

Circulating Plasma Proteins Influence the Risk of Aortic Dissection via Blood Pressure: A Network Mendelian Randomization and Multi-Omics Study

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Background: The causal link between plasma proteins and aortic dissection (AD), and the role of blood pressure (BP) in this relationship, is not well understood.

Methods: We applied an integrated network Mendelian randomization (MR) and multi-omics framework to investigate the causal effects of plasma proteins on AD and the mediating role of BP. Genetic instruments for plasma proteins were derived from deCODE genetics (n = 35,559), and genome-wide association studies (GWAS) data for BP and AD were sourced from UK Biobank (n = 458,855), Million Veteran Program (n = 449,042) and FinnGen (n = 464,256). We conducted proteome-wide MR, mediation MR, and colocalization analyses to pinpoint causal proteins and pathways. Robustness was checked through sensitivity and replication analyses. Validation was implemented by replication MR analyses and our proteomic sequencing of East Asian population. Downstream analyses, including single-cell RNA sequencing analysis, drug target analysis and phenome-wide association study (PheWAS) analysis were performed.

Results: Genetically predicted hypertension and diastolic BP were linked to a higher risk of AD. Proteome-wide MR identified 9 plasma proteins affecting both BP and AD, notably CCN3, COL6A3, NPPB, and NQO1, with BP mediating 5.43–22.74% of their effects on AD. Colocalization analysis showed shared genetic variants between CCN3 and DBP (PP.H4 = 92.10%), and COL6A3 and AD (PP.H4 = 71.60%). Subsequent analyses validated the mediating effects and expression tendency of candidate proteins, revealed their underlying molecular mechanisms, and identified potential targeted drugs.

Conclusion: By mapping plasma proteins that affect AD risk and quantifying the mediation effect of BP, our work nominates CCN3, COL6A3, NPPB, and NQO1 as promising biomarkers and therapeutic targets, aiming to provide novel strategies for the early identification and intervention of AD.

Keywords: plasma proteins, blood pressure, hypertension, aortic dissection, Mendelian randomization, multi-omics

Introduction

Aortic dissection (AD) is a critical cardiovascular condition involving a tear in the aorta's inner layer, allowing blood to create a hematoma between layers,¹ leading to potential complications like aortic rupture and shock, with a high early mortality rate of 30%.² Hypertension (HTN) is the leading risk factor, significantly increasing the likelihood of AD compared to those with normal BP.³

Significant evidence suggests that HTN and AD share common lifestyle and genetic risk factors.^{3–5} However, the molecular links between HTN and AD are not fully understood. Proteomics provides a powerful approach to identify

molecular targets involved in cellular processes and represents a major source of therapeutic targets for cardiovascular diseases (CVDs).^{6–8} Plasma proteins may act as mediators of HTN and AD or biomarkers linked to arterial pathophysiology. Therefore, investigating the proteomic landscape of HTN and AD could yield crucial insights into the molecular determinants and pathways. Mendelian randomization (MR) uses genetic variants to explore causal relationships between plasma proteins, BP, and AD, minimizing confounding issues.^{9–11} Recent large-scale proteomic and genomic data have facilitated the use of MR to systematically identify plasma proteins linked to these conditions.⁶ These proteins served as potential circulating biomarkers and promising therapeutic targets, providing a valuable strategy for the early prediction of AD and aortic aneurysm (AA).⁷

We hypothesize that there exists a portion of the plasma proteome is linked to both HTN and AD, and that these proteins influence the risk of AD by exerting their regulatory effects on BP. This study addresses the knowledge gap on the causal role of plasma proteins in AD by conducting an MR investigation. We aim to identify plasma proteins affecting AD and quantify BP's mediating role. Using network MR, we seek to establish a framework for understanding the “plasma protein-BP-AD” axis and provide insights into the molecular pathophysiology of AD.

Methods

Study Design

As depicted in [Figure 1](#), our network MR analysis encompasses several key steps. Initially, two-sample MR analysis was carried out to determine the causal relationships among BP traits [essential HTN, systolic BP (SBP), and diastolic BP (DBP)] and AD. Subsequently, we conducted a proteome-wide MR analysis utilizing *cis* protein quantitative trait loci (*cis*-pQTL) of plasma proteins to determine their causal effects on BP traits and AD. Following these analyses, we executed functional enrichment and colocalization analysis. Then a mediation MR analysis to estimate the causal effect of plasma proteins on AD mediated by BP traits was performed, along with the corresponding mediation proportion. To ensure the robustness of the MR results, we also conducted sensitivity and replication analyses. In the final phase, to prevent ethnic heterogeneity and enhance validation robustness, we recruited an independent clinical cohort. We engaged in single cell RNA sequencing (scRNA-seq) analysis to explore the cellular localization and interactions of genes encoding proteins and assessed druggability potential through data mining and phenome-wide association studies (PheWAS). The detailed methods are provided in the [Supplementary Material](#).

Data Sources

[Table 1](#) provides details on the genome-wide association studies (GWAS) utilized in this research. The GWAS summary statistics for plasma proteins were obtained from deCODE. Using the SomaScan version 4 assay (SomaLogic), deCODE measured 4,907 plasma proteins in 35,559 Icelandic individuals from the Icelandic Cancer Project and various genetic programs at deCODE genetics, thereby identifying genetic variants associated with distinct plasma proteins.¹² The GWAS summary statistics for BP traits were derived from the UK Biobank (UKB) (discovery cohort) and Million Veteran Program (MVP) (replication cohort) studies, which were stored in GWAS Catalog.¹³ The whole-genome sequencing of 490,640 participants from the UKB produced GWAS datasets encompassing 763 binary and 71 quantitative phenotypes. To avoid sample overlap, we only included 458,855 participants of non-Finnish European ancestry in our analysis.¹⁴ The Department of Veterans Affairs MVP conducted GWAS on 2,068 traits in 635,969 participants. To ensure consistency in population, we only selected 449,042 participants of European ancestry for analysis.¹⁵ The GWAS summary statistics for AD were obtained from the 12th release of the FinnGen study. FinnGen is a large-scale genomics initiative involving more than 500,000 samples from the Finnish biobank, which included 1,150 patients with AD and 463,106 healthy controls.¹⁶ The *cis* expression quantitative trait loci (*cis*-eQTL) data was obtained from eQTLGen Consortium and Genotype-Tissue Expression (GTEx) Portal.^{17,18}

