Supplementary Methods

Selection of genetic instrumental variables

Mendelian randomization (MR) analysis is based on the following three assumptions: (1) the genetic instrumental variables (IVs) must be related to the exposure, (2) IVs should not be related to the outcome through confounders, (3) the IVs affect the outcome only dependently through the exposure.[1] The cis-QTL (pQTL and eQTL) are defined as single-nucleotide polymorphisms (SNPs) that are strongly associated ($P < 5\times10^{-8}$) and located within 1 megabase upstream or downstream of the corresponding gene locus. For other phenotypes, we selected SNPs with genome-wide strong association ($P < 5\times10^{-8}$). Subsequently, these IVs were clumped using a pairwise linkage disequilibrium (LD) threshold of $r^2 < 0.001$ and a window size of 10,000 kilobases.[2] The F-statistic was calculated to assess the strength of IVs, and weak IVs with an F-statistic lower than 10 were excluded.[3] Additionally, SNPs with low minor allele frequency (MAF < 0.01) and those containing palindromic alleles were excluded.

Mendelian randomization

For two-sample MR, the inverse variance weighted (IVW) method under multiplicative random effects were used for more than one independent variable, and the Wald ratio method was applied for a single independent variable to estimate the causal effect between exposure and outcome.[4] Using two-sample MR findings, we applied two-step MR to explore how BP traits mediate the causal link between plasma proteins and AD.[5] Specifically, the effect size of the mediation effect was defined as the product of the effect of exposure on mediator and the effect of mediator on outcome ($\beta_1\times\beta_2$). The mediation proportion was defined as the ratio of the mediation effect to the total effect of exposure on outcome ($\beta_1\times\beta_2/\beta_{total}$). The delta method was used to estimate the standard error (SE) and 95% confidence interval (95% CI).[6] A positive mediation pathway was defined as a consistent direction of significant total effect and mediation effect.

Functional enrichment analysis

The 'clusterProfiler' package was used to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses on proteins associated with BP traits and AD.[7] Due to the small number of proteins and their strong mutual independence, we considered enrichment terms with $P < 0.05$ as significant.

Genetic colocalization analysis

To investigate whether there are shared causal variants underlying the genetic associations across plasma proteins, BP traits, and AD, we performed Bayesian colocalization analysis using the 'coloc' package within the cis-regions of plasma proteins.[8] The colocalization analysis included five hypotheses, H0: no genetic association for either trait in the region, H1 and 2: genetic association for only one trait, H3: genetic associations for both traits with different causal variants, and H4: genetic associations for both traits with a same causal variant. Colocalization of the two traits in the region is considered when the posterior probability (PP) of H4 exceeds 70%. Additionally, we conducted multi-trait colocalization using the 'moloc' package.[9] Colocalization of multiple traits in the region is considered when the PP exceeds 70%, and a PP greater than 50% is regarded as suggestive evidence of colocalization.[10]

Sensitivity analyses

For the positive mediation pathway, sensitivity analyses were performed. The robustness of the primary MR analysis was verified using the MR Egger and weighted median methods for re-evaluation.[11,12] Heterogeneity was detected using the Cochran's Q test, and horizontal pleiotropy was detected using the MR Egger intercept and the Mendelian Randomization pleiotropy residual sum and outlier (MR-PRESSO) test.[11,13,14]

Plasma proteome sequencing

The collected blood samples were sent to Shanghai Personal Biotechnology Co., Ltd. for plasma proteome sequencing. The detailed sequencing methodology is described as follows. The nanomagnetic beads were pretreated in accordance with the protocol of the low-abundance protein enrichment kit, followed by incubating an appropriate amount of nanomagnetic beads with an appropriate volume of blood samples under shaking at room temperature. The magnetic beads were separated from the samples using a magnetic rack, and then washed three times with eluent. At this point, the low-abundance proteins were enriched on the magnetic beads, and protein denaturation, reduction, alkylation, and enzymatic hydrolysis could be directly performed on the nanomagnetic beads. The detailed procedure is as follows. Add 20 μL of Digestion Solution 1 to the centrifuge tube containing magnetic beads, and incubate at 55℃ and 1700 rpm for 0.5 hours. After incubation, allow the samples to return to room temperature, then add 20 μL of Digestion Solution 2, and incubate at 37℃ for 2 hours in the dark with shaking at 1700 rpm. Subsequently, add 20 μL of termination solution, pipette up and down to mix well, place the tube on a magnetic rack and let it stand for 3 minutes. After the enrichment reagent is completely adsorbed by the magnet, transfer the supernatant to a new centrifuge tube.

Peptide samples were desalted using C18 desalting tips. The desalting column was activated with 100% acetonitrile and equilibrated with 0.1% formic acid. The enzymatically digested peptides were loaded onto the column, followed by washing the column with 0.1% formic acid solution. The waste solution was discarded, and the washing step was repeated twice. Finally, the eluent (70% acetonitrile, 0.1% formic acid) was added for elution, and the eluate was collected. The samples were dried using a vacuum centrifugal concentrator.

Each sample was separated using a nano-flow Vanquish Neo UHPLC system. A Thermo Scientific™ EASY-Spray™ column (2 μm C18, 150 μm × 15 cm, part number: ES906) was employed, with the column temperature maintained at 55℃ and the autosampler temperature set at 5℃.

For data-independent acquisition (DIA) analysis, chromatographic separation was performed using a nano-flow Vanquish Neo system (Thermo Scientific). After nano-high-performance liquid chromatography separation, the samples were subjected to DIA mass spectrometry analysis using an Astral high-resolution mass spectrometer (Thermo Scientific). The detection mode was set to DIA. The precursor ion scanning range was 380-980 m/z, the MS1 resolution was 240,000 (at 200 m/z), the Normalized AGC Target was set at 500%, and the Maximum IT was 5 ms. For MS2, the DIA data acquisition mode was adopted, with 299 scanning windows configured. The Isolation Window was 2 m/z, the HCD Collision Energy was 25 eV, the Normalized AGC Target was 500%, and the Maximum IT was 3 ms.

Selecting an appropriate protein sequence database is a fundamental and critical step for the qualitative proteomic analysis of mass spectrometry data. The database used in this project was GCF_000001405.40_id9606_136282s_2025_05_21.fasta. Data analysis was performed using DIA-NN 1.9.2. The main software parameters were set as follows: the enzyme was trypsin, the maximum number of missed cleavages was 1, the fixed modification was carbamidomethylation (C), and the variable modifications were oxidation (M) and acetylation (protein N-terminus). All reported data were based on a 99% protein identification confidence level with a false discovery rate (FDR) ≤ 1%.

Single-cell RNA sequencing analyses

GSE213740 is a scRNA-seq dataset containing 9 cases of human ascending aortic tissues, including 6 dissected, 3 normal aortic tissues.[15] The Seurat package was used to load and process the scRNA-seq data.[16] Firstly, low-quality cells were eliminated for quality control, including those with mitochondrial genes > 10%, erythrocyte genes > 5%, nCount > 40,000 and nFeature > 7,000. Secondly, the standard process of scRNA-seq data was carried out, including normalization, highly variable features identification, scaling and centering, principal component analysis dimensional reduction, integration, adjusting batch effects by Harmony algorithm,[17] shared nearest-neighbor graph construction, cell cluster determination, and uniform manifold approximation and projection (UMAP) dimensional reduction and visualization.

Based on the specific cell markers in aortic tissues described in previous literature,[18,19] including MYH11 (smooth muscle cell, SMC), DCN (fibroblast, FIB), PECAM1 (endothelial cell, EC), MPZ (Schwann cell), PTPRC (immune cell), LYZ (macrophage), CD3D (T cell), CD79A (B cell), and MKI67 (proliferating cell).

The FindAllMarkers function was used to calculate the differentially expressed genes (DEGs) in each cell type. The top 5 DEGs of each cell type with the screening criteria of absolute log2FC of the average expression > 1 and adjusted p-value < 0.05 were shown.

The CellChatDB database integrates signaling molecule interactions from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database, as well as experimentally validated ligand-receptor pairs from literature. The CellChat package can be employed to infer, analyze, and visualize cell-cell communication from scRNA-seq based on the CellChatDB database.[20] The ligand-receptor pair analysis in CellChat primarily quantifies the probability of signal communication between distinct cell types. By using this, we computed cell-cell communication in aortic tissues, focusing on the role of the encoding genes of candidate proteins in cell-cell crosstalk.

Drug Target Analysis

We used the Therapeutic Target Database (TTD), Drug-Gene Interaction Database (DGIdb), DrugBank, and Open Targets Platform to evaluate the druggability of each candidate proteins. We screened out drug molecules that may be potentially used for the treatment of AD.[21-24]

Phenome-wide association study analysis

The AstraZeneca PheWAS Portal is a public repository of gene-phenotype associations generated using sequencing and phenotypic data obtained from the UKB.[25] We conducted an online PheWAS analysis on it to assess the associations between various traits and candidate proteins, determining whether candidate proteins have potential detrimental effects on other phenotypes.

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Supplementary Tables

Table S1. Causal association and sensitivity analyses between blood pressure traits (UKB) and aortic dissection.

Table S2. Causal association between plasma proteins and essential hypertension (UKB).

Table S3. Causal association between plasma proteins and diastolic blood pressure (UKB).

Table S4. Causal association between plasma proteins and aortic dissection.

Table S5. Functional enrichment analysis of causal proteins associated with essential hypertension (UKB).

Table S6. Functional enrichment analysis of causal proteins associated with diastolic blood pressure (UKB).

Table S7. Functional enrichment analysis of causal proteins associated with aortic dissection.

Table S8. Bayesian colocalization analysis for candidate proteins to blood pressure traits (UKB) and aortic dissection.

Table S9. Multi-trait colocalization analysis of candidate proteins, essential hypertension (UKB), and aortic dissection.

Table S10. Multi-trait colocalization analysis of candidate proteins, diastolic blood pressure (UKB), and aortic dissection.

Table S11. Sensitivity analyses between candidate proteins, blood pressure traits (UKB), and aortic dissection.

Table S12. Mediation effect of blood pressure traits (UKB) on protein-associated aortic dissection.

Table S13. Causal association between blood pressure traits (MVP) and aortic dissection.

Table S14. Causal association between plasma proteins and essential hypertension (MVP).

Table S15. Causal association between plasma proteins and diastolic blood pressure (MVP).

Table S16. Functional enrichment analysis of causal proteins associated with essential hypertension (MVP).

Table S17. Functional enrichment analysis of causal proteins associated with diastolic blood pressure (MVP).

Table S18. Bayesian colocalization analysis for candidate proteins to blood pressure traits (MVP).

Table S19. Mediation effect of blood pressure traits (MVP) on protein-associated aortic dissection.

Table S20. Causal association between tissue-specific gene expression and aortic dissection.

Table S21. Potential drugs for candidate proteins in Therapeutic Target Database (TTD).

Table S22. Potential drugs for candidate proteins in Drug-Gene Interaction Database (DGIdb).

Table S23. Potential drugs for candidate proteins in DrugBank.

Table S24. Potential drugs for candidate proteins in Open Targets Platform.

Table S1. Causal association and sensitivity analyses between blood pressure traits (UKB) and aortic dissection.

Exposure	Outcome	Method	nSNP	OR (95% CI)	P value	Adjusted P	Cochran's Q pval	MR Egger intercept pval	MR-PRESSO Global pval
HTN	AD	Inverse variance weighted	201	1.52 (1.27, 1.81)	4.19E-06	2.10E-05	1.66E-03		
HTN	AD	MR Egger	201	1.78 (1.07, 2.95)	2.72E-02	4.53E-02	1.54E-03	5.12E-01	
HTN	AD	Weighted median	201	1.47 (1.16, 1.88)	1.73E-03	3.71E-03			
HTN	AD	MR-PRESSO (Raw)	201	1.52 (1.27, 1.81)	7.44e-06	2.14e-05			0.002
HTN	AD	MR-PRESSO (Outlier-corrected)	197	1.59 (1.35, 1.87)	5.63E-08	8.45E-07			
SBP	AD	Inverse variance weighted	201	1.15 (0.76, 1.74)	5.09E-01	5.10E-01	2.96E-04		
SBP	AD	MR Egger	201	1.85 (0.54, 6.31)	3.26E-01	3.93E-01	2.84E-04	4.19E-01	
SBP	AD	Weighted median	201	1.54 (0.89, 2.65)	1.22E-01	1.67E-01			
SBP	AD	MR-PRESSO (Raw)	201	1.15 (0.76, 1.74)	5.10E-01	5.10E-01			0.002
SBP	AD	MR-PRESSO (Outlier-corrected)	195	1.22 (0.81, 1.82)	3.41E-01	3.93E-01			
DBP	AD	Inverse variance weighted	187	2.97 (1.88, 4.69)	2.94E-06	2.10e-05	7.80E-07		
DBP	AD	MR Egger	187	4.07 (0.90, 18.38)	6.92E-02	1.04E-01	6.49E-07	6.67E-01	
DBP	AD	Weighted median	187	2.20 (1.24, 3.91)	7.38E-03	1.38E-02			
DBP	AD	MR-PRESSO (Raw)	187	2.97 (1.88, 4.69)	5.64e-06	2.12e-05			<0.001
DBP	AD	MR-PRESSO (Outlier-corrected)	181	2.49 (1.69, 3.68)	8.55e-06	2.14e-05			

Table S2. Causal association between plasma proteins and essential hypertension (UKB).

