014 to 0.295)	3.07×10^{-2}	NA	NA
CA5A	Wald ratio	1	−0.187 (−0.310 to −0.064)	2.86×10^{-3}	NA	NA
SHBG	IVW	3	0.046 (0.003 to 0.088)	3.40×10^{-2}	0.372	NA
Antihypertensive drug genes (DBP)						
ADRA1B	IVW	2	0.212 (0.072 to 0.352)	3.00×10^{-3}	0.669	NA
ADRB3	Wald ratio	1	−0.317 (−0.503 to −0.132)	7.98×10^{-4}	NA	NA
KCNH2	IVW	3	0.068 (0.016 to 0.120)	1.03×10^{-2}	0.503	0.582
CACNA1I	Wald ratio	1	0.278 (0.084 to 0.472)	4.88×10^{-3}	NA	NA
AOC1	IVW	3	0.068 (0.016 to 0.120)	1.03×10^{-2}	0.503	0.582
CYP11B2	Wald ratio	1	0.132 (0.009 to 0.255)	3.50×10^{-2}	NA	NA
SCNN1D	Wald ratio	1	−0.215 (−0.391 to −0.038)	1.70×10^{-2}	NA	NA
SHBG	IVW	3	0.086 (0.014 to 0.157)	1.87×10^{-2}	0.415	0.411

Het-P indicates the *P* value of Cochrane's *Q* value in the heterogeneity test and Ple-P indicates the *P* value of the MR-Egger intercept. Due to the limited number of available SNPs, *P* values for heterogeneity and pleiotropy could not be reliably estimated and are therefore reported as NA. Data in parentheses are 95% CIs. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BB, beta blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; IVW, inverse-variance-weighted; MR, Mendelian randomization; SBP, systolic blood pressure; and SNP, single-nucleotide polymorphism.

offering important mechanistic insights and laying the foundation for precision interventions in SVD.

Hypertension is a well-established and highly modifiable risk factor for WMH, with prior MR studies supporting its causal association even in normotensive individuals.[8] Across multiple data sets, both SBP and DBP showed positive associations with WMH, suggesting that lowering blood pressure can attenuate WMH progression, in line with previous epidemiological and clinical observations. To further disentangle blood pressure effects from drug-specific pathways, we examined the genetic proxies of 5 commonly used antihypertensive drug targets. MR analysis revealed that CCB and diuretic targets showed positive associations with WMH, whereas ACE inhibitor, β-blocker, and ARB targets did not exhibit significant effects through SBP or DBP. These discrepancies may reflect differences in their underlying mechanisms, such as modulation of ion channels, enzyme activity, or receptor-mediated pathways. Importantly, these results should not be interpreted as evidence that certain antihypertensive classes increase WMH burden. Instead, the observed associations represent the direction of genetic effects of SNPs regulating these targets. Since these variants are predominantly linked to blood pressure reduction, the findings indicate that pharmacological modulation of these pathways—particularly via CCB and diuretics—may

ultimately delay WMH progression through lowering SBP and DBP. This interpretation aligns our genetic evidence with previous clinical studies reporting protective effects of CCB and other antihypertensive classes against WMH progression.[9,40,41,42,43] Furthermore, by comprehensively incorporating all gene targets across drug classes rather than focusing on single loci, we newly identified *AOC1*, *ADRB3*, *KCNH2*, and *SHBG* as potential modulators of WMH through their regulation of both SBP and DBP. These findings extend the mechanistic understanding of blood pressure-related WMH pathogenesis and provide genetic support for prioritizing specific drug targets in the prevention of WMH, thereby offering a rationale for future clinical and randomized controlled trials.[44,45]

Our mediation analysis further delineates the vascular signaling pathways bridging these proteins to small vessel injury.[35] Specifically, we identified TFPI, ACP1, and LAMC1 as proteins whose effects on WMH are partially mediated by blood pressure traits.[14] These findings imply dual utility: such proteins may not only represent novel biomarkers of early SVD progression but also serve as upstream therapeutic targets for precision blood pressure modulation. For example, TFPI may exert its vascular protective effects through anticoagulant and antiinflammatory pathways, whereas ACP1, through intracellular signaling, may link blood pressure dysregulation to white matter damage. LAMC1, as a key extracellular matrix component, could influence vascular permeability and compliance. These mechanistic insights expand the understanding of how systemic factors converge on cerebral microvascular health and open avenues for targeted interventions aimed at preserving brain integrity.

Our findings represent an important step toward the mechanistic stratification and therapeutic targeting of SVD; however, several limitations should be acknowledged. First, all data were from people of European ancestry. Therefore, the results of this study should be carefully generalized to other populations due to human genetic heterogeneity. Second, we acknowledge that demographic and clinical factors could confound the relationships among plasma proteins, blood pressure, and WMH. However, using publicly available summary-level GWAS and pQTL data with *cis*-acting genetic instruments, which were already adjusted for major covariates, largely minimizes confounding, though residual effects from unmeasured factors cannot be fully excluded. Additionally, some results should be interpreted with caution, as proteins can be sensitive to the *cis*-window, particularly for proteins with numerous *cis*-acting SNPs such as C2, whereas most associations in our study had consistent results under different windows. Third, we focused on WMH as the primary imaging marker of SVD, without including other manifestations such as lacunes, enlarged perivascular spaces, cerebral microbleeds, or brain atrophy, which have also been associated with circulating proteins in previous studies. Finally, future work should explore a broader range of plasma proteins beyond the Olink and SomaScan platforms, such as Aβ42/40,[40,41] and assess causal effects in longitudinal cohorts to strengthen temporal and mechanistic inference.

CONCLUSIONS

These findings define a protein and blood pressure-centered framework contributing to SVD and offer genetic support for specific proteins and antihypertensive targets as candidate biomarkers or therapeutic entry points. Our results provide mechanistic insights into the vascular underpinnings of SVD and support the development of precision strategies for early intervention and disease modification.

PERSPECTIVES

This study presents robust genetic evidence linking circulating plasma proteins and antihypertensive drug targets to the pathogenesis of SVD with blood pressure regulation serving as a partial mediator. By integrating MR and phenome-wide association analyses across more than 7000 plasma proteins and 5 major antihypertensive drug classes, we identified 18 proteins with potential causal roles in WMH, 13 of which were replicated in independent data sets. WMH, a validated neuroimaging biomarker of SVD, enabled accurate quantification of disease burden. Our results confirm that both SBP and DBP are primary causal risk factors for SVD and further highlight gene targets of CCB and diuretics as molecular mediators of blood pressure-driven microvascular injury. Through mediation analysis, we identified mechanistic pathways, demonstrating how specific proteins, particularly TFPI, ACP1, and LAMC1, may influence SVD through coagulation/fibrinolysis pathways, intracellular signaling pathways, and extracellular matrix stability. Collectively, these findings define a protein-based, vascular-centered framework for understanding SVD pathophysiology, revealing multiple actionable candidates for early detection, therapeutic targeting, and precision interventions. This work provides a crucial foundation for translating molecular insights into clinically relevant strategies for addressing the burden of SVD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Expanded Methods
Tables S1–S18
Figure S1

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