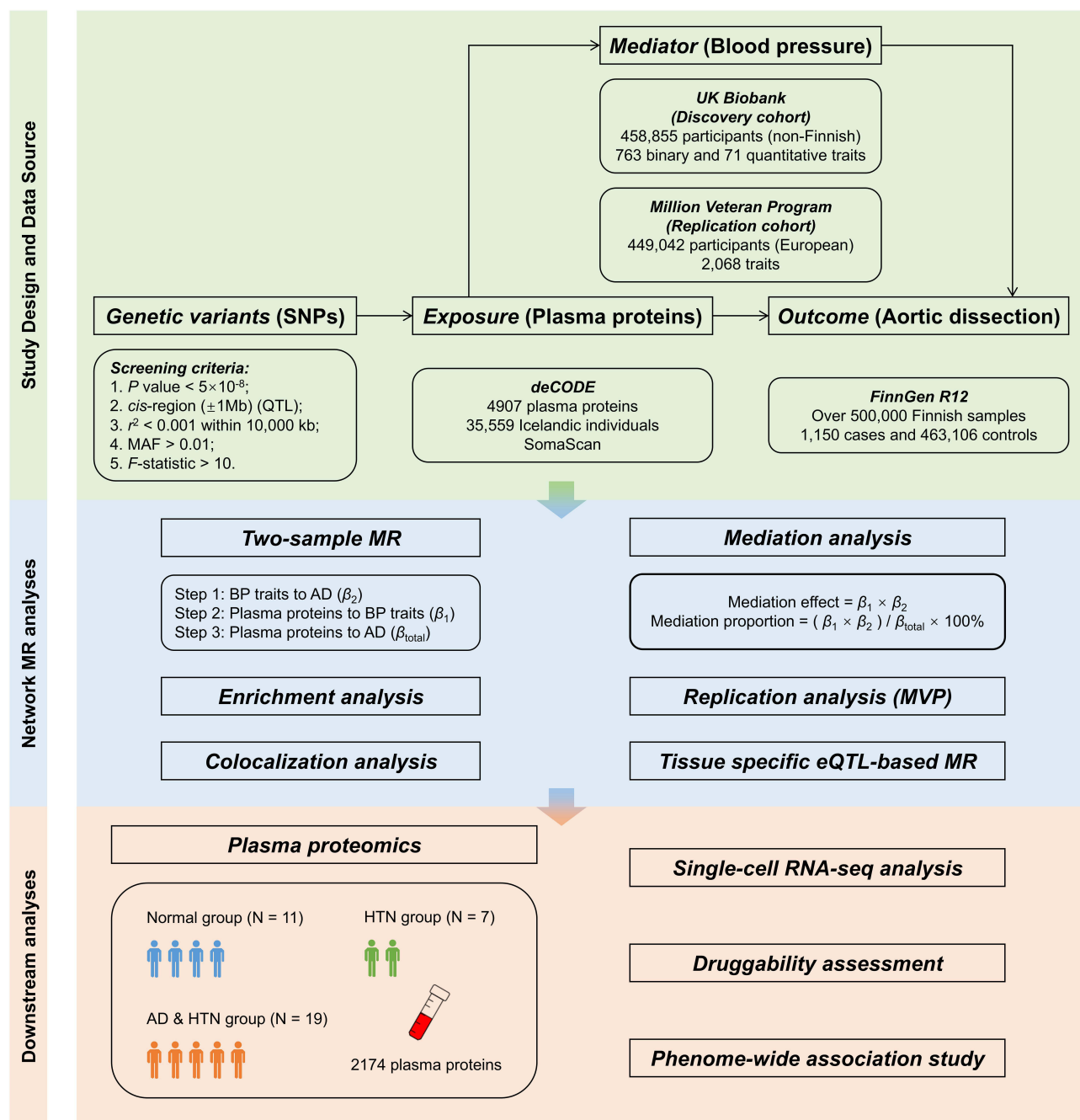


Figure 1 Overview of the study design.

Abbreviations: SNP, single-nucleotide polymorphism; QTL, quantitative trait loci; MAF, minor allele frequency; MR, Mendelian randomization; BP, blood pressure; AD, aortic dissection; MVP, Million Veteran Program; HTN, hypertension; AD, aortic dissection.

Plasma Proteomics

We collected blood samples from patients with acute Stanford type A AD complicated by a history of HTN who were admitted to the Yuanjiagang Branch of the First Affiliated Hospital of Chongqing Medical University between January 2024 and December 2025. The history of HTN was provided by the patients or their relatives, and all patients were diagnosis by aortic computed tomography angiography (CTA). Blood samples from healthy and hypertensive individuals were obtained from participants who underwent health examination at the Health Management Center of the Jingwei Branch of the First Affiliated Hospital of Chongqing Medical University during 2025. The collected blood

Table 1 Detailed Information of GWAS Datasets Used in This Study

Category	Phenotype	Samplesize	Ancestry	Cohort
Exposure	Plasma proteins	35,559	European (Iceland)	deCODE
Mediator	Essential hypertension	184,088 cases and 274,352 controls	European (U.K., non-Finnish)	UKB
		320,429 cases and 107,275 controls	European (U.S.)	MVP
	Systolic blood pressure	431,014	European (U.K., non-Finnish)	UKB
		425,750	European (U.S.)	MVP
	Diastolic blood pressure	431,018	European (U.K., non-Finnish)	UKB
		425,680	European (U.S.)	MVP
Outcome	Aortic dissection	1,150 cases and 463,106 controls	European (Finland)	FinnGen
eQTL	Blood	31,684	Mainly European	eQTLGen
	Aorta	943	/	GTE _x

Abbreviations: GWAS, genome-wide association study; UKB, UK Biobank; MVP, Million Veteran Program; eQTL, expression quantitative trait loci; GTE_x, Genotype-Tissue Expression.

samples were sent to plasma proteomic sequencing by Shanghai Personal Biotechnology Co., Ltd. This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, and written informed consent was obtained from all participants.

Statistical Analyses

All statistical analyses were performed using R software (version 4.3.3). The “TwoSampleMR” and “ieugwasr” packages were used for data acquisition, integration and analysis, the “tidyverse” and “xQTLbiolinks” packages were used for data organization and visualization. The “Seurat” and “CellChat” packages were used for scRNA-seq analyses. To identify more causal proteins, the Benjamini-Hochberg (BH) method was applied to correct for multiple testing of the false discovery rate (FDR) for the MR results excluding plasma protein to AD.

Results

Association Between BP Traits and AD

The results from two-sample MR analysis showed that genetically predicted HTN (OR = 1.52 [95% CI, 1.27–1.81], Adjusted P = 2.10×10^{-5}) and DBP (OR = 2.97 [95% CI, 1.88–4.69], Adjusted P = 2.10×10^{-5}) were associated with an increased risk of AD, and no significant causal association was observed between genetically predicted SBP and AD (OR = 1.15 [95% CI, 0.76–1.74], Adjusted P = 0.51) (Figure 2A and Table S1). However, heterogeneity and horizontal pleiotropy were detected in all the above results. After correcting for outlier SNPs that indicated potential horizontal pleiotropy, the associations remained (Table S1).