Exposure	Outcome	Beta (95% CI)	P value	Adjusted P
ABLIM3	HTN	-0.13 (-0.22, -0.05)	2.09E-03	3.29E-02
ACADVL	HTN	-0.51 (-0.7, -0.32)	1.07E-07	9.98E-06
ACVRL1	HTN	-0.08 (-0.13, -0.03)	3.35E-03	4.47E-02
ADH5	HTN	0.09 (0.03, 0.15)	1.61E-03	2.80E-02
ADK	HTN	-0.3 (-0.48, -0.12)	1.27E-03	2.32E-02
AGT	HTN	0.17 (0.12, 0.22)	5.56E-11	1.05E-08
AIF1	HTN	-0.14 (-0.21, -0.06)	2.08E-04	5.63E-03
ALDH2	HTN	0.58 (0.43, 0.72)	3.75E-15	1.42E-12
ALOX15B	HTN	-0.21 (-0.34, -0.08)	1.27E-03	2.32E-02
ANTXR1	HTN	0.6 (0.41, 0.79)	9.79E-10	1.65E-07
APOC3	HTN	-0.12 (-0.18, -0.05)	2.43E-04	6.46E-03
ARHGEF25	HTN	0.18 (0.1, 0.25)	8.63E-06	4.08E-04
ARL3	HTN	0.16 (0.1, 0.22)	2.02E-07	1.57E-05
ASPN	HTN	0.05 (0.02, 0.08)	2.59E-03	3.66E-02
BRD2	HTN	0.41 (0.22, 0.6)	1.60E-05	6.21E-04
C3	HTN	0.19 (0.09, 0.3)	3.40E-04	8.87E-03
C3	HTN	-0.17 (-0.27, -0.06)	2.03E-03	3.29E-02
CALB2	HTN	0.4 (0.22, 0.58)	1.97E-05	7.27E-04
CCM2	HTN	0.23 (0.08, 0.38)	2.72E-03	3.81E-02
CD46	HTN	-0.06 (-0.1, -0.02)	3.09E-03	4.17E-02
CD86	HTN	0.27 (0.1, 0.43)	1.36E-03	2.43E-02
CHRDL1	HTN	0.11 (0.06, 0.15)	9.23E-07	6.07E-05
CHST12	HTN	-0.08 (-0.13, -0.03)	3.77E-03	4.92E-02
CLMP	HTN	0.07 (0.03, 0.11)	5.81E-04	1.35E-02
LAYN	HTN	-0.42 (-0.59, -0.24)	2.80E-06	1.63E-04
LEAP2	HTN	-0.06 (-0.09, -0.02)	8.11E-04	1.70E-02
LIMA1	HTN	-0.56 (-0.72, -0.41)	4.44E-13	9.60E-11
LYPLAL1	HTN	0.14 (0.05, 0.24)	3.37E-03	4.47E-02
MANBA	HTN	-0.08 (-0.11, -0.05)	2.08E-07	1.57E-05
MAP3K3	HTN	0.3 (0.11, 0.49)	2.29E-03	3.46E-02
MCEE	HTN	-0.24 (-0.38, -0.1)	1.03E-03	2.05E-02
MCEMP1	HTN	-0.27 (-0.45, -0.1)	1.87E-03	3.11E-02
MET	HTN	0.14 (0.07, 0.21)	6.13E-05	1.97E-03
MGAT1	HTN	-0.29 (-0.45, -0.12)	5.46E-04	1.31E-02
NADK	HTN	-0.18 (-0.26, -0.11)	1.03E-06	6.48E-05
NCAN	HTN	-0.09 (-0.14, -0.04)	7.95E-04	1.69E-02
NCF1	HTN	0.06 (0.03, 0.08)	3.07E-05	1.08E-03
NMT1	HTN	0.75 (0.56, 0.95)	7.59E-14	1.91E-11
NPPB	HTN	-0.49 (-0.59, -0.39)	1.03E-21	1.56E-18
NPTX1	HTN	-0.07 (-0.1, -0.04)	4.39E-06	2.46E-04
NQO1	HTN	-0.08 (-0.13, -0.04)	3.46E-04	8.88E-03
NTRK3	HTN	-0.07 (-0.11, -0.03)	6.39E-04	1.44E-02
PCSK1N	HTN	0.09 (0.03, 0.15)	2.19E-03	3.41E-02
PDGFRA	HTN	-0.15 (-0.24, -0.06)	1.27E-03	2.32E-02
PDXK	HTN	-0.22 (-0.29, -0.14)	1.02E-08	1.40E-06
PGLYRP2	HTN	0.05 (0.02, 0.08)	3.84E-03	4.97E-02
PGP	HTN	0.07 (0.03, 0.12)	2.83E-03	3.89E-02
PIANP	HTN	0.09 (0.04, 0.14)	1.12E-03	2.17E-02

COMT	HTN	-0.32 (-0.43, -0.21)	8.89E-09	1.35E-06
CRAT	HTN	0.17 (0.06, 0.28)	2.31E-03	3.46E-02
CRLF1	HTN	-0.09 (-0.13, -0.05)	2.15E-05	7.75E-04
CSK	HTN	0.71 (0.56, 0.86)	1.19E-20	8.98E-18
DBNL	HTN	0.2 (0.07, 0.34)	2.82E-03	3.89E-02
DCTPP1	HTN	-0.38 (-0.55, -0.2)	3.99E-05	1.31E-03
ENDOU	HTN	0.23 (0.08, 0.38)	2.08E-03	3.29E-02
ENPEP	HTN	-0.12 (-0.15, -0.09)	7.37E-14	1.91E-11
ENTPD6	HTN	0.13 (0.06, 0.21)	3.89E-04	9.82E-03
EPB41	HTN	-0.28 (-0.41, -0.16)	1.36E-05	6.07E-04
EPHB2	HTN	0.05 (0.02, 0.09)	2.49E-03	3.56E-02
FABP2	HTN	-0.07 (-0.11, -0.04)	1.41E-05	6.11E-04
FN1	HTN	0.15 (0.08, 0.21)	7.75E-06	3.85E-04
FN1	HTN	0.15 (0.08, 0.21)	7.75E-06	3.85E-04
FN1	HTN	-0.13 (-0.19, -0.07)	7.88E-06	3.85E-04
FUT5	HTN	0.03 (0.01, 0.05)	1.45E-03	2.56E-02
GFER	HTN	-0.34 (-0.51, -0.18)	6.68E-05	2.11E-03
GHR	HTN	0.09 (0.05, 0.14)	8.55E-05	2.59E-03
GPT	HTN	0.28 (0.1, 0.46)	2.21E-03	3.41E-02
GUK1	HTN	-0.13 (-0.2, -0.07)	8.52E-05	2.59E-03
HEXIM1	HTN	0.3 (0.19, 0.41)	9.08E-08	9.82E-06
HEXIM2	HTN	0.29 (0.18, 0.4)	1.63E-07	1.37E-05
HGF	HTN	0.14 (0.06, 0.22)	8.20E-04	1.70E-02
HGFAC	HTN	-0.03 (-0.04, -0.01)	1.69E-04	4.82E-03
HS6ST1	HTN	-0.12 (-0.18, -0.07)	1.70E-05	6.43E-04
ICAM4	HTN	0.17 (0.08, 0.25)	1.81E-04	5.08E-03
PIANP	HTN	0.08 (0.03, 0.13)	1.12E-03	2.17E-02
POGLUT1	HTN	-0.07 (-0.12, -0.03)	1.14E-03	2.17E-02
POR	HTN	0.09 (0.03, 0.14)	3.03E-03	4.14E-02
PPIC	HTN	0.06 (0.02, 0.09)	7.31E-04	1.60E-02
PRKCB	HTN	0.2 (0.07, 0.32)	1.98E-03	3.25E-02
PRSS8	HTN	0.26 (0.09, 0.43)	2.08E-03	3.29E-02
PSMD9	HTN	-0.12 (-0.2, -0.04)	2.39E-03	3.51E-02
PTK7	HTN	0.24 (0.13, 0.34)	1.60E-05	6.21E-04
RAB1A	HTN	0.44 (0.28, 0.61)	1.12E-07	9.98E-06
RAB31	HTN	0.12 (0.04, 0.2)	3.73E-03	4.91E-02
RARRES1	HTN	0.04 (0.02, 0.06)	6.22E-04	1.43E-02
RBP7	HTN	-0.14 (-0.23, -0.06)	9.77E-04	2.00E-02
RELT	HTN	-0.31 (-0.49, -0.13)	7.25E-04	1.60E-02
RIGI	HTN	0.21 (0.1, 0.33)	1.99E-04	5.47E-03
RNASE4	HTN	0.05 (0.02, 0.08)	2.33E-03	3.46E-02
ROBO1	HTN	0.16 (0.06, 0.25)	9.90E-04	2.00E-02
SAT2	HTN	0.12 (0.08, 0.17)	4.07E-08	5.13E-06
SDF2	HTN	-0.06 (-0.1, -0.02)	1.74E-03	2.99E-02
SEMA7A	HTN	-0.18 (-0.29, -0.07)	1.30E-03	2.34E-02
SHBG	HTN	0.1 (0.04, 0.15)	4.86E-04	1.19E-02
SYT11	HTN	-0.33 (-0.47, -0.18)	5.84E-06	3.15E-04
TCEA2	HTN	-0.17 (-0.23, -0.1)	6.12E-07	4.21E-05
TEK	HTN	0.09 (0.03, 0.15)	2.33E-03	3.46E-02
TIE1	HTN	-0.13 (-0.18, -0.08)	6.86E-08	7.99E-06
TMEM106B	HTN	-0.2 (-0.28, -0.12)	1.57E-06	9.48E-05
TNFRSF17	HTN	-0.11 (-0.18, -0.04)	1.76E-03	3.00E-02

IL11RA	HTN	-0.05 (-0.09, -0.02)	2.44E-03	3.52E-02
IL13RA1	HTN	0.05 (0.02, 0.08)	7.94E-04	1.69E-02
ITIH1	HTN	-0.06 (-0.09, -0.03)	3.38E-05	1.14E-03
ITIH4	HTN	0.17 (0.07, 0.27)	5.82E-04	1.35E-02
ITPKA	HTN	0.28 (0.15, 0.41)	3.38E-05	1.14E-03
KIR2DL3	HTN	0.02 (0.01, 0.03)	3.87E-03	4.97E-02
KIT	HTN	0.3 (0.11, 0.5)	2.42E-03	3.52E-02
KLC1	HTN	0.24 (0.13, 0.35)	1.32E-05	6.03E-04
KYAT3	HTN	-0.09 (-0.12, -0.06)	1.01E-07	9.98E-06
TNFSF12	HTN	0.1 (0.06, 0.14)	3.23E-07	2.33E-05
TNFSF14	HTN	-0.25 (-0.41, -0.09)	1.87E-03	3.11E-02
TTL	HTN	0.38 (0.21, 0.55)	1.60E-05	6.21E-04
TYRO3	HTN	-0.15 (-0.24, -0.06)	1.19E-03	2.26E-02
UBE2C	HTN	0.13 (0.06, 0.2)	1.52E-04	4.42E-03
ULK3	HTN	0.52 (0.41, 0.64)	7.86E-19	3.96E-16
VTN	HTN	-0.03 (-0.05, -0.01)	4.25E-04	1.05E-02
WARS1	HTN	0.08 (0.04, 0.12)	1.27E-04	3.77E-03
WBP2	HTN	0.41 (0.22, 0.59)	1.46E-05	6.14E-04

Table S3. Causal association between plasma proteins and diastolic blood pressure (UKB).

Exposure	Outcome	Beta (95% CI)	P value	Adjusted P
ACADVL	DBP	-0.26 (-0.34, -0.17)	1.11E-08	1.20E-06
ADH1C	DBP	-0.07 (-0.11, -0.04)	1.52E-05	7.19E-04
AGT	DBP	0.09 (0.06, 0.11)	5.31E-13	8.93E-11
AIF1	DBP	-0.07 (-0.1, -0.03)	6.42E-05	2.70E-03
AK1	DBP	-0.13 (-0.22, -0.05)	1.10E-03	2.39E-02
ALDH2	DBP	0.28 (0.22, 0.35)	6.45E-17	1.39E-14
ANTXR1	DBP	0.17 (0.09, 0.26)	1.26E-04	4.14E-03
AOC1	DBP	-0.01 (-0.01, 0)	8.25E-04	1.88E-02
APOB	DBP	-0.12 (-0.18, -0.06)	1.07E-04	3.87E-03
ARHGEF25	DBP	0.08 (0.04, 0.12)	2.32E-04	6.49E-03
ARL3	DBP	0.05 (0.02, 0.08)	2.12E-03	3.87E-02
ARL4D	DBP	0.16 (0.08, 0.25)	7.45E-05	3.03E-03
AZGP1	DBP	-0.04 (-0.06, -0.02)	9.27E-06	4.52E-04
BDH2	DBP	-0.05 (-0.07, -0.03)	7.78E-07	4.90E-05
BRD2	DBP	0.22 (0.14, 0.31)	4.27E-07	2.94E-05
CCN3	DBP	-0.31 (-0.38, -0.25)	7.89E-22	3.98E-19
CD300A	DBP	-0.02 (-0.02, -0.01)	8.06E-04	1.88E-02
CDH17	DBP	-0.02 (-0.04, -0.01)	2.29E-03	4.08E-02
CFHR3	DBP	-0.08 (-0.12, -0.04)	1.41E-04	4.45E-03
CFHR4	DBP	-0.01 (-0.02, -0.01)	3.46E-04	9.35E-03
CNTFR	DBP	0.04 (0.02, 0.06)	1.28E-03	2.61E-02
CNTN5	DBP	0.03 (0.01, 0.05)	5.32E-04	1.33E-02
COL6A3	DBP	-0.1 (-0.17, -0.04)	1.61E-03	3.08E-02
CPLX1	DBP	0.13 (0.05, 0.2)	8.22E-04	1.88E-02
ITPKA	DBP	0.15 (0.09, 0.21)	2.16E-06	1.30E-04
KIT	DBP	0.16 (0.07, 0.25)	6.24E-04	1.52E-02
KLC1	DBP	0.13 (0.08, 0.18)	3.17E-07	2.30E-05
LEAP2	DBP	-0.02 (-0.04, -0.01)	1.95E-03	3.60E-02
LGALS4	DBP	0.22 (0.15, 0.3)	1.63E-08	1.54E-06
LIMA1	DBP	-0.34 (-0.41, -0.27)	3.56E-21	1.35E-18
LRRTM2	DBP	0.09 (0.03, 0.14)	1.37E-03	2.73E-02
MANBA	DBP	-0.03 (-0.04, -0.02)	8.49E-06	4.28E-04
MARK3	DBP	0.14 (0.05, 0.22)	1.44E-03	2.80E-02
MFGE8	DBP	0.03 (0.01, 0.05)	8.49E-04	1.89E-02
MXRA7	DBP	-0.03 (-0.05, -0.02)	9.85E-05	3.63E-03
NCAN	DBP	-0.06 (-0.09, -0.04)	1.18E-07	1.05E-05
NMT1	DBP	0.38 (0.28, 0.47)	9.17E-16	1.73E-13
NPPB	DBP	-0.21 (-0.25, -0.16)	2.25E-18	6.79E-16
NPPB	DBP	-0.06 (-0.1, -0.02)	1.26E-03	2.61E-02
NT5C3A	DBP	0.09 (0.03, 0.14)	1.66E-03	3.15E-02
NUDT2	DBP	-0.04 (-0.06, -0.02)	4.30E-04	1.14E-02
PARP1	DBP	0.14 (0.05, 0.24)	1.88E-03	3.51E-02
PCNP	DBP	0.08 (0.03, 0.13)	2.73E-03	4.65E-02
PCOLCE	DBP	-0.05 (-0.08, -0.03)	7.62E-05	3.03E-03
PCSK1N	DBP	0.04 (0.02, 0.07)	2.22E-03	4.01E-02
PDCD6IP	DBP	-0.08 (-0.13, -0.04)	9.84E-05	3.63E-03
PDE5A	DBP	-0.06 (-0.09, -0.04)	3.19E-07	2.30E-05
PDE5A	DBP	-0.06 (-0.08, -0.04)	3.19E-07	2.30E-05