Genetically Predicted Proteins Associated with BP Traits and AD

The proteome-wide MR analysis identified 176 plasma proteins associated with HTN or DBP (118 with HTN, 90 with DBP, and 32 overlaps), as well as 73 plasma proteins associated with AD (Figure 2B and Tables S2–S4). Causal proteins were enriched in biological processes like regulation of cell junction assembly, leukocyte proliferation, angiogenesis and vasculature development, and pathways like cytokine-cytokine receptor interaction and biosynthesis of cofactors, suggesting that these proteins may exert their effects in HTN and AD through these pathophysiological progressions (Figure 2C and Tables S5–S7). Among these, 9 proteins exhibited causal relationships with both BP traits and AD (5 with HTN, 4 with DBP) (Figure 3A). Colocalization analysis showed that CCN3 and DBP (PPH4 = 92.10%), as well as COL6A3 and AD (PPH4 = 71.60%), shared a single causal variant (Figure 3B–D and Table S8). Multi-trait

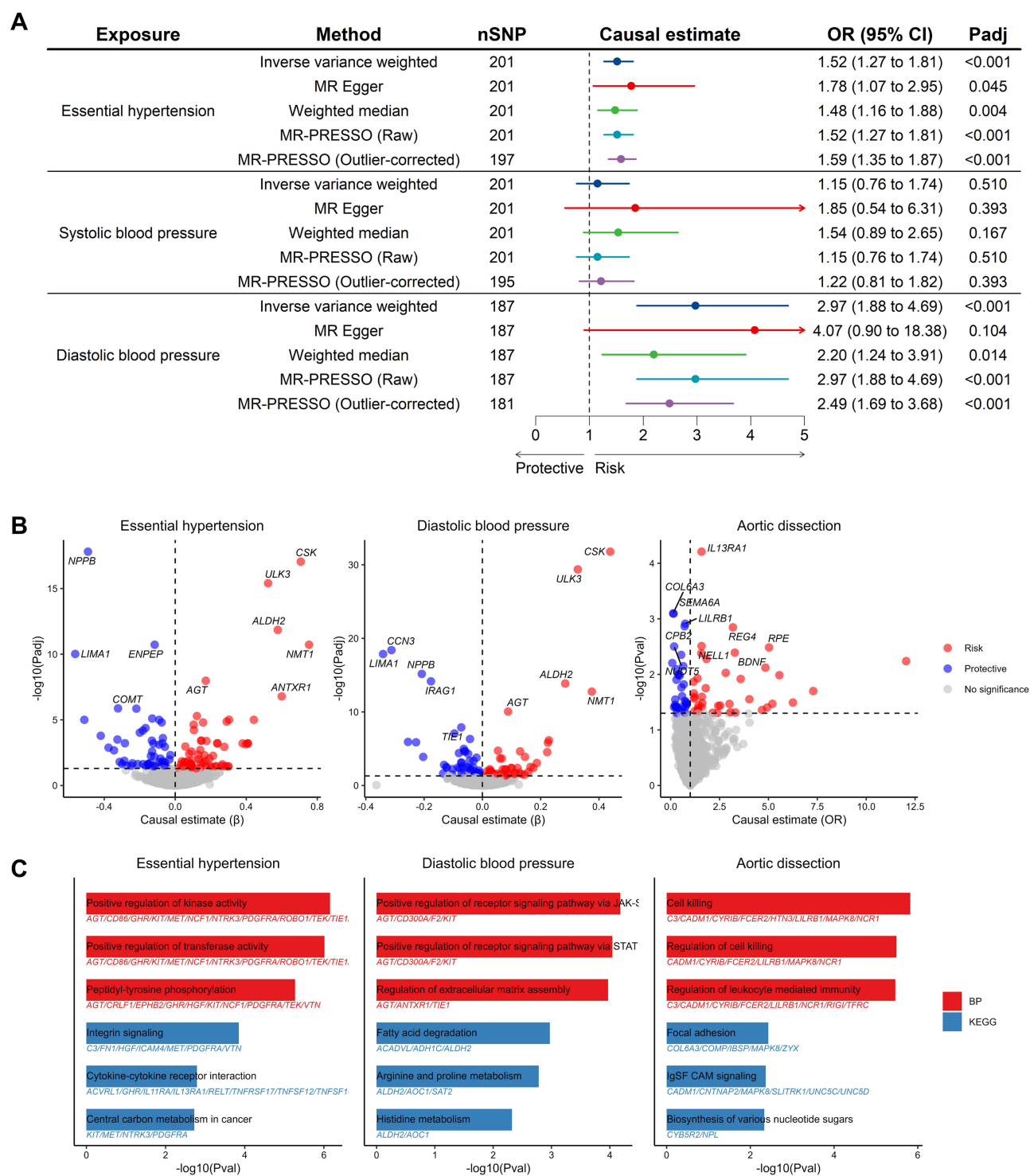


Figure 2 Causal association between plasma proteins, BP traits, and AD. **(A)** Causal association between BP traits and AD. **(B)** Causal association between plasma proteins and HTN, DBP, and AD, respectively. **(C)** Functional enrichment analysis of causal plasma proteins of HTN, DBP, and AD.

Abbreviations: BP, blood pressure; HTN, hypertension; DBP, diastolic blood pressure; AD, aortic dissection.

colocalization analysis did not identify genetic colocalization among plasma proteins, BP traits, and AD, but the strong colocalization between *CCN3* and DBP was confirmed (PP = 92.08%, lending by rs56013326) (Tables S9–S10). Sensitivity analyses showed no horizontal pleiotropy, but heterogeneity was detected in *NPPB* to DBP, and MR results by different methods were consistent in causal direction except *SHMT1* to AD (Table S11).