CSGALNACT2	DBP	0.06 (0.02, 0.1)	2.94E-03	4.94E-02
CSK	DBP	0.44 (0.37, 0.51)	1.09E-35	1.65E-32
DNER	DBP	-0.03 (-0.04, -0.01)	2.63E-03	4.57E-02
ENPEP	DBP	-0.04 (-0.06, -0.03)	3.78E-09	4.77E-07
EPO	DBP	0.12 (0.06, 0.18)	1.23E-04	4.13E-03
ERAP2	DBP	0.02 (0.01, 0.03)	2.57E-03	4.52E-02
ERLEC1	DBP	-0.1 (-0.16, -0.05)	1.95E-04	5.91E-03
F2	DBP	0.07 (0.03, 0.11)	2.21E-04	6.30E-03
F2	DBP	0.08 (0.04, 0.12)	2.21E-04	6.30E-03
FCMR	DBP	0.06 (0.03, 0.1)	1.37E-03	2.73E-02
FGL1	DBP	-0.03 (-0.04, -0.01)	4.69E-04	1.21E-02
GFER	DBP	-0.23 (-0.31, -0.15)	1.33E-08	1.34E-06
HEXIM1	DBP	0.1 (0.05, 0.15)	1.32E-04	4.26E-03
HEXIM2	DBP	0.1 (0.05, 0.15)	1.14E-04	3.93E-03
HP	DBP	-0.02 (-0.03, -0.01)	2.92E-06	1.64E-04
HP	DBP	-0.02 (-0.03, -0.01)	1.25E-03	2.61E-02
HSPA1L	DBP	0.06 (0.03, 0.09)	3.98E-06	2.15E-04
HSPG2	DBP	0.03 (0.01, 0.05)	5.37E-04	1.33E-02
IGFLR1	DBP	0.02 (0.01, 0.04)	2.66E-03	4.58E-02
IL17RD	DBP	0.02 (0.01, 0.04)	8.31E-04	1.88E-02
IRAG1	DBP	-0.18 (-0.22, -0.14)	2.75E-17	6.93E-15
PLCG1	DBP	-0.13 (-0.19, -0.07)	3.69E-05	1.59E-03
PRSS8	DBP	0.23 (0.15, 0.31)	6.22E-09	7.23E-07
PTPN9	DBP	0.11 (0.04, 0.18)	1.40E-03	2.75E-02
QSOX2	DBP	0.03 (0.01, 0.04)	3.43E-04	9.35E-03
RELT	DBP	-0.2 (-0.29, -0.12)	2.23E-06	1.30E-04
SAT2	DBP	0.05 (0.03, 0.07)	2.23E-07	1.87E-05
SCUBE3	DBP	-0.04 (-0.06, -0.02)	1.81E-04	5.59E-03
SHMT1	DBP	0.02 (0.01, 0.03)	4.71E-04	1.21E-02
SPATA20	DBP	0.03 (0.01, 0.04)	2.06E-04	6.10E-03
SULT1A3	DBP	-0.08 (-0.11, -0.05)	6.03E-07	3.97E-05
TCEA2	DBP	-0.1 (-0.13, -0.07)	6.14E-10	8.45E-08
THBS2	DBP	-0.12 (-0.19, -0.06)	7.81E-05	3.03E-03
TIE1	DBP	-0.07 (-0.09, -0.05)	8.33E-11	1.26E-08
TNFRSF11B	DBP	-0.05 (-0.07, -0.02)	1.11E-04	3.91E-03
TNFRSF17	DBP	-0.07 (-0.11, -0.04)	1.87E-05	8.58E-04
TXNL4B	DBP	0.05 (0.02, 0.08)	1.16E-03	2.47E-02
TYRO3	DBP	-0.07 (-0.11, -0.03)	9.86E-04	2.16E-02
ULK3	DBP	0.33 (0.27, 0.38)	5.66E-33	4.28E-30
VARS1	DBP	0.07 (0.04, 0.1)	4.11E-06	2.15E-04
VAT1	DBP	0.11 (0.05, 0.18)	8.09E-04	1.88E-02
WBP2	DBP	0.19 (0.1, 0.27)	1.97E-05	8.75E-04

Table S4. Causal association between plasma proteins and aortic dissection.

Exposure	Outcome	OR (95% CI)	P value
ADI1	AD	0.39 (0.16, 0.96)	4.14E-02
B3GLCT	AD	0.64 (0.46, 0.89)	7.11E-03
BDNF	AD	3.28 (1.46, 7.38)	4.06E-03
C3	AD	0.26 (0.07, 0.93)	3.84E-02
C3	AD	0.32 (0.11, 0.94)	3.84E-02
C3	AD	0.26 (0.07, 0.93)	3.84E-02
CADM1	AD	0.54 (0.29, 0.99)	4.69E-02
CCDC126	AD	1.39 (1, 1.92)	4.74E-02
CCL19	AD	0.08 (0.01, 0.49)	6.24E-03
CCN3	AD	0.22 (0.06, 0.9)	3.53E-02
CHI3L1	AD	1.19 (1.02, 1.4)	2.71E-02
CHKB	AD	0.23 (0.06, 0.86)	2.83E-02
CNPY3	AD	2.15 (1, 4.61)	4.90E-02
CNTNAP2	AD	0.75 (0.57, 0.98)	3.84E-02
COL6A3	AD	0.12 (0.04, 0.42)	8.00E-04
COMP	AD	0.55 (0.33, 0.9)	1.72E-02
CPB2	AD	0.71 (0.58, 0.88)	1.36E-03
CYB5R2	AD	1.39 (1.01, 1.92)	4.10E-02
CYRIB	AD	6.25 (1.17, 33.44)	3.21E-02
DECR1	AD	0 (0, 0.47)	3.13E-02
DUSP13B	AD	0.38 (0.18, 0.79)	1.01E-02
FAH	AD	1.43 (1.02, 1.99)	3.58E-02
FCER2	AD	1.39 (1.01, 1.92)	4.64E-02
FCRL6	AD	2.82 (1.29, 6.15)	9.40E-03
LRIG3	AD	1.23 (1, 1.5)	4.57E-02
MANSC4	AD	0.58 (0.36, 0.93)	2.47E-02
MAPK8	AD	4.93 (1.08, 22.54)	3.95E-02
MESD	AD	12.04 (2.06, 70.5)	5.78E-03
MST1	AD	1.17 (1.03, 1.32)	1.36E-02
NCR1	AD	1.57 (1.15, 2.13)	4.18E-03
NELL1	AD	1.58 (1.17, 2.14)	3.09E-03
NPL	AD	1.61 (1.04, 2.51)	3.28E-02
NPPB	AD	0.73 (0.54, 1)	4.88E-02
NQO1	AD	0.73 (0.55, 0.97)	2.99E-02
NUDT5	AD	0.18 (0.06, 0.56)	3.15E-03
PCOLCE2	AD	0.82 (0.68, 0.99)	3.49E-02
PDCD1LG2	AD	0.67 (0.48, 0.93)	1.51E-02
PLEK	AD	0.3 (0.11, 0.77)	1.25E-02
PLOD2	AD	3.01 (1.09, 8.32)	3.40E-02
POR	AD	1.58 (1.02, 2.44)	3.90E-02
PPCS	AD	0.31 (0.13, 0.74)	8.09E-03
PRTN3	AD	1.37 (1.07, 1.76)	1.18E-02
PTGR1	AD	1.22 (1.02, 1.45)	2.53E-02
REG4	AD	3.18 (1.56, 6.48)	1.42E-03
RIGI	AD	3.58 (1.32, 9.7)	1.21E-02
RPE	AD	5.03 (1.71, 14.77)	3.28E-03
SCO2	AD	2.53 (1.06, 6.06)	3.64E-02
SEMA6A	AD	0.15 (0.05, 0.45)	8.05E-04

GHR	AD	1.83 (1.2, 2.81)	5.27E-03
GLIPR2	AD	1.41 (1.01, 1.97)	4.43E-02
GPC5	AD	0.78 (0.63, 0.98)	3.18E-02
HTN3	AD	0.43 (0.23, 0.82)	9.92E-03
IBSP	AD	2.39 (1, 5.71)	4.94E-02
IDS	AD	3.06 (1.01, 9.26)	4.80E-02
IL13RA1	AD	1.58 (1.26, 1.97)	6.18E-05
IL17B	AD	5.56 (1.5, 20.65)	1.03E-02
INHBC	AD	1.19 (1.02, 1.37)	2.20E-02
IRF3	AD	4.03 (1.16, 13.95)	2.80E-02
KRT20	AD	0.31 (0.1, 1)	4.96E-02
LILRB1	AD	0.74 (0.62, 0.89)	1.22E-03
LMAN2L	AD	7.29 (1.37, 38.86)	2.00E-02
SHMT1	AD	0.81 (0.67, 0.98)	3.33E-02
SIRPG	AD	0.46 (0.26, 0.84)	1.06E-02
SLITRK1	AD	4.67 (1.04, 20.88)	4.38E-02
SNPH	AD	5.2 (1.13, 23.85)	3.38E-02
SPOCK2	AD	0.53 (0.35, 0.82)	4.45E-03
TFRC	AD	3.31 (1.01, 10.87)	4.85E-02
THSD1	AD	1.59 (1.06, 2.4)	2.53E-02
UNC5C	AD	0.62 (0.39, 0.97)	3.81E-02
UNC5D	AD	2.43 (1.06, 5.59)	3.69E-02
VOPP1	AD	0.17 (0.03, 0.91)	3.88E-02
VPS26A	AD	1.79 (1.11, 2.9)	1.77E-02
ZYX	AD	4.84 (1.52, 15.42)	7.57E-03

Table S5. Functional enrichment analysis of causal proteins associated with essential hypertension (UKB).

Type	Description	GeneRatio	BgRatio	RichFactor	FoldEnrichment	zScore	pvalue	p.adjust
BP	positive regulation of kinase activity	12/111	337/18870	0.04	6.05	7.20	7.02E-07	1.16E-03
BP	positive regulation of transferase activity	13/111	414/18870	0.03	5.34	6.87	9.69E-07	1.16E-03
BP	peptidyl-tyrosine phosphorylation	10/111	276/18870	0.04	6.16	6.64	5.36E-06	3.42E-03
BP	peptidyl-tyrosine modification	10/111	278/18870	0.04	6.12	6.61	5.71E-06	3.42E-03
BP	positive regulation of protein kinase B signaling	8/111	171/18870	0.05	7.95	7.03	7.71E-06	3.69E-03
BP	positive regulation of cytokine production	12/111	499/18870	0.02	4.09	5.38	3.77E-05	1.50E-02
BP	protein kinase B signaling	9/111	290/18870	0.03	5.28	5.64	5.43E-05	1.83E-02
BP	positive regulation of peptidyl-tyrosine phosphorylation	7/111	168/18870	0.04	7.08	6.09	6.11E-05	1.83E-02
BP	regulation of immune effector process	10/111	389/18870	0.03	4.37	5.17	1.00E-04	2.62E-02
BP	regulation of protein kinase B signaling	8/111	248/18870	0.03	5.48	5.47	1.10E-04	2.62E-02
BP	positive regulation of vascular endothelial growth factor receptor signaling pathway	3/111	18/18870	0.17	28.33	8.92	1.52E-04	3.30E-02
BP	regulation of angiogenesis	9/111	349/18870	0.03	4.38	4.91	2.20E-04	3.74E-02
BP	positive regulation of phosphatidylinositol 3-kinase activity	3/111	21/18870	0.14	24.29	8.21	2.44E-04	3.74E-02
BP	regulation of extracellular matrix assembly	3/111	21/18870	0.14	24.29	8.21	2.44E-04	3.74E-02
BP	regulation of vasculature development	9/111	354/18870	0.03	4.32	4.85	2.45E-04	3.74E-02
BP	positive regulation of cell projection organization	9/111	355/18870	0.03	4.31	4.84	2.50E-04	3.74E-02
BP	substrate adhesion-dependent cell spreading	5/111	100/18870	0.05	8.50	5.78	3.11E-04	4.38E-02
BP	small molecule catabolic process	9/111	375/18870	0.02	4.08	4.63	3.73E-04	4.97E-02
KEGG	Integrin signaling	7/71	154/9521	0.05	6.10	5.53	1.41E-04	2.95E-02

Table S6. Functional enrichment analysis of causal proteins associated with diastolic blood pressure (UKB).

Type	Description	GeneRatio	BgRatio	RichFactor	FoldEnrichment	zScore	pvalue	p.adjust
BP	positive regulation of receptor signaling pathway via JAK-STAT	4/84	49/18870	0.08	18.34	8.13	6.65E-05	5.00E-02
BP	positive regulation of receptor signaling pathway via STAT	4/84	53/18870	0.08	16.95	7.78	9.06E-05	5.00E-02
BP	ethanol metabolic process	3/84	21/18870	0.14	32.09	9.53	1.07E-04	5.00E-02
BP	regulation of extracellular matrix assembly	3/84	21/18870	0.14	32.09	9.53	1.07E-04	5.00E-02
BP	positive regulation of cardiac muscle hypertrophy	3/84	35/18870	0.09	19.26	7.23	5.02E-04	1.42E-01
BP	positive regulation of muscle hypertrophy	3/84	36/18870	0.08	18.72	7.12	5.46E-04	1.42E-01
BP	biogenic amine metabolic process	4/84	99/18870	0.04	9.08	5.39	9.97E-04	1.42E-01
BP	negative regulation of protein serine/threonine kinase activity	4/84	100/18870	0.04	8.99	5.35	1.04E-03	1.42E-01
BP	positive regulation of intracellular estrogen receptor signaling pathway	2/84	11/18870	0.18	40.84	8.84	1.05E-03	1.42E-01
BP	renal sodium excretion	2/84	11/18870	0.18	40.84	8.84	1.05E-03	1.42E-01
BP	regulation of excretion	2/84	11/18870	0.18	40.84	8.84	1.05E-03	1.42E-01
BP	receptor signaling pathway via JAK-STAT	5/84	174/18870	0.03	6.46	4.83	1.08E-03	1.42E-01
BP	extracellular matrix assembly	3/84	46/18870	0.07	14.65	6.20	1.13E-03	1.42E-01
BP	ethanol catabolic process	2/84	12/18870	0.17	37.44	8.44	1.26E-03	1.42E-01
BP	positive regulation of intracellular steroid hormone receptor signaling pathway	2/84	12/18870	0.17	37.44	8.44	1.26E-03	1.42E-01
BP	acute-phase response	3/84	48/18870	0.06	14.04	6.05	1.27E-03	1.42E-01
BP	regulation of receptor signaling pathway via JAK-STAT	4/84	106/18870	0.04	8.48	5.16	1.29E-03	1.42E-01
BP	alcohol metabolic process	7/84	373/18870	0.02	4.22	4.19	1.37E-03	1.42E-01
BP	activation of Janus kinase activity	2/84	13/18870	0.15	34.56	8.09	1.48E-03	1.42E-01
BP	receptor signaling pathway via STAT	5/84	188/18870	0.03	5.97	4.58	1.52E-03	1.42E-01
BP	amine metabolic process	4/84	119/18870	0.03	7.55	4.79	1.97E-03	1.57E-01
BP	regulation of receptor signaling pathway via STAT	4/84	119/18870	0.03	7.55	4.79	1.97E-03	1.57E-01

BP	primary alcohol catabolic process	2/84	15/18870	0.13	29.95	7.50	1.98E-03	1.57E-01
BP	negative regulation of immune response	5/84	205/18870	0.02	5.48	4.31	2.22E-03	1.57E-01
BP	low-density lipoprotein particle remodeling	2/84	16/18870	0.13	28.08	7.25	2.26E-03	1.57E-01
BP	negative regulation of bone resorption	2/84	16/18870	0.13	28.08	7.25	2.26E-03	1.57E-01
BP	epithelial cell-cell adhesion	2/84	16/18870	0.13	28.08	7.25	2.26E-03	1.57E-01
BP	cGMP metabolic process	2/84	17/18870	0.12	26.43	7.01	2.55E-03	1.70E-01
BP	regulation of extracellular matrix organization	3/84	62/18870	0.05	10.87	5.21	2.66E-03	1.70E-01
BP	polyamine metabolic process	2/84	18/18870	0.11	24.96	6.80	2.86E-03	1.70E-01
BP	negative regulation of bone remodeling	2/84	18/18870	0.11	24.96	6.80	2.86E-03	1.70E-01
BP	positive regulation of macrophage derived foam cell differentiation	2/84	19/18870	0.11	23.65	6.60	3.19E-03	1.70E-01
BP	renal tubular secretion	2/84	19/18870	0.11	23.65	6.60	3.19E-03	1.70E-01
BP	negative regulation of cell activation	5/84	223/18870	0.02	5.04	4.05	3.19E-03	1.70E-01
BP	regulation of cardiac muscle hypertrophy	3/84	67/18870	0.04	10.06	4.97	3.32E-03	1.70E-01
BP	negative regulation of toll-like receptor signaling pathway	2/84	20/18870	0.10	22.46	6.42	3.53E-03	1.70E-01
BP	negative regulation of transcription elongation by RNA polymerase II	2/84	20/18870	0.10	22.46	6.42	3.53E-03	1.70E-01
BP	response to estrogen	3/84	69/18870	0.04	9.77	4.88	3.61E-03	1.70E-01
BP	cell junction assembly	7/84	446/18870	0.02	3.53	3.61	3.73E-03	1.70E-01
BP	regulation of muscle hypertrophy	3/84	70/18870	0.04	9.63	4.84	3.76E-03	1.70E-01
BP	negative regulation of tissue remodeling	2/84	21/18870	0.10	21.39	6.25	3.89E-03	1.70E-01
BP	negative regulation of phagocytosis	2/84	21/18870	0.10	21.39	6.25	3.89E-03	1.70E-01
BP	positive regulation of kinase activity	6/84	337/18870	0.02	4.00	3.72	3.92E-03	1.70E-01
BP	phagocytosis	5/84	237/18870	0.02	4.74	3.87	4.14E-03	1.70E-01
BP	regulation of renal system process	2/84	22/18870	0.09	20.42	6.09	4.27E-03	1.70E-01
BP	negative regulation of angiogenesis	4/84	150/18870	0.03	5.99	4.10	4.52E-03	1.70E-01

BP	negative regulation of endocytosis	3/84	75/18870	0.04	8.99	4.63	4.56E-03	1.70E-01
BP	negative regulation of DNA-templated transcription, elongation	2/84	23/18870	0.09	19.53	5.95	4.66E-03	1.70E-01
BP	peptide catabolic process	2/84	23/18870	0.09	19.53	5.95	4.66E-03	1.70E-01
BP	AMP metabolic process	2/84	23/18870	0.09	19.53	5.95	4.66E-03	1.70E-01
BP	negative regulation of blood vessel morphogenesis	4/84	152/18870	0.03	5.91	4.07	4.74E-03	1.70E-01
BP	negative regulation of vasculature development	4/84	153/18870	0.03	5.87	4.05	4.85E-03	1.70E-01
BP	nucleoside monophosphate metabolic process	3/84	77/18870	0.04	8.75	4.56	4.91E-03	1.70E-01
KEGG	Fatty acid degradation	3/45	43/9521	0.07	14.76	6.23	1.07E-03	1.22E-01
KEGG	Arginine and proline metabolism	3/45	50/9521	0.06	12.69	5.71	1.66E-03	1.22E-01
KEGG	Histidine metabolism	2/45	22/9521	0.09	19.23	5.90	4.75E-03	1.53E-01

Table S7. Functional enrichment analysis of causal proteins associated with aortic dissection.

Type	Description	GeneRatio	BgRatio	RichFactor	FoldEnrichment	zScore	pvalue	p.adjust
BP	cell killing	8/69	223/18870	0.04	9.81	8.02	1.51E-06	1.72E-03
BP	regulation of cell killing	6/69	111/18870	0.05	14.78	8.82	3.21E-06	1.72E-03
BP	regulation of leukocyte mediated immunity	8/69	249/18870	0.03	8.79	7.49	3.43E-06	1.72E-03
BP	regulation of lymphocyte mediated immunity	7/69	188/18870	0.04	10.18	7.67	5.58E-06	1.87E-03
BP	positive regulation of immune effector process	8/69	270/18870	0.03	8.10	7.12	6.23E-06	1.87E-03
BP	regulation of immune effector process	9/69	389/18870	0.02	6.33	6.43	1.17E-05	2.92E-03
BP	positive regulation of leukocyte mediated immunity	6/69	151/18870	0.04	10.87	7.37	1.88E-05	4.04E-03
BP	regulation of adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	6/69	193/18870	0.03	8.50	6.35	7.43E-05	1.36E-02
BP	positive regulation of cytokine production	9/69	499/18870	0.02	4.93	5.39	8.15E-05	1.36E-02
BP	positive regulation of lymphocyte mediated immunity	5/69	129/18870	0.04	10.60	6.63	1.09E-04	1.54E-02
BP	regulation of adaptive immune response	6/69	208/18870	0.03	7.89	6.05	1.12E-04	1.54E-02
BP	positive regulation of cell killing	4/69	76/18870	0.05	14.39	7.09	1.72E-04	2.16E-02
BP	leukocyte mediated immunity	8/69	466/18870	0.02	4.69	4.89	2.91E-04	3.34E-02
BP	positive regulation of T cell activation	6/69	251/18870	0.02	6.54	5.35	3.10E-04	3.34E-02
BP	positive regulation of cell adhesion	8/69	482/18870	0.02	4.54	4.77	3.65E-04	3.64E-02
BP	lymphocyte mediated immunity	7/69	368/18870	0.02	5.20	4.93	3.87E-04	3.64E-02
BP	regulation of leukocyte mediated cytotoxicity	4/69	96/18870	0.04	11.39	6.19	4.22E-04	3.74E-02
BP	positive regulation of leukocyte cell-cell adhesion	6/69	275/18870	0.02	5.97	5.03	5.04E-04	3.91E-02
BP	positive regulation of B cell mediated immunity	3/69	43/18870	0.07	19.08	7.19	5.20E-04	3.91E-02
BP	positive regulation of immunoglobulin mediated immune response	3/69	43/18870	0.07	19.08	7.19	5.20E-04	3.91E-02
BP	cellular response to leukemia inhibitory factor	4/69	104/18870	0.04	10.52	5.90	5.72E-04	3.98E-02
BP	positive regulation of cell activation	7/69	396/18870	0.02	4.83	4.67	5.99E-04	3.98E-02

BP	response to leukemia inhibitory factor	4/69	106/18870	0.04	10.32	5.83	6.14E-04	3.98E-02
BP	dendritic cell differentiation	3/69	46/18870	0.07	17.84	6.93	6.35E-04	3.98E-02
BP	regulation of neuron migration	3/69	48/18870	0.06	17.09	6.76	7.19E-04	4.33E-02
BP	regulation of natural killer cell mediated cytotoxicity	3/69	49/18870	0.06	16.74	6.68	7.64E-04	4.42E-02
BP	dendritic cell apoptotic process	2/69	12/18870	0.17	45.58	9.36	8.49E-04	4.57E-02
BP	regulation of dendritic cell apoptotic process	2/69	12/18870	0.17	45.58	9.36	8.49E-04	4.57E-02
BP	regulation of natural killer cell mediated immunity	3/69	53/18870	0.06	15.48	6.39	9.62E-04	4.99E-02

Table S8. Bayesian colocalization analysis for candidate proteins to blood pressure traits (UKB) and aortic dissection.

Exposure	Outcome	nSNP	PP.H0.abf	PP.H1.abf	PP.H2.abf	PP.H3.abf	PP.H4.abf
GHR	HTN	12237	0.00%	0.11%	0.00%	99.64%	0.25%
IL13RA1	HTN	8473	0.00%	0.73%	0.00%	59.57%	39.70%
NQO1	HTN	11864	0.00%	0.05%	0.00%	99.95%	0.00%
POR	HTN	10932	0.00%	0.00%	0.00%	100.00%	0.00%
RIGI	HTN	13432	0.00%	65.23%	0.00%	34.53%	0.24%
CCN3	DBP	12182	0.00%	0.00%	0.00%	7.90%	92.10%
COL6A3	DBP	13582	0.00%	53.09%	0.00%	32.40%	14.51%
NPPB	DBP	12499	0.00%	0.00%	0.00%	100.00%	0.00%
SHMT1	DBP	9599	0.00%	6.56%	0.00%	93.39%	0.04%
CCN3	AD	10064	0.00%	47.16%	0.00%	43.62%	9.22%
COL6A3	AD	11020	0.00%	12.82%	0.00%	15.58%	71.60%
GHR	AD	9953	0.00%	25.47%	0.00%	51.96%	22.58%
IL13RA1	AD	6506	0.00%	42.91%	0.00%	55.15%	1.94%
NPPB	AD	10291	0.00%	49.73%	0.00%	47.30%	2.97%
NQO1	AD	8163	0.00%	24.27%	0.00%	29.59%	46.13%
POR	AD	8107	0.00%	55.98%	0.00%	38.91%	5.11%
RIGI	AD	11010	0.00%	56.05%	0.00%	41.52%	2.43%
SHMT1	AD	6697	0.00%	61.77%	0.00%	36.77%	1.46%

Table S9. Multi-trait colocalization analysis of candidate proteins, essential hypertension (UKB), and aortic dissection.

TraitID	coloc_ppas	best.snp.coloc	nSNP	Traits
ab	0.17%	rs4357043	8894	a = GHR, b = HTN, c = AD
ac	4.13%	rs4357043	8894	a = GHR, b = HTN, c = AD
bc	0.22%	rs10941611	8894	a = GHR, b = HTN, c = AD
abc	0.01%	rs4357043	8894	a = GHR, b = HTN, c = AD
ab	23.27%	rs2495635	5797	a = IL13RA1, b = HTN, c = AD
ac	0.12%	rs2255275	5797	a = IL13RA1, b = HTN, c = AD
bc	0.32%	rs5957062	5797	a = IL13RA1, b = HTN, c = AD
abc	0.03%	rs2495635	5797	a = IL13RA1, b = HTN, c = AD
ab	0.00%	rs2161631	7289	a = NQO1, b = HTN, c = AD
ac	3.32%	rs2161631	7289	a = NQO1, b = HTN, c = AD
bc	0.80%	rs2161631	7289	a = NQO1, b = HTN, c = AD
abc	0.00%	rs2161631	7289	a = NQO1, b = HTN, c = AD
ab	0.00%	rs59882870	7114	a = POR, b = HTN, c = AD
ac	0.40%	rs59882870	7114	a = POR, b = HTN, c = AD
bc	3.65%	rs59882870	7114	a = POR, b = HTN, c = AD
abc	0.00%	rs59882870	7114	a = POR, b = HTN, c = AD
ab	0.11%	rs1133071	9925	a = RIGI, b = HTN, c = AD
ac	0.19%	rs1133071	9925	a = RIGI, b = HTN, c = AD
bc	0.41%	rs1133071	9925	a = RIGI, b = HTN, c = AD
abc	0.00%	rs1133071	9925	a = RIGI, b = HTN, c = AD

Table S10. Multi-trait colocalization analysis of candidate proteins, diastolic blood pressure (UKB), and aortic dissection.

TraitID	coloc_ppas	best.snp.coloc	nSNP	Traits
ab	92.08%	rs56013326	9021	a = CCN3, b = DBP, c = AD
ac	1.77%	rs11782222	9021	a = CCN3, b = DBP, c = AD
bc	1.80%	rs57333327	9021	a = CCN3, b = DBP, c = AD
abc	1.66%	rs57333327	9021	a = CCN3, b = DBP, c = AD
ab	17.45%	rs2029998	9919	a = COL6A3, b = DBP, c = AD
ac	28.45%	rs2029998	9919	a = COL6A3, b = DBP, c = AD
bc	5.80%	rs2029998	9919	a = COL6A3, b = DBP, c = AD
abc	5.46%	rs2029998	9919	a = COL6A3, b = DBP, c = AD
ab	0.00%	rs198389	8800	a = NPPB, b = DBP, c = AD
ac	0.14%	rs198389	8800	a = NPPB, b = DBP, c = AD
bc	0.39%	rs198389	8800	a = NPPB, b = DBP, c = AD
abc	0.00%	rs198389	8800	a = NPPB, b = DBP, c = AD
ab	0.02%	rs652093	6003	a = SHMT1, b = DBP, c = AD
ac	0.04%	rs652093	6003	a = SHMT1, b = DBP, c = AD
bc	0.24%	rs652093	6003	a = SHMT1, b = DBP, c = AD
abc	0.00%	rs652093	6003	a = SHMT1, b = DBP, c = AD

Table S11. Sensitivity analyses between candidate proteins, blood pressure traits (UKB), and aortic dissection.