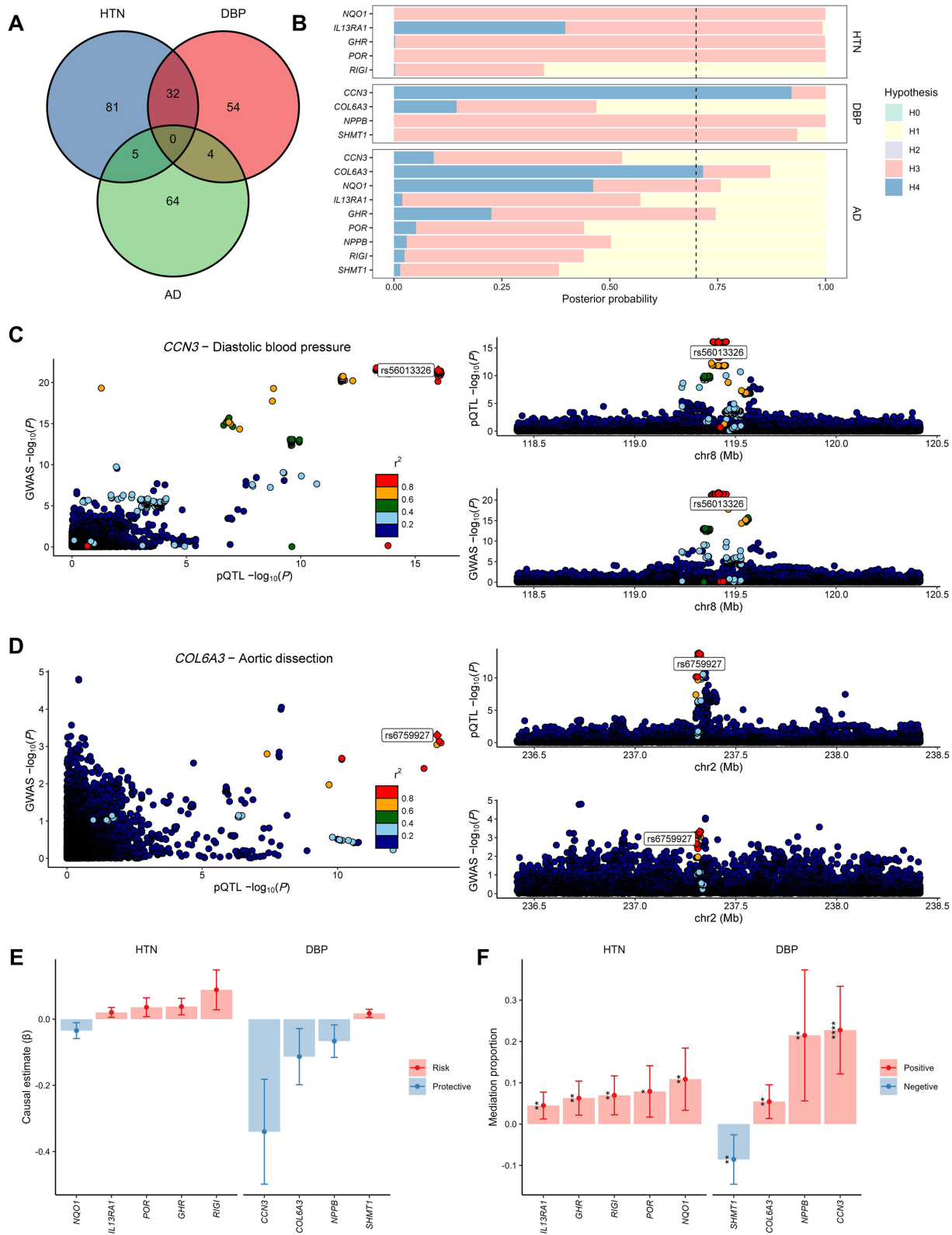


Figure 3 Colocalization and mediation analysis of causal proteins. **(A)** Venn diagram of the causal proteins between BP traits and AD. **(B)** Posterior probability of colocalization hypotheses on the overlapped causal proteins to BP traits and AD. The black dashed line represents the positive threshold (70%) for the posterior probability of hypothesis 4. **(C)** Combined comparing and visualizing regional signals plots between *CCN3* cis-pQTL and DBP GWAS data. **(D)** Combined comparing and visualizing regional signals plots between *COL6A3* cis-pQTL and AD GWAS data. **(E)** Mediation effects of overlapped causal proteins on AD mediated by BP traits. **(F)** Mediation proportion of overlapped causal proteins on AD mediated by BP traits (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$).
Abbreviations: BP, blood pressure; AD, aortic dissection; pQTL, protein quantitative trait loci; DBP, diastolic blood pressure; GWAS, genome-wide association study.

Interestingly, previous studies have shown that increased levels of COL6A3 and its carboxyl terminus product are associated with a higher risk of coronary artery diseases, which is contrary to our results.^{19,20} Therefore, we conducted MR and colocalization analyses between COL6A3 and various CVDs. The results revealed that COL6A3 acts as a protective factor for aortic diseases with evidence of colocalization, while it is a risk factor for coronary artery diseases ([Figure S1](#)).

Mediation Effect of BP Traits on Protein-Associated AD

Among the 5 proteins associated with both HTN and AD, 5 mediation pathways were identified, in which the direction of mediating effect and total effect remained consistent. Specifically, 10.86% ([95% CI, 3.33–18.40%], $P = 4.73 \times 10^{-3}$) of the effect of NQO1 on AD may be mediated by HTN ([Figure 3E–F](#) and [Table S12](#)). Among the 4 proteins associated with both DBP and AD, 3 mediation pathways were identified. DBP explained 22.74% ([95% CI, 12.14–33.35%], $P = 2.63 \times 10^{-5}$), 5.43% ([95% CI, 1.36–9.51%], $P = 8.93 \times 10^{-3}$), and 21.47% ([95% CI, 5.62–37.31%], $P = 7.94 \times 10^{-3}$) of the effect of CCN3, COL6A3, and NPPB on AD, respectively ([Figure 3E–F](#) and [Table S12](#)).

Replication Analyses in MVP Cohort

We replicated MR analyses in MVP study and found that HTN and DBP also exhibited a risk effect on AD, while there was still no significant causal link found between SBP and AD ([Figure 4A](#) and [Table S13](#)). The proteome-wide MR identified 235 plasma proteins associated with HTN or DBP (150 with HTN, 147 with DBP, and 62 overlaps) ([Figure 4B](#) and [Tables S14–S15](#)). The biological processes and pathways causal proteins enriched in were almost consistent with the results of the discovery cohort, which emphasizes the importance of these progressions in the pathogenesis of BP traits and AD ([Figure 4C](#) and [Tables S16–17](#)). Integrating the MR results of the discovery and replication cohorts, 1 plasma protein (NQO1) was causally associated with AD via HTN, and 3 plasma proteins (CCN3, COL6A3, and NPPB) were causally associated with AD via DBP ([Figure 4D–E](#)), among which CCN3 (PPH4 = 61.76%) and COL6A3 (PPH4 = 69.53%) showed suggestive colocalization with DBP ([Figure 4F](#) and [Table S18](#)). Mediation analysis showed high consistency in both cohorts. Specifically, HTN could mediate the effects of NQO1 on AD, with mediation proportions of 12.04%. DBP could mediate the effects of CCN3, COL6A3, and NPPB on AD, with mediation proportions ranging from 10.22% to 26.24% ([Figure 4G](#) and [Table S19](#)).

Tissue Specific eQTL-Based MR

Summary-level *cis*-eQTL statistics of whole blood and aorta were respectively retrieved from the eQTLGen Consortium and GTEx Portal, aiming to investigate whether genetically predicted tissue-specific gene expression levels have a causal relationship with AD. Owing to discrepancies between transcriptomic and proteomic detection methodologies, NPPB was not found in the two eQTL cohorts. Two-sample MR results demonstrated that the expression levels of CCN3 in both whole blood and aorta, and COL6A3 in aorta, showed a protective effect against AD ([Figure 4H](#) and [Table S20](#)). These findings suggest that CCN3 and COL6A3 prevent AD at both transcriptional and translational levels, serving as potential robust therapeutic targets for AD.

Plasma Proteomics

We collected blood samples from 7 patients with HTN (HTN group), 19 patients with AD and history of HTN (AD_HTN group), and 11 healthy controls (Normal group), followed by plasma proteomic sequencing. After quality control, 2,174 plasma proteins were finally identified. Due to the diversity in sequencing platforms, methodologies, and sequencing depths between our study and the deCODE genetics, only CCN3 and COL6A3 were detected in our plasma proteome. Compared with Normal group, CCN3 in HTN group was significantly decreased. Whereas compared with HTN group, CCN3 in AD_HTN group was significantly increased. However, no significant difference was observed in CCN3 between Normal and AD_HTN group. The levels of COL6A3 showed a stepwise significant decrease across Normal, HTN, and AD_HTN group, indicating that the reduction of protective factor COL6A3 plays an important role in the progression from HTN to AD ([Figure 4I](#)).