Exposure	Outcome	Method	nSNP	Beta	SE	P value	Cochran's Q pval	MR Egger intercept pval
GHR	HTN	Inverse variance weighted	2	0.09	0.02	8.55E-05	7.05E-01	
IL13RA1	HTN	Inverse variance weighted	2	0.05	0.01	7.94E-04	8.40E-01	
NQO1	HTN	Inverse variance weighted	3	-0.08	0.02	3.46E-04	1.05E-01	
NQO1	HTN	MR Egger	3	-0.19	0.07	2.15E-01	2.76E-01	3.43E-01
NQO1	HTN	Weighted median	3	-0.09	0.02	5.73E-08		
POR	HTN	Inverse variance weighted	2	0.09	0.03	3.03E-03	6.64E-01	
RIGI	HTN	Wald ratio	1	0.21	0.06	1.99E-04		
CCN3	DBP	Wald ratio	1	-0.31	0.03	7.89E-22		
COL6A3	DBP	Wald ratio	1	-0.10	0.03	1.61E-03		
NPPB	DBP	Inverse variance weighted	3	-0.06	0.02	1.26E-03	2.68E-03	8.42E-01
NPPB	DBP	MR Egger	3	-0.10	0.02	1.56E-01	8.84E-02	3.30E-01
NPPB	DBP	Weighted median	3	-0.06	0.01	2.42E-13		
SHMT1	DBP	Inverse variance weighted	4	0.02	0.00	4.71E-04	9.96E-01	
SHMT1	DBP	MR Egger	4	0.01	0.02	5.34E-01	9.96E-01	
SHMT1	DBP	Weighted median	4	0.02	0.01	2.75E-03		
CCN3	AD	Wald ratio	1	-1.50	0.71	3.53E-02		
COL6A3	AD	Wald ratio	1	-2.08	0.62	8.00E-04		
GHR	AD	Inverse variance weighted	2	0.61	0.22	5.27E-03	7.55E-01	
IL13RA1	AD	Inverse variance weighted	2	0.46	0.11	6.18E-05	6.57E-01	
NPPB	AD	Inverse variance weighted	3	-0.31	0.16	4.88E-02	9.04E-01	
NPPB	AD	MR Egger	3	-0.22	0.28	5.81E-01	8.15E-01	7.67E-01
NPPB	AD	Weighted median	3	-0.31	0.17	6.21E-02		
NQO1	AD	Inverse variance weighted	3	-0.32	0.15	2.99E-02	8.18E-01	
NQO1	AD	MR Egger	3	-0.61	0.62	5.04E-01	6.84E-01	7.12E-01

NQO1	AD	Weighted median	3	-0.34	0.15	2.69E-02		
POR	AD	Inverse variance weighted	2	0.46	0.22	3.90E-02	4.93E-01	
RIGI	AD	Wald ratio	1	1.28	0.51	1.21E-02		
SHMT1	AD	Inverse variance weighted	4	-0.21	0.10	3.33E-02	3.83E-01	
SHMT1	AD	MR Egger	4	0.11	0.35	7.83E-01	3.46E-01	4.47E-01
SHMT1	AD	Weighted median	4	-0.20	0.11	6.79E-01		

Table S12. Mediation effect of blood pressure traits (UKB) on protein-associated aortic dissection.

Exposure	Mediator	Outcome	Beta (95% CI)	Proportion (95% CI)	P value
GHR	HTN	AD	0.04 (0.01, 0.06)	6.28% (2.16%, 10.40%)	2.81E-03
IL13RA1	HTN	AD	0.02 (0.01, 0.04)	4.49% (1.24%, 7.74%)	6.71E-03
NQO1	HTN	AD	-0.03 (-0.06, -0.01)	10.86% (3.33%, 18.40%)	4.73E-03
POR	HTN	AD	0.04 (0.01, 0.06)	7.91% (1.69%, 14.13%)	1.27E-02
RIGI	HTN	AD	0.09 (0.03, 0.15)	6.96% (2.24%, 11.67%)	3.82E-03
CCN3	DBP	AD	-0.34 (-0.5, -0.18)	22.74% (12.14%, 33.35%)	2.63E-05
COL6A3	DBP	AD	-0.11 (-0.2, -0.03)	5.43% (1.36%, 9.51%)	8.93E-03
NPPB	DBP	AD	-0.07 (-0.12, -0.02)	21.47% (5.62%, 37.31%)	7.94E-03
SHMT1	DBP	AD	0.02 (0.01, 0.03)	-8.55% (-14.54%, -2.57%)	5.11E-03

Table S13. Causal association between blood pressure traits (MVP) and aortic dissection.

Exposure	Outcome	Method	nSNP	Beta	SE	P value	Adjusted P
HTN	Aortic dissection	Inverse variance weighted	176	0.38	0.09	8.92E-06	3.35E-05
HTN	Aortic dissection	MR Egger	176	0.44	0.30	1.43E-01	2.38E-01
HTN	Aortic dissection	Weighted median	176	0.30	0.13	2.10E-02	3.94E-02
HTN	Aortic dissection	MR-PRESSO (Raw)	176	0.38	0.09	1.58E-05	4.73E-05
HTN	Aortic dissection	MR-PRESSO (Outlier-corrected)	NA				
SBP	Aortic dissection	Inverse variance weighted	297	0.05	0.15	7.52E-01	8.06E-01
SBP	Aortic dissection	MR Egger	297	-0.42	0.48	3.83E-01	4.78E-01
SBP	Aortic dissection	Weighted median	297	0.18	0.20	3.65E-01	4.78E-01
SBP	Aortic dissection	MR-PRESSO (Raw)	297	0.05	0.15	7.52E-01	8.06E-01
SBP	Aortic dissection	MR-PRESSO (Outlier-corrected)	291	0.19	0.14	1.93E-01	2.89E-01
DBP	Aortic dissection	Inverse variance weighted	199	1.29	0.19	4.97E-12	7.46E-11
DBP	Aortic dissection	MR Egger	199	1.86	0.66	5.07E-03	1.09E-02
DBP	Aortic dissection	Weighted median	199	1.02	0.25	3.34E-05	8.35E-05
DBP	Aortic dissection	MR-PRESSO (Raw)	199	1.29	0.19	6.61E-11	4.96E-10
DBP	Aortic dissection	MR-PRESSO (Outlier-corrected)	194	1.20	0.18	1.16E-10	5.78E-10

Table S14. Causal association between plasma proteins and essential hypertension (MVP).

Exposure	Outcome	Beta	SE	P value	Adjusted P
A4GNT	HTN	0.24	0.08	2.01E-03	2.89E-02
ACADVL	HTN	-0.47	0.10	1.67E-06	1.05E-04
ACE	HTN	0.06	0.02	1.94E-03	2.89E-02
ADAMTSL2	HTN	-0.13	0.04	2.29E-03	3.09E-02
ADH5	HTN	0.11	0.03	2.57E-04	7.17E-03
ADH6	HTN	0.10	0.03	1.12E-03	2.06E-02
AGRN	HTN	0.07	0.02	2.16E-04	6.38E-03
AGT	HTN	0.16	0.03	9.45E-10	1.42E-07
AK1	HTN	-0.29	0.09	1.52E-03	2.60E-02
ALDH2	HTN	0.58	0.07	5.81E-15	4.38E-12
ALOX15B	HTN	-0.25	0.07	6.50E-04	1.37E-02
AMBP	HTN	0.17	0.05	9.59E-04	1.83E-02
ANTXR1	HTN	0.39	0.09	3.30E-05	1.42E-03
ANXA11	HTN	0.12	0.03	2.12E-04	6.38E-03
APOB	HTN	0.18	0.06	2.16E-03	2.93E-02
APOC1	HTN	-0.31	0.08	1.14E-04	3.93E-03
APOC3	HTN	-0.22	0.03	1.78E-11	6.69E-09
ARG1	HTN	-0.21	0.06	1.10E-03	2.04E-02
ARHGEF25	HTN	0.13	0.05	4.41E-03	4.55E-02
ARL3	HTN	0.19	0.03	1.62E-10	3.05E-08
ASAH2	HTN	-0.07	0.02	4.15E-03	4.38E-02
ASIP	HTN	-0.07	0.02	6.54E-04	1.37E-02
ATRN	HTN	-0.04	0.01	2.83E-03	3.49E-02
AZGP1	HTN	-0.09	0.02	1.15E-04	3.93E-03
ITIH1	HTN	-0.06	0.02	1.18E-03	2.15E-02
ITIH4	HTN	0.23	0.06	1.29E-04	4.22E-03
ITPKA	HTN	0.33	0.08	1.60E-05	7.74E-04
IVD	HTN	-0.14	0.04	2.73E-04	7.49E-03
KLC1	HTN	0.23	0.06	1.28E-04	4.22E-03
KNG1	HTN	0.05	0.02	2.65E-03	3.36E-02
KYAT3	HTN	-0.10	0.02	4.85E-07	3.48E-05
LAYN	HTN	-0.40	0.09	2.31E-05	1.05E-03
LGALS4	HTN	-0.30	0.09	7.67E-04	1.52E-02
LHB	HTN	-0.07	0.02	2.12E-03	2.93E-02
LIMA1	HTN	-0.50	0.08	2.78E-10	4.66E-08
LRRC15	HTN	-0.06	0.02	7.39E-04	1.51E-02
LRRTM4	HTN	-0.40	0.10	4.27E-05	1.79E-03
LYZ	HTN	0.05	0.01	3.68E-04	9.91E-03
MAP3K3	HTN	0.32	0.10	1.68E-03	2.70E-02
MAPK3	HTN	-0.09	0.02	1.02E-04	3.67E-03
MARK3	HTN	0.58	0.11	4.76E-08	3.99E-06
MATN2	HTN	-0.13	0.04	2.04E-03	2.89E-02
MDH1	HTN	-0.24	0.08	1.74E-03	2.75E-02
METAP1	HTN	0.23	0.07	1.66E-03	2.70E-02
MSR1	HTN	0.07	0.02	1.75E-03	2.75E-02
NADK	HTN	-0.18	0.04	4.19E-06	2.43E-04
NAPG	HTN	0.22	0.08	3.95E-03	4.25E-02
NCAN	HTN	-0.10	0.03	1.60E-03	2.69E-02

BMP7	HTN	-0.30	0.10	3.00E-03	3.65E-02
BRD2	HTN	0.44	0.15	2.99E-03	3.65E-02
CALB2	HTN	0.25	0.09	4.82E-03	4.91E-02
CAT	HTN	0.08	0.03	1.80E-03	2.75E-02
CCDC50	HTN	-0.35	0.11	1.80E-03	2.75E-02
CCL17	HTN	0.07	0.02	4.85E-03	4.91E-02
CCN3	HTN	0.22	0.07	6.12E-04	1.36E-02
CD46	HTN	-0.08	0.02	6.15E-04	1.36E-02
CD72	HTN	0.13	0.05	4.75E-03	4.87E-02
CDH5	HTN	-0.15	0.03	1.86E-06	1.12E-04
CFI	HTN	-0.29	0.10	3.14E-03	3.73E-02
CHMP3	HTN	-0.45	0.10	5.94E-06	3.20E-04
CLEC11A	HTN	-0.09	0.02	1.54E-04	4.85E-03
CNPY3	HTN	-0.16	0.04	8.90E-05	3.35E-03
COMT	HTN	-0.21	0.06	4.61E-04	1.14E-02
CRAT	HTN	0.19	0.06	1.26E-03	2.23E-02
CREB3L4	HTN	-0.08	0.02	4.39E-04	1.10E-02
CRLF1	HTN	-0.07	0.02	2.05E-03	2.89E-02
CSK	HTN	0.62	0.08	1.74E-14	8.75E-12
CSNK2B	HTN	0.59	0.20	3.36E-03	3.86E-02
DBI	HTN	-0.06	0.02	3.08E-03	3.71E-02
DEF6	HTN	-0.07	0.03	4.96E-03	4.98E-02
DUSP13B	HTN	-0.17	0.05	1.63E-03	2.70E-02
DYNLL2	HTN	-0.30	0.09	1.27E-03	2.23E-02
EGLN1	HTN	0.21	0.07	3.74E-03	4.08E-02
EMILIN3	HTN	-0.06	0.02	2.68E-03	3.36E-02
NCF1	HTN	0.18	0.03	1.67E-08	1.68E-06
NDE1	HTN	0.48	0.08	1.54E-09	2.10E-07
NEGR1	HTN	-0.15	0.04	7.78E-04	1.52E-02
NEGR1	HTN	-0.15	0.05	3.23E-03	3.78E-02
NLGN1	HTN	0.14	0.04	8.62E-05	3.33E-03
NMB	HTN	-0.12	0.03	2.36E-04	6.71E-03
NME4	HTN	0.30	0.09	5.65E-04	1.33E-02
NMRAL1	HTN	0.06	0.02	6.64E-04	1.37E-02
NMT1	HTN	0.59	0.12	5.36E-07	3.67E-05
NPNT	HTN	0.09	0.03	2.41E-03	3.19E-02
NPPB	HTN	-0.51	0.06	8.13E-20	1.23E-16
NPPB	HTN	-0.16	0.05	5.45E-04	1.33E-02
NQO1	HTN	-0.10	0.02	1.99E-09	2.51E-07
NRP2	HTN	-0.14	0.04	4.38E-04	1.10E-02
NUDT2	HTN	-0.06	0.02	2.78E-03	3.46E-02
NUDT9	HTN	-0.16	0.05	8.40E-04	1.62E-02
OLFML3	HTN	0.18	0.06	1.80E-03	2.75E-02
PDK1	HTN	0.25	0.08	2.46E-03	3.23E-02
PDXK	HTN	-0.27	0.04	3.48E-11	1.05E-08
PFKM	HTN	0.09	0.03	2.05E-03	2.89E-02
PGP	HTN	0.18	0.03	1.01E-07	8.00E-06
PLEKHA7	HTN	0.11	0.02	2.59E-07	1.95E-05
PTK7	HTN	0.22	0.06	1.02E-04	3.67E-03
PTN	HTN	-0.10	0.03	2.40E-03	3.19E-02
QDPR	HTN	0.04	0.01	2.00E-03	2.89E-02
RAB1A	HTN	0.55	0.10	1.52E-08	1.63E-06

ENPEP	HTN	-0.06	0.02	6.76E-05	2.68E-03
ENTPD6	HTN	0.13	0.04	2.11E-03	2.93E-02
EPHB6	HTN	0.10	0.02	1.23E-05	6.20E-04
ESAM	HTN	-0.12	0.04	7.57E-04	1.52E-02
F2	HTN	0.16	0.06	4.03E-03	4.28E-02
F2	HTN	0.18	0.06	4.03E-03	4.28E-02
FABP2	HTN	-0.06	0.01	4.49E-06	2.51E-04
FAM171B	HTN	0.11	0.04	3.49E-03	3.95E-02
FCN1	HTN	0.05	0.02	2.52E-03	3.24E-02
FCN3	HTN	0.04	0.01	1.02E-03	1.92E-02
FN1	HTN	0.09	0.03	3.54E-03	3.95E-02
FN1	HTN	0.09	0.03	3.54E-03	3.95E-02
FN1	HTN	-0.08	0.03	3.90E-03	4.23E-02
FSTL3	HTN	-0.28	0.07	1.59E-04	4.89E-03
GAS6	HTN	-0.06	0.02	3.53E-03	3.95E-02
GSTP1	HTN	0.13	0.04	1.27E-03	2.23E-02
H1-10	HTN	-0.38	0.12	1.57E-03	2.65E-02
HEXIM1	HTN	0.27	0.07	1.49E-04	4.77E-03
HEXIM2	HTN	0.22	0.07	1.51E-03	2.60E-02
HTATIP2	HTN	0.06	0.02	4.29E-03	4.50E-02
ICAM4	HTN	0.26	0.05	3.79E-08	3.36E-06
IGLON5	HTN	-0.21	0.06	6.17E-04	1.36E-02
INHBC	HTN	-0.16	0.05	2.04E-03	2.89E-02
INPP5B	HTN	0.07	0.02	3.58E-03	3.96E-02
ISOC1	HTN	0.10	0.03	2.15E-03	2.93E-02
RARRES1	HTN	0.04	0.01	3.62E-03	3.99E-02
RARRES2	HTN	-0.08	0.03	2.53E-03	3.24E-02
ROR2	HTN	-0.12	0.04	1.88E-03	2.83E-02
RPS6KA1	HTN	0.18	0.05	6.23E-04	1.36E-02
SAT2	HTN	0.10	0.02	3.10E-05	1.38E-03
SCARF1	HTN	0.08	0.02	1.07E-05	5.57E-04
SDF2	HTN	-0.10	0.02	1.02E-06	6.68E-05
SEMA6A	HTN	-0.28	0.08	5.65E-04	1.33E-02
SFRP4	HTN	0.07	0.02	2.49E-03	3.23E-02
SHMT1	HTN	0.07	0.03	3.29E-03	3.82E-02
SNAP29	HTN	-0.19	0.07	3.21E-03	3.78E-02
SYT11	HTN	-0.25	0.09	4.36E-03	4.54E-02
TBCE	HTN	-0.17	0.05	4.14E-04	1.10E-02
TCEA2	HTN	-0.20	0.04	7.32E-09	8.49E-07
TCN2	HTN	-0.04	0.01	5.36E-05	2.18E-03
TFRC	HTN	-0.22	0.06	2.22E-04	6.44E-03
THBS1	HTN	-0.33	0.11	1.68E-03	2.70E-02
TIE1	HTN	-0.09	0.03	4.36E-04	1.10E-02
TMEM106B	HTN	-0.24	0.04	2.72E-08	2.56E-06
TTL	HTN	0.34	0.11	3.14E-03	3.73E-02
ULK3	HTN	0.41	0.06	1.30E-10	2.81E-08
UROD	HTN	0.08	0.02	6.50E-04	1.37E-02
VTN	HTN	-0.05	0.02	6.08E-04	1.36E-02
WARS1	HTN	0.09	0.02	1.64E-05	7.74E-04
WBP2	HTN	0.60	0.09	8.14E-11	2.05E-08

Table S15. Causal association between plasma proteins and diastolic blood pressure (MVP).

Exposure	Outcome	Beta	SE	P value	Adjusted P
ACADVL	DBP	-0.36	0.05	9.17E-12	2.32E-09
ADAMTS13	DBP	-0.02	0.01	1.65E-03	2.10E-02
ADH1C	DBP	-0.07	0.02	5.80E-04	9.39E-03
ADK	DBP	-0.18	0.05	4.40E-04	7.86E-03
AGRN	DBP	0.05	0.01	2.41E-06	1.50E-04
AGT	DBP	0.10	0.01	3.39E-13	1.72E-10
AK1	DBP	-0.27	0.05	1.92E-07	1.82E-05
ALDH1A1	DBP	-0.10	0.03	2.91E-04	5.89E-03
ALDH2	DBP	0.24	0.04	6.06E-10	1.30E-07
ALOX15B	DBP	-0.17	0.04	2.48E-06	1.50E-04
ANTXR1	DBP	0.17	0.05	1.21E-03	1.68E-02
ANXA11	DBP	0.05	0.02	3.31E-03	3.73E-02
AP2A2	DBP	-0.15	0.04	5.08E-04	8.68E-03
APOC3	DBP	-0.09	0.02	2.29E-08	2.68E-06
ARF4	DBP	0.10	0.03	3.70E-03	4.02E-02
AZGP1	DBP	-0.05	0.01	4.17E-06	2.26E-04
BCAN	DBP	-0.05	0.02	6.86E-04	1.07E-02
BDH2	DBP	-0.04	0.01	1.34E-03	1.80E-02
BMP1	DBP	0.11	0.04	3.45E-03	3.86E-02
BTC	DBP	-0.06	0.02	3.18E-04	6.28E-03
CALB2	DBP	0.22	0.05	1.40E-05	5.75E-04
CCL19	DBP	-0.23	0.05	3.33E-05	1.15E-03
CCL21	DBP	-0.10	0.02	5.05E-05	1.61E-03
CCN3	DBP	-0.27	0.04	1.35E-12	5.11E-10
LIMA1	DBP	-0.15	0.04	5.42E-04	9.00E-03
LRP11	DBP	0.04	0.01	6.46E-06	3.17E-04
LRRC15	DBP	-0.04	0.01	6.81E-06	3.23E-04
LRRTM4	DBP	-0.16	0.05	3.12E-03	3.55E-02
LTF	DBP	-0.06	0.02	1.28E-04	3.10E-03
LYZ	DBP	0.03	0.01	2.00E-06	1.38E-04
MARK3	DBP	0.31	0.06	3.09E-08	3.35E-06
MASP1	DBP	-0.14	0.03	2.94E-05	1.09E-03
MDH1	DBP	-0.15	0.04	5.42E-05	1.68E-03
METAP1	DBP	0.12	0.04	2.61E-03	3.09E-02
MFAP4	DBP	0.05	0.02	1.54E-03	2.00E-02
MSR1	DBP	0.05	0.01	1.42E-04	3.32E-03
MXRA7	DBP	-0.03	0.01	3.60E-04	6.93E-03
NADK	DBP	-0.08	0.02	9.61E-05	2.53E-03
NCAN	DBP	-0.09	0.02	4.98E-09	6.31E-07
NCF1	DBP	0.06	0.02	3.75E-05	1.24E-03
NDE1	DBP	0.12	0.04	1.76E-03	2.21E-02
NLGN2	DBP	0.18	0.05	4.56E-04	8.06E-03
NME2	DBP	0.07	0.02	3.52E-04	6.86E-03
NMT1	DBP	0.20	0.05	1.94E-04	4.09E-03
NPPB	DBP	-0.21	0.03	2.34E-13	1.72E-10
NPPB	DBP	-0.06	0.02	5.20E-04	8.79E-03
NQO1	DBP	-0.03	0.01	1.66E-04	3.72E-03
NT5C2	DBP	0.09	0.02	1.10E-04	2.83E-03

CD48	DBP	-0.06	0.02	4.36E-04	7.86E-03
CFHR1	DBP	-0.02	0.00	8.89E-04	1.30E-02
CINP	DBP	0.19	0.05	1.30E-04	3.10E-03
CLEC11A	DBP	-0.03	0.01	3.85E-03	4.12E-02
CLINT1	DBP	-0.20	0.05	2.85E-05	1.08E-03
CNPY3	DBP	-0.09	0.02	6.24E-06	3.16E-04
COL6A3	DBP	-0.17	0.04	2.37E-05	9.25E-04
COMT	DBP	-0.09	0.03	2.93E-03	3.37E-02
CREB3L4	DBP	-0.06	0.01	1.17E-06	8.47E-05
CRLF1	DBP	-0.07	0.01	3.04E-09	4.20E-07
CSK	DBP	0.34	0.04	3.26E-17	4.96E-14
CSNK2B	DBP	-0.28	0.09	3.13E-03	3.55E-02
CTSF	DBP	-0.07	0.01	4.44E-06	2.33E-04
CYRIB	DBP	0.16	0.05	2.14E-03	2.63E-02
DBNL	DBP	0.11	0.04	3.54E-03	3.93E-02
DEF6	DBP	-0.06	0.01	3.47E-05	1.17E-03
DHX58	DBP	0.05	0.02	1.43E-03	1.89E-02
DLL1	DBP	-0.13	0.02	4.24E-08	4.30E-06
DPP7	DBP	0.06	0.02	4.95E-04	8.54E-03
ECI1	DBP	-0.07	0.02	6.71E-05	2.00E-03
ENPEP	DBP	-0.04	0.01	1.39E-03	1.85E-02
ENPP2	DBP	-0.06	0.02	6.56E-04	1.04E-02
EPHA2	DBP	-0.24	0.06	1.23E-04	3.10E-03
EPO	DBP	0.14	0.04	1.26E-04	3.10E-03
ESAM	DBP	-0.07	0.02	8.40E-05	2.28E-03
FABP2	DBP	-0.04	0.01	6.83E-10	1.30E-07
NUDCD3	DBP	-0.11	0.04	3.62E-03	3.99E-02
OLFML3	DBP	0.09	0.03	3.77E-03	4.07E-02
PARP1	DBP	0.21	0.05	7.76E-05	2.19E-03
PCDH10	DBP	-0.08	0.02	1.29E-05	5.60E-04
PCNP	DBP	0.09	0.03	4.78E-03	4.95E-02
PCOLCE	DBP	-0.06	0.02	1.48E-04	3.41E-03
PCSK2	DBP	-0.10	0.03	2.38E-03	2.87E-02
PDXK	DBP	-0.08	0.02	4.07E-04	7.64E-03
PGP	DBP	0.10	0.02	9.04E-10	1.37E-07
PLA2G12B	DBP	-0.09	0.03	1.67E-03	2.11E-02
PLEKHA7	DBP	0.04	0.01	2.09E-04	4.29E-03
PPCS	DBP	-0.08	0.03	2.86E-03	3.34E-02
PRKCA	DBP	-0.10	0.03	3.03E-04	6.06E-03
PRKCSH	DBP	0.09	0.03	4.87E-04	8.52E-03
PROC	DBP	0.08	0.02	9.55E-06	4.40E-04
PRSS27	DBP	-0.06	0.02	3.86E-04	7.34E-03
PRSS8	DBP	0.21	0.05	1.35E-05	5.70E-04
PTPN9	DBP	0.15	0.04	1.73E-04	3.80E-03
QDPR	DBP	0.02	0.01	1.90E-03	2.34E-02
QSOX2	DBP	0.04	0.01	7.82E-05	2.19E-03
RAB1A	DBP	0.14	0.05	2.28E-03	2.77E-02
RARRES2	DBP	-0.04	0.01	4.19E-04	7.73E-03
SDF2	DBP	-0.04	0.01	7.93E-05	2.19E-03
SELE	DBP	-0.09	0.02	9.65E-05	2.53E-03
SEPTIN11	DBP	-0.15	0.04	5.50E-04	9.00E-03
SERPING1	DBP	-0.02	0.01	4.50E-03	4.71E-02

FAM171B	DBP	0.06	0.02	8.39E-04	1.28E-02
FCN3	DBP	0.02	0.01	2.42E-03	2.89E-02
FGFBP1	DBP	-0.11	0.03	8.53E-04	1.28E-02
FLRT2	DBP	0.03	0.01	6.06E-04	9.69E-03
G3BP1	DBP	0.13	0.04	2.62E-03	3.09E-02
GHR	DBP	0.06	0.01	1.08E-06	8.21E-05
GNMT	DBP	-0.05	0.01	3.16E-05	1.14E-03
GREM1	DBP	-0.02	0.01	1.09E-03	1.53E-02
GSTP1	DBP	0.07	0.02	1.67E-04	3.72E-03
HABP4	DBP	0.04	0.01	3.10E-06	1.81E-04
HAGH	DBP	0.07	0.02	2.01E-04	4.19E-03
HYAL1	DBP	0.07	0.02	5.45E-04	9.00E-03
ICAM1	DBP	0.01	0.00	1.28E-03	1.75E-02
ICAM4	DBP	0.12	0.02	3.62E-07	2.90E-05
IL17B	DBP	-0.10	0.04	4.56E-03	4.75E-02
IL18R1	DBP	-0.02	0.01	1.10E-03	1.53E-02
INHBB	DBP	0.04	0.01	7.66E-05	2.19E-03
INPP5B	DBP	0.06	0.01	2.50E-07	2.24E-05
INSR	DBP	-0.11	0.04	2.89E-03	3.35E-02
ITPKA	DBP	0.16	0.04	1.51E-05	6.05E-04
KLC1	DBP	0.18	0.03	8.55E-10	1.37E-07
LAMC2	DBP	0.03	0.01	7.90E-04	1.21E-02
LAYN	DBP	-0.16	0.05	9.75E-04	1.40E-02
LEAP2	DBP	-0.05	0.01	2.83E-07	2.39E-05
SLMAP	DBP	0.18	0.06	3.70E-03	4.02E-02
SPP1	DBP	0.17	0.04	1.85E-04	4.02E-03
SRL	DBP	-0.07	0.02	1.62E-03	2.08E-02
STIM1	DBP	-0.09	0.03	1.34E-03	1.80E-02
TCL1A	DBP	0.04	0.01	8.89E-04	1.30E-02
TCN2	DBP	-0.03	0.01	5.80E-05	1.76E-03
TESC	DBP	-0.02	0.01	1.45E-03	1.90E-02
THYN1	DBP	0.22	0.06	1.92E-04	4.09E-03
TMEM106B	DBP	-0.08	0.02	4.22E-04	7.73E-03
TNFAIP3	DBP	0.06	0.02	8.89E-04	1.30E-02
TNFRSF11B	DBP	-0.06	0.01	1.30E-04	3.10E-03
TNFRSF17	DBP	-0.09	0.02	2.25E-06	1.48E-04
TRDMT1	DBP	-0.03	0.01	9.70E-04	1.40E-02
TRIL	DBP	-0.10	0.04	4.44E-03	4.69E-02
TTL	DBP	0.22	0.05	3.75E-06	2.11E-04
TYRO3	DBP	-0.10	0.03	5.08E-05	1.61E-03
UBE2C	DBP	0.05	0.02	3.96E-03	4.21E-02
ULK3	DBP	0.22	0.03	3.98E-12	1.21E-09
VTN	DBP	-0.02	0.00	9.96E-06	4.45E-04
WARS1	DBP	0.05	0.01	3.28E-05	1.15E-03
WBP2	DBP	0.17	0.05	1.03E-03	1.46E-02
WFDC5	DBP	0.15	0.05	1.89E-03	2.34E-02
ZFAND1	DBP	-0.06	0.02	7.79E-04	1.21E-02

Table S16. Functional enrichment analysis of causal proteins associated with essential hypertension (MVP).