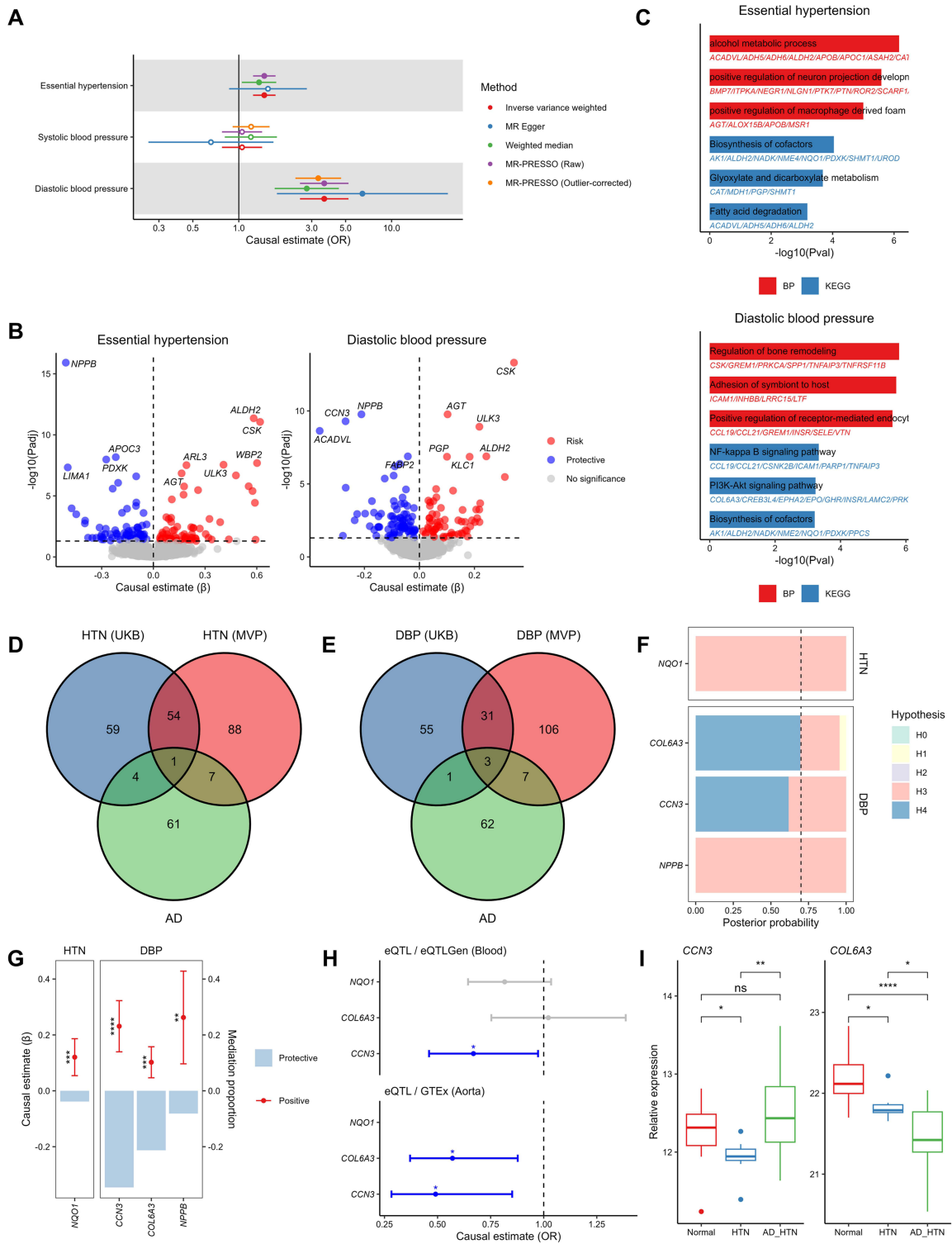


Figure 4 Replication analyses in MVP cohort and validation analyses. **(A)** Causal association between BP traits and AD. **(B)** Causal effect of genetically predicted plasma proteins on BP traits. **(C)** Functional enrichment analysis of causal plasma proteins of BP traits. **(D)** Venn diagram of the causal proteins between HTN in both cohorts and AD. **(E)** Venn diagram of the causal proteins between DBP in both cohorts and AD. **(F)** Posterior probability of colocalization hypotheses on the candidate causal proteins to BP traits. The black dashed line represents the positive threshold (70%) for the posterior probability of hypothesis 4. **(G)** Mediation effects (left y-axis) and proportion (right y-axis) of candidate causal proteins on AD mediated by BP traits. **(H)** Causal association between tissue specific genes encoding candidate causal proteins and AD (* $P < 0.05$). **(I)** The relative expression differences of candidate causal proteins among Normal, HTN, and AD_HTN group in our plasma proteomic sequencing (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$).

Abbreviations: MVP, Million Veteran Program; BP, blood pressure; AD, aortic dissection; HTN, hypertension; DBP, diastolic blood pressure; AD_HTN, aortic dissection with history of hypertension.