Type	Description	GeneRatio	BgRatio	RichFactor	FoldEnrichment	zScore	pvalue	p.adjust
BP	alcohol metabolic process	14/139	373/18870	0.04	5.10	6.88	6.84E-07	1.88E-03
BP	positive regulation of neuron projection development	9/139	158/18870	0.06	7.73	7.32	2.61E-06	3.58E-03
BP	positive regulation of macrophage derived foam cell differentiation	4/139	19/18870	0.21	28.58	10.36	1.00E-05	9.17E-03
BP	fatty acid metabolic process	12/139	401/18870	0.03	4.06	5.34	4.23E-05	1.54E-02
BP	negative regulation of viral life cycle	4/139	28/18870	0.14	19.39	8.39	5.03E-05	1.54E-02
BP	plasma lipoprotein particle clearance	5/139	55/18870	0.09	12.34	7.26	5.22E-05	1.54E-02
BP	negative regulation of catalytic activity	13/139	480/18870	0.03	3.68	5.12	5.61E-05	1.54E-02
BP	regulation of plasma lipoprotein particle levels	6/139	91/18870	0.07	8.95	6.55	5.72E-05	1.54E-02
BP	regulation of endocytosis	10/139	291/18870	0.03	4.67	5.43	6.03E-05	1.54E-02
BP	regulation of lipid localization	8/139	183/18870	0.04	5.93	5.78	6.41E-05	1.54E-02
BP	positive regulation of cell projection organization	11/139	355/18870	0.03	4.21	5.25	6.54E-05	1.54E-02
BP	response to metal ion	11/139	359/18870	0.03	4.16	5.21	7.23E-05	1.54E-02
BP	very-low-density lipoprotein particle assembly	3/139	12/18870	0.25	33.94	9.83	8.20E-05	1.54E-02
BP	regulation of macrophage derived foam cell differentiation	4/139	33/18870	0.12	16.46	7.65	9.77E-05	1.54E-02
BP	protein-lipid complex remodeling	4/139	33/18870	0.12	16.46	7.65	9.77E-05	1.54E-02
BP	plasma lipoprotein particle remodeling	4/139	33/18870	0.12	16.46	7.65	9.77E-05	1.54E-02
BP	organic hydroxy compound biosynthetic process	9/139	251/18870	0.04	4.87	5.31	1.03E-04	1.54E-02
BP	negative regulation of fibrinolysis	3/139	13/18870	0.23	31.33	9.42	1.06E-04	1.54E-02
BP	small molecule catabolic process	11/139	375/18870	0.03	3.98	5.02	1.06E-04	1.54E-02
BP	protein-containing complex remodeling	4/139	35/18870	0.11	15.51	7.40	1.24E-04	1.70E-02
BP	lipid transport	12/139	453/18870	0.03	3.60	4.82	1.35E-04	1.73E-02
BP	biological process involved in symbiotic interaction	10/139	322/18870	0.03	4.22	5.01	1.39E-04	1.73E-02
BP	positive regulation of dendrite development	3/139	16/18870	0.19	25.45	8.43	2.04E-04	2.35E-02

BP	macrophage derived foam cell differentiation	4/139	40/18870	0.10	13.58	6.86	2.10E-04	2.35E-02
BP	negative regulation of hydrolase activity	8/139	218/18870	0.04	4.98	5.09	2.15E-04	2.35E-02
BP	foam cell differentiation	4/139	41/18870	0.10	13.24	6.76	2.31E-04	2.35E-02
BP	transmembrane receptor protein serine/threonine kinase signaling pathway	11/139	410/18870	0.03	3.64	4.66	2.31E-04	2.35E-02
BP	regulation of transforming growth factor beta production	4/139	42/18870	0.10	12.93	6.67	2.54E-04	2.46E-02
BP	positive regulation of response to wounding	5/139	77/18870	0.06	8.82	5.92	2.61E-04	2.46E-02
BP	cellular ketone metabolic process	8/139	226/18870	0.04	4.81	4.96	2.74E-04	2.51E-02
BP	regulation of fibrinolysis	3/139	18/18870	0.17	22.63	7.91	2.94E-04	2.61E-02
BP	transforming growth factor beta production	4/139	45/18870	0.09	12.07	6.40	3.32E-04	2.61E-02
BP	regulation of leukocyte chemotaxis	6/139	126/18870	0.05	6.46	5.30	3.42E-04	2.61E-02
BP	reactive oxygen species metabolic process	8/139	234/18870	0.03	4.64	4.83	3.47E-04	2.61E-02
BP	positive regulation of macrophage chemotaxis	3/139	19/18870	0.16	21.44	7.68	3.48E-04	2.61E-02
BP	neural crest cell development	5/139	82/18870	0.06	8.28	5.69	3.49E-04	2.61E-02
BP	regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	9/139	297/18870	0.03	4.11	4.66	3.61E-04	2.61E-02
BP	extracellular matrix assembly	4/139	46/18870	0.09	11.80	6.32	3.62E-04	2.61E-02
BP	phagocytosis	8/139	237/18870	0.03	4.58	4.78	3.77E-04	2.66E-02
BP	acute-phase response	4/139	48/18870	0.08	11.31	6.16	4.27E-04	2.79E-02
BP	negative regulation of blood coagulation	4/139	48/18870	0.08	11.31	6.16	4.27E-04	2.79E-02
BP	apoptotic cell clearance	4/139	48/18870	0.08	11.31	6.16	4.27E-04	2.79E-02
BP	negative regulation of hemostasis	4/139	49/18870	0.08	11.08	6.09	4.62E-04	2.80E-02
BP	ethanol metabolic process	3/139	21/18870	0.14	19.39	7.26	4.72E-04	2.80E-02
BP	negative regulation of lipoprotein particle clearance	3/139	21/18870	0.14	19.39	7.26	4.72E-04	2.80E-02
BP	regulation of extracellular matrix assembly	3/139	21/18870	0.14	19.39	7.26	4.72E-04	2.80E-02
BP	stem cell development	5/139	88/18870	0.06	7.71	5.44	4.84E-04	2.80E-02

BP	movement in host	7/139	188/18870	0.04	5.05	4.81	4.92E-04	2.80E-02
BP	plasma lipoprotein particle organization	4/139	50/18870	0.08	10.86	6.01	4.99E-04	2.80E-02
BP	regulation of neuron projection development	11/139	453/18870	0.02	3.30	4.26	5.37E-04	2.87E-02
BP	kidney development	9/139	314/18870	0.03	3.89	4.45	5.40E-04	2.87E-02
BP	regulation of renal system process	3/139	22/18870	0.14	18.51	7.08	5.44E-04	2.87E-02
BP	negative regulation of coagulation	4/139	52/18870	0.08	10.44	5.87	5.80E-04	2.89E-02
BP	cholesterol metabolic process	6/139	140/18870	0.04	5.82	4.93	6.00E-04	2.89E-02
BP	negative regulation of viral entry into host cell	3/139	23/18870	0.13	17.71	6.91	6.22E-04	2.89E-02
BP	positive regulation of transforming growth factor beta production	3/139	23/18870	0.13	17.71	6.91	6.22E-04	2.89E-02
BP	negative regulation of viral process	5/139	93/18870	0.05	7.30	5.25	6.24E-04	2.89E-02
BP	alpha-amino acid catabolic process	5/139	93/18870	0.05	7.30	5.25	6.24E-04	2.89E-02
BP	protein-lipid complex subunit organization	4/139	53/18870	0.08	10.25	5.81	6.24E-04	2.89E-02
BP	viral life cycle	9/139	321/18870	0.03	3.81	4.37	6.32E-04	2.89E-02
BP	humoral immune response	8/139	258/18870	0.03	4.21	4.47	6.61E-04	2.94E-02
BP	renal system development	9/139	324/18870	0.03	3.77	4.33	6.75E-04	2.94E-02
BP	regulation of systemic arterial blood pressure	5/139	95/18870	0.05	7.15	5.17	6.87E-04	2.94E-02
BP	neural crest cell differentiation	5/139	95/18870	0.05	7.15	5.17	6.87E-04	2.94E-02
BP	response to calcium ion	6/139	144/18870	0.04	5.66	4.83	6.95E-04	2.94E-02
BP	regulation of systemic arterial blood pressure by renin-angiotensin	3/139	24/18870	0.13	16.97	6.74	7.07E-04	2.94E-02
BP	positive regulation of leukocyte chemotaxis	5/139	96/18870	0.05	7.07	5.14	7.21E-04	2.95E-02
BP	ureteric bud development	5/139	98/18870	0.05	6.93	5.07	7.92E-04	3.19E-02
BP	mesonephric epithelium development	5/139	99/18870	0.05	6.86	5.03	8.29E-04	3.24E-02
BP	mesonephric tubule development	5/139	99/18870	0.05	6.86	5.03	8.29E-04	3.24E-02
BP	lipid catabolic process	9/139	334/18870	0.03	3.66	4.22	8.37E-04	3.24E-02
BP	secondary alcohol metabolic process	6/139	150/18870	0.04	5.43	4.69	8.61E-04	3.26E-02

BP	regulation of phagocytosis	5/139	100/18870	0.05	6.79	5.00	8.67E-04	3.26E-02
BP	negative regulation of fatty acid biosynthetic process	3/139	26/18870	0.12	15.66	6.45	8.98E-04	3.29E-02
BP	positive regulation of macrophage migration	3/139	26/18870	0.12	15.66	6.45	8.98E-04	3.29E-02
BP	neural crest cell migration	4/139	59/18870	0.07	9.20	5.44	9.37E-04	3.31E-02
BP	regulation of lipid transport	6/139	153/18870	0.04	5.32	4.63	9.54E-04	3.31E-02
BP	biological process involved in interaction with host	7/139	211/18870	0.03	4.50	4.41	9.72E-04	3.31E-02
BP	sterol metabolic process	6/139	154/18870	0.04	5.29	4.60	9.87E-04	3.31E-02
BP	mesonephros development	5/139	103/18870	0.05	6.59	4.90	9.91E-04	3.31E-02
KEGG	Biosynthesis of cofactors	8/89	154/9521	0.05	5.56	5.54	9.10E-05	2.16E-02
KEGG	Glyoxylate and dicarboxylate metabolism	4/89	32/9521	0.13	13.37	6.81	2.10E-04	2.49E-02
KEGG	Fatty acid degradation	4/89	43/9521	0.09	9.95	5.71	6.67E-04	4.23E-02
KEGG	Carbon metabolism	6/89	117/9521	0.05	5.49	4.74	7.68E-04	4.23E-02
KEGG	Pyruvate metabolism	4/89	47/9521	0.09	9.10	5.41	9.36E-04	4.23E-02

Table S17. Functional enrichment analysis of causal proteins associated with diastolic blood pressure (MVP).

Type	Description	GeneRatio	BgRatio	RichFactor	FoldEnrichment	zScore	pvalue	p.adjust
BP	regulation of bone remodeling	6/140	49/18870	0.12	16.50	9.40	1.61E-06	2.35E-03
BP	adhesion of symbiont to host	4/140	13/18870	0.31	41.47	12.62	1.97E-06	2.35E-03
BP	positive regulation of receptor-mediated endocytosis	6/140	53/18870	0.11	15.26	8.99	2.58E-06	2.35E-03
BP	bone remodeling	7/140	89/18870	0.08	10.60	7.85	4.42E-06	3.02E-03
BP	negative regulation of bone remodeling	4/140	18/18870	0.22	29.95	10.62	8.19E-06	4.48E-03
BP	response to interleukin-1	8/140	140/18870	0.06	7.70	6.88	9.84E-06	4.49E-03
BP	regulation of bone resorption	5/140	42/18870	0.12	16.05	8.44	1.43E-05	5.38E-03
BP	negative regulation of tissue remodeling	4/140	21/18870	0.19	25.67	9.78	1.57E-05	5.38E-03
BP	positive regulation of endocytosis	8/140	155/18870	0.05	6.96	6.44	2.07E-05	5.95E-03
BP	receptor-mediated endocytosis	10/140	258/18870	0.04	5.22	5.91	2.32E-05	5.95E-03
BP	regulation of receptor-mediated endocytosis	7/140	115/18870	0.06	8.20	6.70	2.39E-05	5.95E-03
BP	positive regulation of peptidyl-tyrosine phosphorylation	8/140	168/18870	0.05	6.42	6.10	3.68E-05	7.89E-03
BP	regulation of tissue remodeling	6/140	85/18870	0.07	9.51	6.80	4.05E-05	7.89E-03
BP	tissue homeostasis	10/140	279/18870	0.04	4.83	5.57	4.51E-05	7.89E-03
BP	anatomical structure homeostasis	10/140	279/18870	0.04	4.83	5.57	4.51E-05	7.89E-03
BP	adhesion of symbiont to host cell	3/140	10/18870	0.30	40.44	10.78	4.62E-05	7.89E-03
BP	cell adhesion mediated by integrin	6/140	88/18870	0.07	9.19	6.66	4.93E-05	7.92E-03
BP	positive regulation of transferase activity	12/140	414/18870	0.03	3.91	5.17	6.17E-05	8.35E-03
BP	negative regulation of response to external stimulus	13/140	481/18870	0.03	3.64	5.08	6.18E-05	8.35E-03
BP	complement activation, lectin pathway	3/140	11/18870	0.27	36.76	10.26	6.31E-05	8.35E-03
BP	regulation of endocytosis	10/140	291/18870	0.03	4.63	5.40	6.41E-05	8.35E-03
BP	tissue remodeling	8/140	184/18870	0.04	5.86	5.73	7.01E-05	8.71E-03
BP	bone resorption	5/140	65/18870	0.08	10.37	6.54	1.21E-04	1.44E-02
BP	negative regulation of response to biotic stimulus	7/140	150/18870	0.05	6.29	5.62	1.30E-04	1.45E-02

BP	humoral immune response	9/140	258/18870	0.03	4.70	5.18	1.34E-04	1.45E-02
BP	response to tumor necrosis factor	9/140	259/18870	0.03	4.68	5.16	1.38E-04	1.45E-02
BP	response to ketone	8/140	208/18870	0.04	5.18	5.25	1.64E-04	1.66E-02
BP	biological process involved in interaction with host	8/140	211/18870	0.04	5.11	5.19	1.81E-04	1.77E-02
BP	negative regulation of bone resorption	3/140	16/18870	0.19	25.27	8.40	2.09E-04	1.94E-02
BP	positive regulation of kinase activity	10/140	337/18870	0.03	4.00	4.80	2.13E-04	1.94E-02
BP	peptidyl-tyrosine phosphorylation	9/140	276/18870	0.03	4.40	4.91	2.22E-04	1.96E-02
BP	peptidyl-tyrosine modification	9/140	278/18870	0.03	4.36	4.88	2.34E-04	2.00E-02
BP	purine-containing compound metabolic process	12/140	493/18870	0.02	3.28	4.44	3.13E-04	2.59E-02
BP	regulation of peptidyl-tyrosine phosphorylation	8/140	231/18870	0.03	4.67	4.85	3.34E-04	2.67E-02
BP	response to testosterone	4/140	45/18870	0.09	11.98	6.38	3.42E-04	2.67E-02
BP	positive regulation of macrophage derived foam cell differentiation	3/140	19/18870	0.16	21.28	7.65	3.55E-04	2.70E-02
BP	cellular response to tumor necrosis factor	8/140	238/18870	0.03	4.53	4.74	4.07E-04	3.01E-02
BP	purine ribonucleoside metabolic process	3/140	21/18870	0.14	19.26	7.24	4.82E-04	3.47E-02
BP	negative regulation of innate immune response	5/140	91/18870	0.05	7.41	5.30	5.83E-04	4.09E-02
BP	viral life cycle	9/140	321/18870	0.03	3.78	4.34	6.65E-04	4.13E-02
BP	extracellular matrix organization	9/140	321/18870	0.03	3.78	4.34	6.65E-04	4.13E-02
BP	negative regulation of defense response	9/140	321/18870	0.03	3.78	4.34	6.65E-04	4.13E-02
BP	extracellular structure organization	9/140	322/18870	0.03	3.77	4.33	6.80E-04	4.13E-02
BP	biological process involved in symbiotic interaction	9/140	322/18870	0.03	3.77	4.33	6.80E-04	4.13E-02
BP	purine nucleotide metabolic process	11/140	463/18870	0.02	3.20	4.15	6.83E-04	4.13E-02
BP	external encapsulating structure organization	9/140	323/18870	0.03	3.76	4.32	6.96E-04	4.13E-02
KEGG	NF-kappa B signaling pathway	6/90	105/9521	0.06	6.05	5.08	4.59E-04	3.93E-02
KEGG	PI3K-Akt signaling pathway	11/90	362/9521	0.03	3.21	4.20	5.79E-04	3.93E-02
KEGG	Biosynthesis of cofactors	7/90	154/9521	0.05	4.81	4.65	6.14E-04	3.93E-02
KEGG	Fatty acid degradation	4/90	43/9521	0.09	9.84	5.68	6.95E-04	3.93E-02

KEGG	Pyruvate metabolism	4/90	47/9521	0.09	9.00	5.37	9.76E-04	4.41E-02
KEGG	Complement and coagulation cascades	5/90	88/9521	0.06	6.01	4.61	1.43E-03	4.84E-02
KEGG	ECM-receptor interaction	5/90	89/9521	0.06	5.94	4.58	1.50E-03	4.84E-02

Table S18. Bayesian colocalization analysis for candidate proteins to blood pressure traits (MVP).