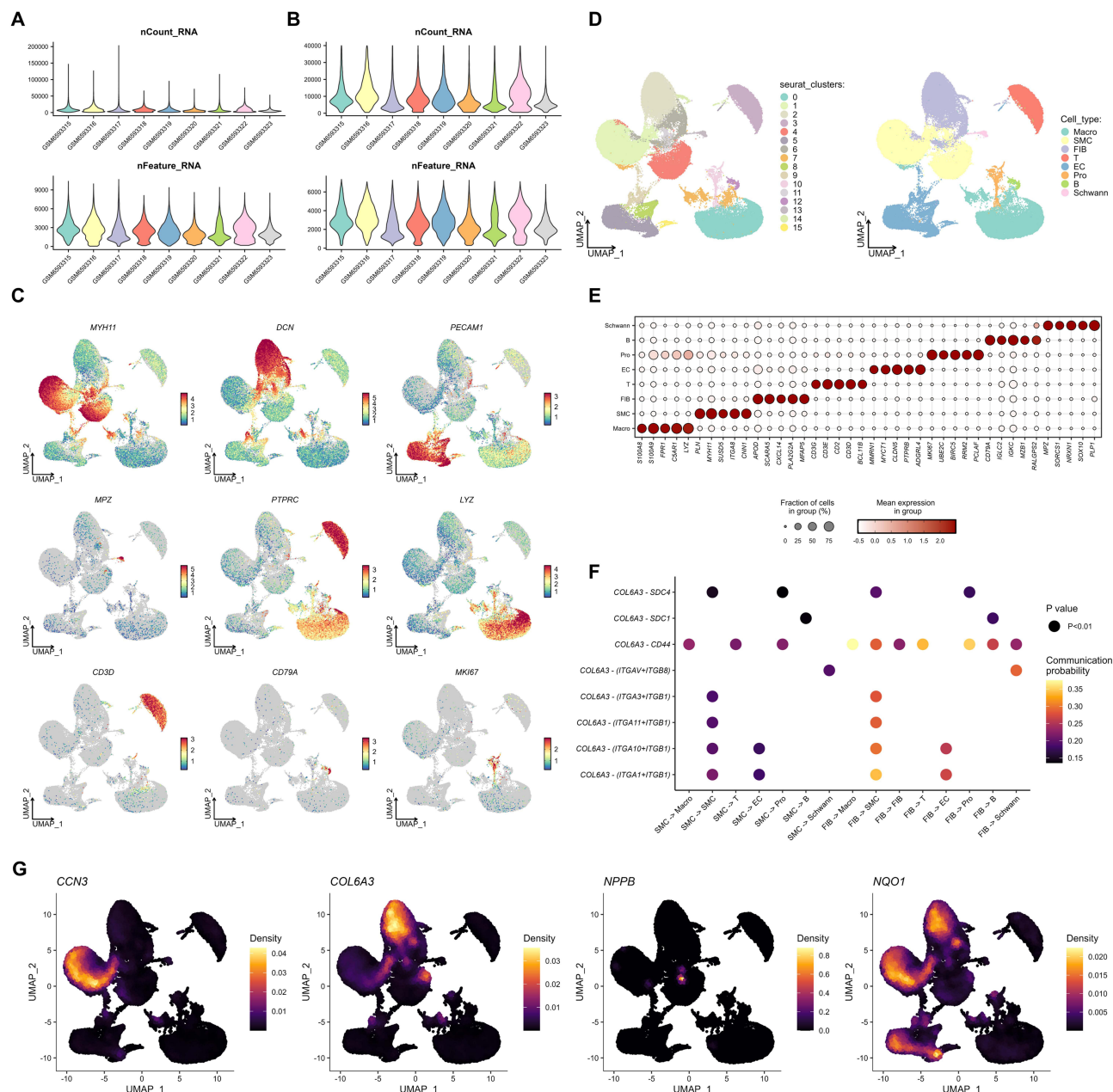


Figure 5 Single-cell RNA-seq analyses. (A) Number of counts and features of each sample before quality control. (B) Number of counts and features of each sample after quality control. (C) UMAP plots of expression distribution of the aortic cell-specific markers. (D) UMAP plots of 16 cell clusters and annotated 8 cell types. (E) Top 5 DEGs of each cell type. (F) Cell-cell communication in AD mediated by receptor-ligand pairs involving COL6A3. (G) Distribution density UMAP plots of genes encoding candidate causal proteins in AD cells.

Abbreviations: UMAP, uniform manifold approximation and projection; DEG, differentially expressed genes; AD, aortic dissection.

Single-Cell RNA-Seq Analyses

After quality control of the scRNA-seq data of acute Stanford type A AD from GSE213740, we implemented a standard data process pipeline (Figure 5A and B). Based on the established aortic cell-specific markers reported in previous literature, we annotated 16 cell clusters into 8 distinct cell types, including smooth muscle cells (SMC), fibroblasts (FIB), endothelial cells (EC), Schwann cells, macrophages, T cells, B cells, and proliferating cells (Figure 5C and D). The top 5 differentially expressed genes of each cell type were consistent with the corresponding cell identity (Figure 5E). Cell-cell communication analysis revealed that COL6A3, which is expressed by SMC and FIB, engages in extensive cell-cell crosstalk with various cell types. Among these, the ligand-receptor pair consisting of COL6A3 derived from FIB and

CD44 derived from macrophages exhibited the highest communication probability, suggesting that the cell-cell communication mediated by this pair may play a role in the pathological progression of AD (Figure 5F). CCN3 was predominantly expressed in SMC, NPPB showed low expression levels in aortic tissues, and NQO1 was mainly expressed in SMC, FIB, and EC (Figure 5G).

Drug Target Analysis

We searched and evaluated the druggability and drug development status of candidate proteins in the Therapeutic Target Database, Drug-Gene Interaction Database, DrugBank, and Open Targets Platform (Tables S21–S24). CCN3 is one of the targets of insulin human. Ocriplasmin, which is used to treat symptomatic vitreomacular adhesion, and collagenase *Clostridium histolyticum*, which is used to treat Dupuytren's contracture and Peyronie's disease, are drugs targeting COL6A3. Carvedilol, which targets NPPB, is widely used in the treatment of CVDs such as HTN, and the B-type natriuretic peptide analogue BD-NP is also under investigation. NQO1 is associated with beta-lapachone analogue, vitamin E analogue, and coenzyme Q10 analogue. Beta-lapachone analogue can promote NQO1-mediated programmed tumor cell necrosis, which is used in the treatment of solid tumors. Vitamin E analogue and coenzyme Q10 analogue act as effective cellular oxidative stress protectants. Drugs targeting these proteins hold significant potential for research in the treatment of aortic dissection.

Phenome-Wide Association Study Analysis

We conducted a PheWAS analysis on candidate proteins using the AstraZeneca PheWAS Portal. No gene-level results were available for CCN3 (also known as NOV). For the remaining proteins, none was significantly associated ($P < 1 \times 10^{-6}/1 \times 10^{-8}$) with other phenotypes as risk factor ($OR > 1$ or $\beta > 0$), indicating that no detrimental or adverse effects were examined in other binary or continuous phenotypes according to the gene-level results (Figure 6).

Discussion

Our network MR identified CCN3, COL6A3, NPPB and NQO1 as key plasma proteins causally associated with both BP traits and AD. CCN3 exhibited protective effects against AD with DBP serving as its mediator (mediation proportion = 22.74%) and strong colocalization with DBP (PPH4 = 92.10% in discovery, 61.76% in replication). COL6A3 showed colocalization with AD (PPH4 = 71.60%) and suggestive colocalization with DBP (PPH4 = 69.54% in replication), and was mediated by DBP in its protective effect on AD (mediation proportion = 5.43%). NPPB and NQO1 prevent AD via DBP and HTN, respectively, with similar mediation effects observed across cohorts. Analyses of our plasma proteomic sequencing and scRNA-seq from public databases suggested that COL6A3 may serve as an important trigger in the development and progression of HTN and subsequent AD. Drug database mining revealed potential therapeutics targeting these proteins, and PheWAS analysis demonstrated that these proteins, which serve as protective factors, were not significantly associated with other phenotypes as risk factors, suggesting that therapeutic strategies targeting these proteins may possess favorable safety profiles.

HTN is a key risk factor for AD, as confirmed by research. A study of over 276,000 participants identified HTN as an independent risk factor for aortic-related deaths, with critical BP thresholds at 130/82 mmHg.²¹ Studies indicate DBP has a more direct impact on AD-related mortality, especially in individuals aged 50–75.^{21,22} Research by Rapsomaniki E et al found that DBP, rather than SBP, is a risk factor for AA in those over 60.²³ A meta-analysis confirmed DBP ≥ 80 mmHg as a risk factor for AA, with better prognostic value than SBP.²⁴ Our study provides evidence that HTN and DBP are causal risk factors for AD, whereas no causal association was identified between SBP and AD. These results suggest that DBP could play a more crucial part in preventing AD.

CCN3 is a cytokine that regulates the extracellular matrix and offers vascular protection by inhibiting vascular SMC migration and proliferation, reducing neointimal thickening, and protecting EC.²⁵ It also has anti-inflammatory effects by downregulating NF- κ B activity and suppressing inflammation-related molecules like MMP9 and MMP2.^{26,27} These actions are relevant to HTN-related changes such as endothelial inflammation and vascular thickening.^{28–30} CCN3 is significantly reduced in AD and AA, and its deficiency in animal studies leads to vascular issues, highlighting its protective role against AA.^{31,32} The study shows that over 20% of CCN3's effect on AD is mediated by DBP, with strong

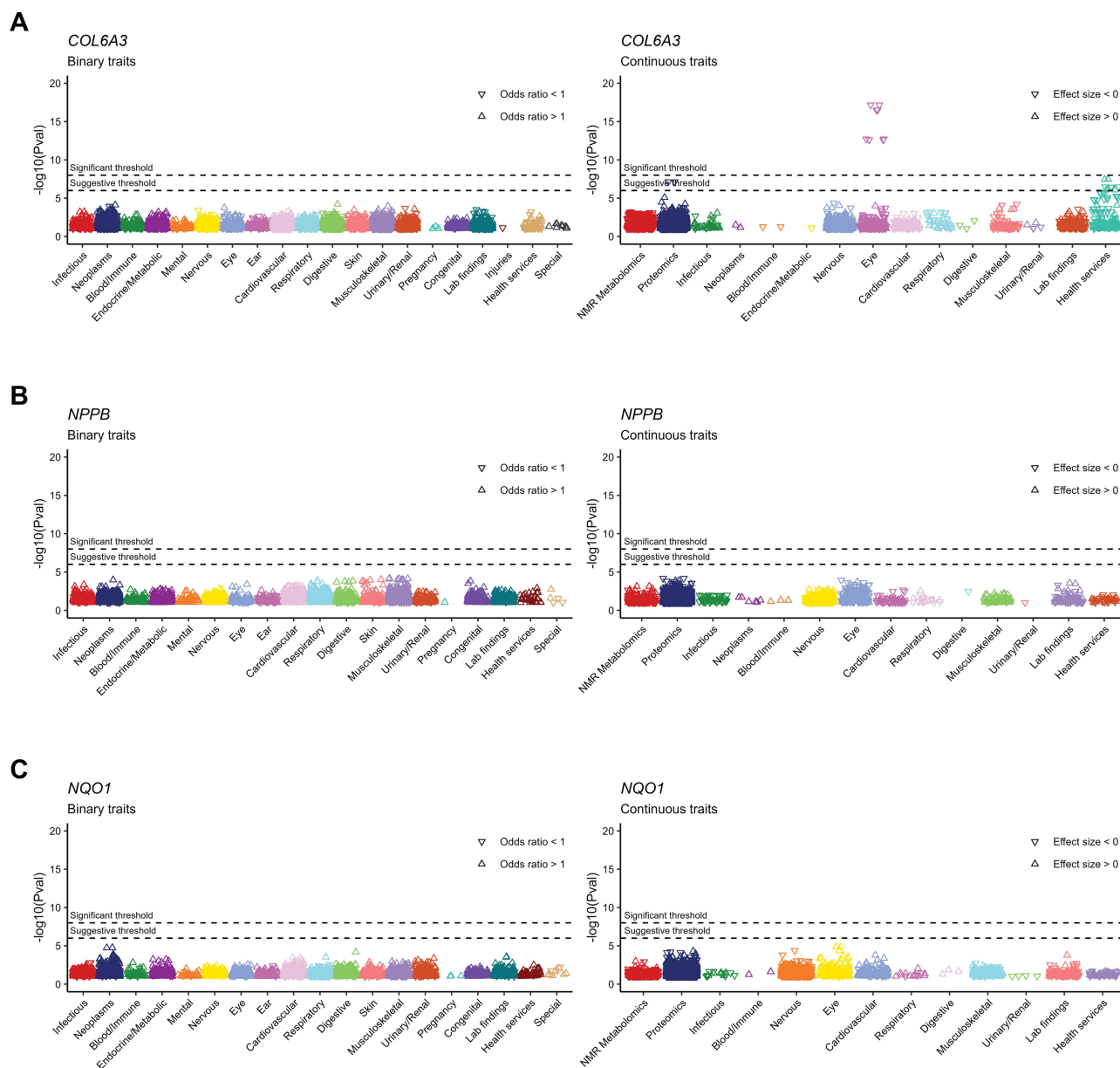


Figure 6 Phenome-wide association study analysis on candidate causal proteins and both binary and continuous traits. **(A)** COL6A3. **(B)** NPPB. **(C)** NQO1.

colocalization observed in two independent cohorts, suggesting it may be a key molecule linking hemodynamic stress to vascular integrity. Our plasma proteomic sequencing analysis revealed decreased expression of CCN3 in patients with HTN, whereas an upward trend was observed in those with AD. This finding is not entirely consistent with previous reports indicating reduced CCN3 levels in AD. We speculate that the elevated CCN3 observed in AD patients may represent a compensatory or stress-induced response triggered following the acute onset of the disease. The specific underlying mechanisms and pathophysiological implications warrant further investigation.

COL6A3, a collagen family member, is vital for the extracellular matrix and cell interactions. It is associated with early-onset HTN in the Japanese population, suggesting a role in BP regulation.³³ Reduced circulating COL6A3 levels were identified as a key risk factor for AA, likely due to their role in compromising vascular wall stability through disruptions in lipid metabolism, immune responses, and matrix remodeling.³⁴ Hypertensive patients have lower serum endotrophin, a degradation product of COL6A3, compared to healthy individuals, indicating reduced aortic elasticity and increased stiffness, key features of HTN linked to negative cardiovascular outcomes.³⁵ COL6A3 is also associated with

coronary artery disease risk, and serum endotrophin correlates with higher cardiovascular event and mortality risk in atherosclerotic patients.^{19,20,36} COL6A3 consistently showed protective effects against aortic conditions like AD and AA, with confirmed genetic colocalization of COL6A3 with AA and AD. In contrast, it was associated with an increased risk of atherosclerotic diseases such as coronary artery disease. This indicates that COL6A3 may have different roles in various vascular areas, likely through distinct biological pathways related to each disease's pathophysiology. Our plasma proteomic sequencing analysis validated the stepwise significant low expression of COL6A3 in the serum of patients with HTN and AD. Single-cell transcriptomic analysis revealed that COL6A3 is predominantly expressed in FIB. The potential COL6A3-CD44 receptor-ligand pair between FIB and macrophages indicates intercellular communication. CD44, a multifunctional receptor on macrophages, profoundly influences macrophage's behavior in various physiological and pathological contexts. It mediates interactions between macrophages and the extracellular matrix as well as other cells, affecting macrophage migration, localization, polarization (particularly towards the M2 phenotype), initiation, and progression of inflammatory responses, and contributing to immunosuppression and chemotherapy resistance in the tumor microenvironment.³⁷⁻³⁹ These findings collectively suggest that COL6A3 serves as a pivotal molecular hub connecting mechanical integrity with the immune microenvironment.