Exposure	Outcome	nSNP	PP.H0.abf	PP.H1.abf	PP.H2.abf	PP.H3.abf	PP.H4.abf
NQO1	HTN	7965	0.00%	0.02%	0.00%	99.97%	0.00%
CCN3	DBP	9238	0.00%	0.00%	0.00%	38.24%	61.76%
COL6A3	DBP	10530	0.00%	4.43%	0.00%	26.03%	69.53%
NPPB	DBP	8666	0.00%	0.00%	0.00%	100.00%	0.00%

Table S19. Mediation effect of blood pressure traits (MVP) on protein-associated aortic dissection.

Exposure	Mediator	Outcome	Beta (95% CI)	Proportion (95% CI)	P value
NQO1	HTN	AD	-0.04 (-0.06, -0.02)	12.04% (5.43%, 18.65%)	3.58E-04
CCN3	DBP	AD	-0.35 (-0.48, -0.21)	23.11% (13.96%, 32.27%)	7.54E-07
COL6A3	DBP	AD	-0.21 (-0.33, -0.1)	10.22% (4.66%, 15.77%)	3.12E-04
NPPB	DBP	AD	-0.08 (-0.13, -0.03)	26.24% (9.65%, 42.83%)	1.93E-03

Table S20. Causal association between tissue-specific gene expression and aortic dissection.

Exposure	Outcome	Method	nSNP	Beta	SE	P value	Cohort	Tissue
CCN3	AD	Wald ratio	1	-0.40	0.19	3.56E-02	eQTLGen	Blood
COL6A3	AD	Wald ratio	1	0.02	0.16	8.89E-01	eQTLGen	Blood
NQO1	AD	Wald ratio	1	-0.20	0.12	9.36E-02	eQTLGen	Blood
CCN3	AD	Wald ratio	1	-0.71	0.28	1.13E-02	GTEx	Aorta
COL6A3	AD	Wald ratio	1	-0.56	0.22	1.07E-02	GTEx	Aorta

Table S21. Potential drugs for candidate proteins in Therapeutic Target Database (TTD).

Gene	Target Type	Disease	Drugs	Drug Status	Mode of Action
CCN3	/	/	/	/	/
COL6A3	Literature-reported target	/	/	/	/
NPPB	Literature-reported target	Hypertension	BD-NP	Investigative	Modulator
NQO1	Clinical trial target	Choreiform disorder; CNS anomalies syndrome; Inborn energy metabolism error; Intellectual development disorder; Pancreatic cancer; Solid tumour/cancer	ARQ 761	Clinical Trial Drug (Phase 2, Pancreatic cancer)	Inhibitor
			BioE-743	Clinical Trial Drug (Phase 2, Leigh syndrome)	Modulator
			Coenzyme Q10 analog	Clinical Trial Drug (Phase 2, Huntington disease)	Modulator

Table S22. Potential drugs for candidate proteins in Drug-Gene Interaction Database (DGIdb).

Gene	Drug	Regulatory approval	Indication	Interaction type	Direct interaction	Mechanism of action	Interaction score
CCN3	/	/	/	/	/	/	/
COL6A3	OCRIPLASMIN	Approved		cleavage	TRUE	Collagen hydrolytic enzyme	0.34
	ESI-09	Not Approved		inhibitor	FALSE	Inhibition	6.53
	COLLAGENASE CLOSTRIDIUM HISTOLYTICUM	Approved	for treatment of Dupuytren's contracture	cleavage	TRUE	Collagen hydrolytic enzyme	0.47
	HJC 0350	Not Approved		inhibitor	FALSE	Inhibition	13.05
NPPB	/	/	/	/	/	/	/
NQO1	ORAL CONTRACEPTIVE	Not Approved					0.37
	VITAMIN K3	Approved	for reducing EGFR-inhibitor-induced dermatological side effects				0.07
	VATIQUINONE	Not Approved	for treatment of ulcerative colitis, for treatment of Chron's disease				2.01
	HYDROQUINONE	Approved					0.24
	DICUMAROL	Approved	Anticoagulants				0.75
	CYTARABINE	Approved	antineoplastic agent				0.05
	ACETAMINOPHEN	Approved	analgesic				0.08
	SULFORAPHANE	Not Approved					0.57
	RECOMBINANT 70-KD HEAT-SHOCK PROTEIN	Not Approved					0.40
	DOXORUBICIN HYDROCHLORIDE	Approved	antineoplastic agent				0.09
	CHEMBL:CHEMBL1983317	Not Approved					2.01
	ETOPOSIDE	Approved	Antineoplastic Agents				0.07

CHEMBL:CHEMBL476968	Not Approved					2.01
METHOTREXATE	Approved	DMARD				0.04
TYROSINE KINASE INHIBITOR	Not Approved					0.15
ITRACONAZOLE	Approved					0.45
CHEMBL:CHEMBL1288281	Not Approved					2.01
BETA-LAPACHONE PRODRUG ARQ 761	Not Approved					2.01
BENZENE	Not Approved					6.02
ETHACRYNIC ACID	Approved	Antihypertensive Agents; Diuretics				0.25
CHEMBL:CHEMBL1287866	Not Approved					2.01
IDARUBICIN	Approved	Antineoplastic Agents				0.08
CHEMBL:CHEMBL1287895	Not Approved					2.01
CHEMBL:CHEMBL1288253	Not Approved					2.01
VATIQUINONE	Not Approved		modulator	TRUE	Quinone reductase 1) modulator	2.01
CHEMBL:CHEMBL1287867	Not Approved					2.01

Table S23. Potential drugs for candidate proteins in DrugBank.

Gene	Drug	Drug group	Pharmacological action	Type	Actions
CCN3	Insulin human	approved, investigational	unknown	target	downregulator
COL6A3	/	/	/	/	/
NPPB	Carvedilol	approved, investigational	unknown	target	other
NQO1	3-(HYDROXYMETHYL)-1-METHYL-5-(2-METHYLAZIRIDIN-1-YL)-2-PHENYL-1H-INDOLE-4,7-DIONE	experimental	unknown	target	
	3-Hydroxymethyl-5-Aziridinyl-1methyl-2-[1h-Indole-4,7-Dione]-Propanol	experimental	unknown	target	
	5-Methoxy-1,2-Dimethyl-3-(Phenoxymethyl)Indole-4,7-Dione	experimental	unknown	target	
	alpha-Tocopherol succinate	approved, nutraceutical, vet_approved	unknown	enzyme	inducer
	Bishydroxy[2h-1-Benzopyran-2-One,1,2-Benzopyrone]	experimental	yes	target	inhibitor
	Cannabidiol	approved, investigational	unknown	target	inhibitor
	Carboplatin	approved, investigational	unknown	enzyme	substrate
	Cibacron Blue	experimental	unknown	target	
	Cisplatin	approved, investigational	unknown	enzyme	substrate
	D-alpha-Tocopherol acetate	approved, nutraceutical, vet_approved	unknown	enzyme	inducer
	Dicoumarol	approved	unknown	target	inhibitor
	Doxorubicin	approved, investigational	no	enzyme	substrate
	Duroquinone	experimental	yes	target	inhibitor
	ES-936	experimental	yes	target	inhibitor
	Flavin adenine dinucleotide	approved	yes	target	inhibitor
	Menadione	approved, nutraceutical	unknown	target	
	Oxaliplatin	approved, investigational	no	enzyme	substrate
	Phenytoin	approved, investigational,	no	enzyme	substrate

	vet_approved			
RH-1	investigational	unknown	target	
Vitamin E	approved, investigational, nutraceutical, vet_approved	unknown	enzyme	inducer

Table S24. Potential drugs for candidate proteins in Open Targets Platform.

Gene	Drug name	Type	Mechanism of action	Action type	Disease name
CCN3	/	/	/	/	/
COL6A3	COLLAGENASE CLOSTRIDIUM HISTOLYTICUM	Enzyme	Collagen hydrolytic enzyme	Hydrolytic enzyme	Abnormality of connective tissue; contracture; decubitus ulcer; diabetic foot; Dupuytren Contracture; etc.
	OCRIPLASMIN	Protein	Collagen hydrolytic enzyme	Hydrolytic enzyme	Abnormal retinal morphology; deep vein thrombosis; diabetic macular edema; eye disease; macular degeneration; etc.
NPPB	/	/	/	/	/
NQO1	VATIQUINONE	Small molecule	Quinone reductase 1) modulator	Modulator	autism spectrum disorder; Friedreich ataxia; Leigh syndrome; mitochondrial disease; myopathy; etc.

Supplementary Figures

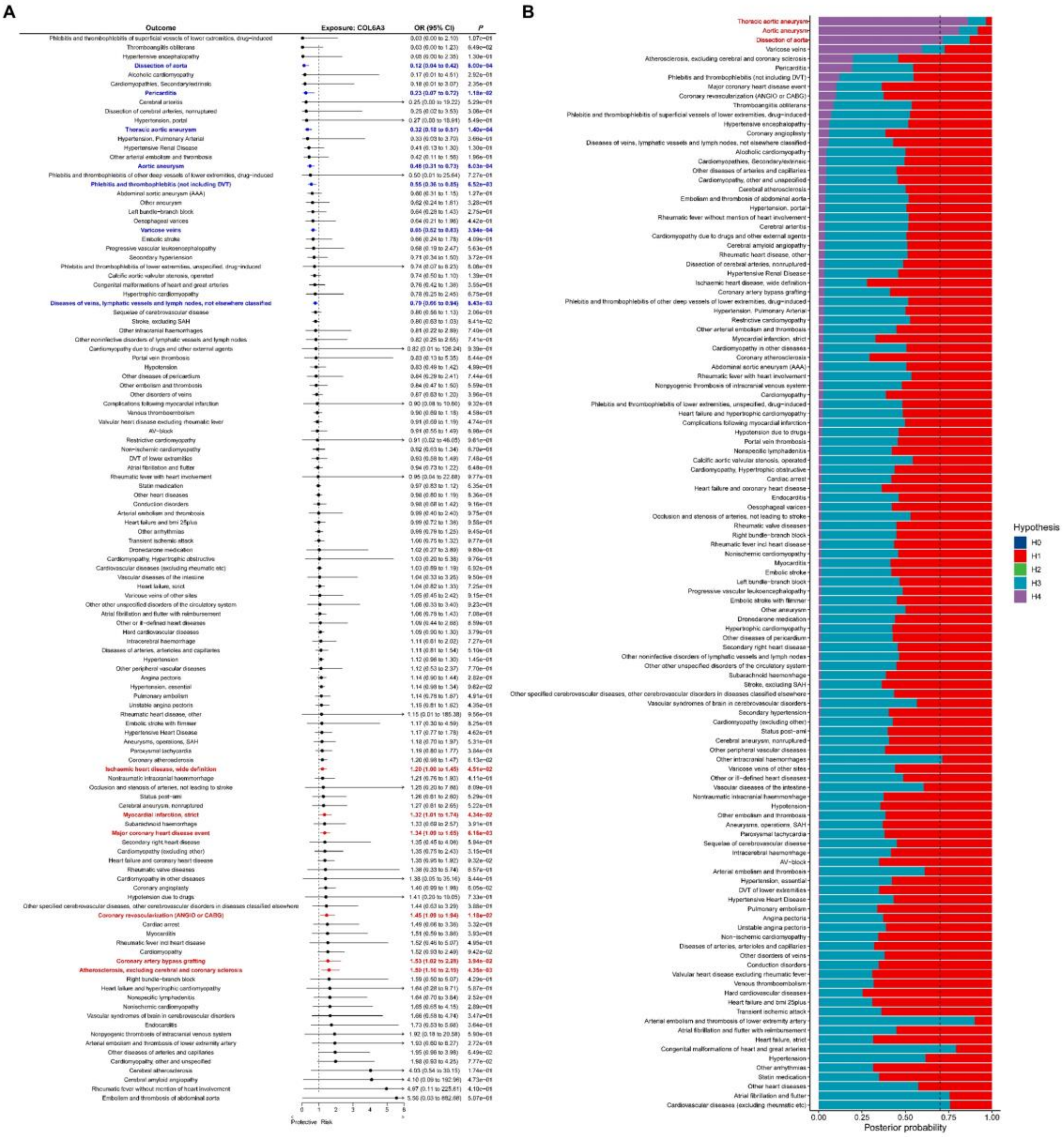

Figure S1. Causal association and colocalization analysis between COL6A3 and CVDs. (**A**) Causal estimates between COL6A3 and CVDs. The blue text represents significant protective factors, and the red text represents significant risk factors. (**B**) Colocalization analysis between COL6A3 and CVDs. The black dashed line represents the positive threshold (70%) for the posterior probability of hypothesis 4 (PPH4). Abbreviation: CVD, cardiovascular disease.