NPPB is a prohormone secreted by ventricular cardiomyocytes, released in response to increased ventricular load (often associated with elevated blood volume). Its core functions include lowering BP, promoting diuresis, and inhibiting sodium and water reabsorption, making it a key substance in maintaining cardiovascular homeostasis.⁴⁰ Consequently, the natriuretic peptide system may become a major therapeutic target for various related diseases and for reducing HTN and metabolism-related cardiovascular risks in the future.⁴¹ However, in pathological states, elevated levels of NPPB serve as a risk marker. In hypertensive patients, it reflects cardiac stress due to sustained high pressure, indicating early cardiac involvement;⁴² in acute AD, its elevation is associated with a sharp increase in right heart load, acting as a strong predictor of short-term mortality risk (with mortality potentially increasing up to fourfold in high-risk individuals).⁴⁰ Furthermore, it correlates positively with aortic diameter and holds significant prognostic value.^{43,44} Interestingly, our study suggests that genetically determined higher levels of NPPB may be a protective factor against HTN, with approximately 20% of its effect on AD being mediated by DBP. This highlights the complexity of the system. While the natriuretic peptide pathway is inherently protective, its sustained elevation in disease essentially reflects the body's challenging transition from compensation to decompensation, thereby transforming it into a signal of risk.

NQO1 exerts its antihypertensive effects through two core mechanisms. First, by elevating NAD⁺ levels, it activates SIRT1, leading to the deacetylation and activation of eNOS, which collectively improves endothelial function and promotes vasodilation.^{45,46} Second, as a key target gene of Nrf2, NQO1 constitutes a crucial antioxidant defense pathway, scavenging reactive oxygen species to mitigate oxidative damage in blood vessels and kidneys, and its downregulation in pathological conditions such as obesity and chronic kidney disease exacerbates oxidative stress and the progression of hypertension.^{47,48} Consistent with previous research, our study identifies NQO1 as a protective factor against both hypertension and aortic dissection.^{49,50}

The intersections of biological processes and pathways enriched by the causal proteins for BP traits and AD highlight the roles of proteins in interconnected pathways. Key pathways include renal sodium excretion, crucial for fluid balance and BP regulation, whose dysfunction can trigger HTN and cardiovascular issues like AD.^{51,52} Cell junction assembly is vital for aortic wall integrity, and changes in adhesion genes and excessive calpain activation can reduce vascular SMC contractility and disrupt endothelial function.^{53,54} Angiogenesis regulation is crucial, as inhibitors of angiogenesis can raise AD risk.^{55,56} Inflammation and immune regulation are crucial, with phagocytosis preventing thoracic AD by clearing apoptotic cells.⁵⁷ Leukocyte proliferation regulation plays a pivotal role in cardiovascular inflammation. Diseases such as HTN can lead to endothelial dysfunction in the bone marrow and increase inflammatory myeloid cells.⁵⁸ In summary, these enriched biological processes and pathways may collectively constitute a dynamic pathological network that drives the development of HTN and AD.

Large samples from four major biobanks offer high statistical power, however, our study had some limitations. First, the GWAS datasets used in this study are predominantly from participants of European ancestry. While this reduces confounding from population stratification, differences in allele frequencies, linkage disequilibrium structure, and genetic diversity may limit the generalizability of our findings to other populations. Though we performed plasma proteomic

validation in an East Asian cohort, this cohort was relatively small and did not involve whole-genome sequencing, failing to link phenotypes to genetic architecture. The validation would be strongly influenced by confounding factors such as diet, environment, and comorbidities, making it inadequate to fully validate our MR results. Future studies should conduct cross-ancestry validation in diverse large non-European cohorts to improve the applicability of our findings. Second, despite leveraging one of the most extensive proteome-wide GWAS resources, some proteins lacked significant instrumental variables (IVs), which restricted the exploration of their causal associations and potential therapeutic value. Additionally, heterogeneity and pleiotropy could not be effectively assessed. This requires GWAS data with larger scale and greater sequencing depth to identify more significant IVs. Third, although this study suggested causal associations and pathways linking plasma proteins, BP, and AD, further experimental researches are needed to elucidate the underlying molecular mechanisms. Future research could focus on constructing relevant models to explore the pathophysiological processes of specific proteins in maintaining vascular homeostasis and the development of AD, and evaluating the potential of targeting these proteins for the prevention or treatment of AD, with the aim of achieving early identification and stratified management of AD.

Conclusion

In summary, this study mapped how plasma proteins affect AD risk, highlighting BP's key role. We identified new biomarkers and targets like CCN3, COL6A3, NPPB and NQO1. Subsequent investigations should seek to validate these findings among diverse populations and examine the molecular mechanisms of these proteins and pathways. These insights aim to advance precise prevention and targeted treatment of HTN and AD.

Abbreviations

AA, aortic aneurysm; AD, aortic dissection; BH, Benjamini-Hochberg; BP, blood pressure; CTA, computed tomography angiography; CVD, cardiovascular disease; DBP, diastolic blood pressure; EC, endothelial cell; eQTL, expression quantitative trait loci; FDR, false discovery rate; FIB, fibroblast; GTEx, Genotype-Tissue Expression; GWAS, genome-wide association study; HTN, hypertension; IV, instrumental variable; MR, Mendelian randomization; MVP, Million Veteran Program; PheWAS, phenome-wide association study; pQTL, protein quantitative trait loci; SBP, systolic blood pressure; scRNA-seq, single cell RNA sequencing; SMC, smooth muscle cell; UKB, UK Biobank.

Data Sharing Statement

The GWAS data used in this study are publicly available. The plasma proteomic sequencing data is available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study adhered to the STROBE-MR guidelines, and was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No. 2024-397-01), and followed the guidelines stated in the Helsinki Declaration. Written informed consent was obtained from all participants.

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Author Contributions

Zhenghao Li: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review and editing. Jian Liu: Formal analysis, Visualization. Xiaoxi Fan: Data curation, Validation. Liangtao Shi: Data curation, Validation. Haoming Shi: Conceptualization, Writing – review and editing. Changying Li: Data curation, Validation. Changzhu Duan: Conceptualization, Resources, Supervision, Writing – review and editing. Cheng Zhang: Conceptualization, Resources, Supervision, Funding acquisition, Writing – review and editing. Qingchen Wu:

Conceptualization, Resources, Supervision, Funding acquisition, Writing – review and editing. Yue Shao: Conceptualization, Writing – original draft, Writing – review and editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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