

Risk Prediction and Therapeutic Targets for Incident Pulmonary Hypertension: A Large-Scale Proteomic Profiling and Mendelian Randomization Study

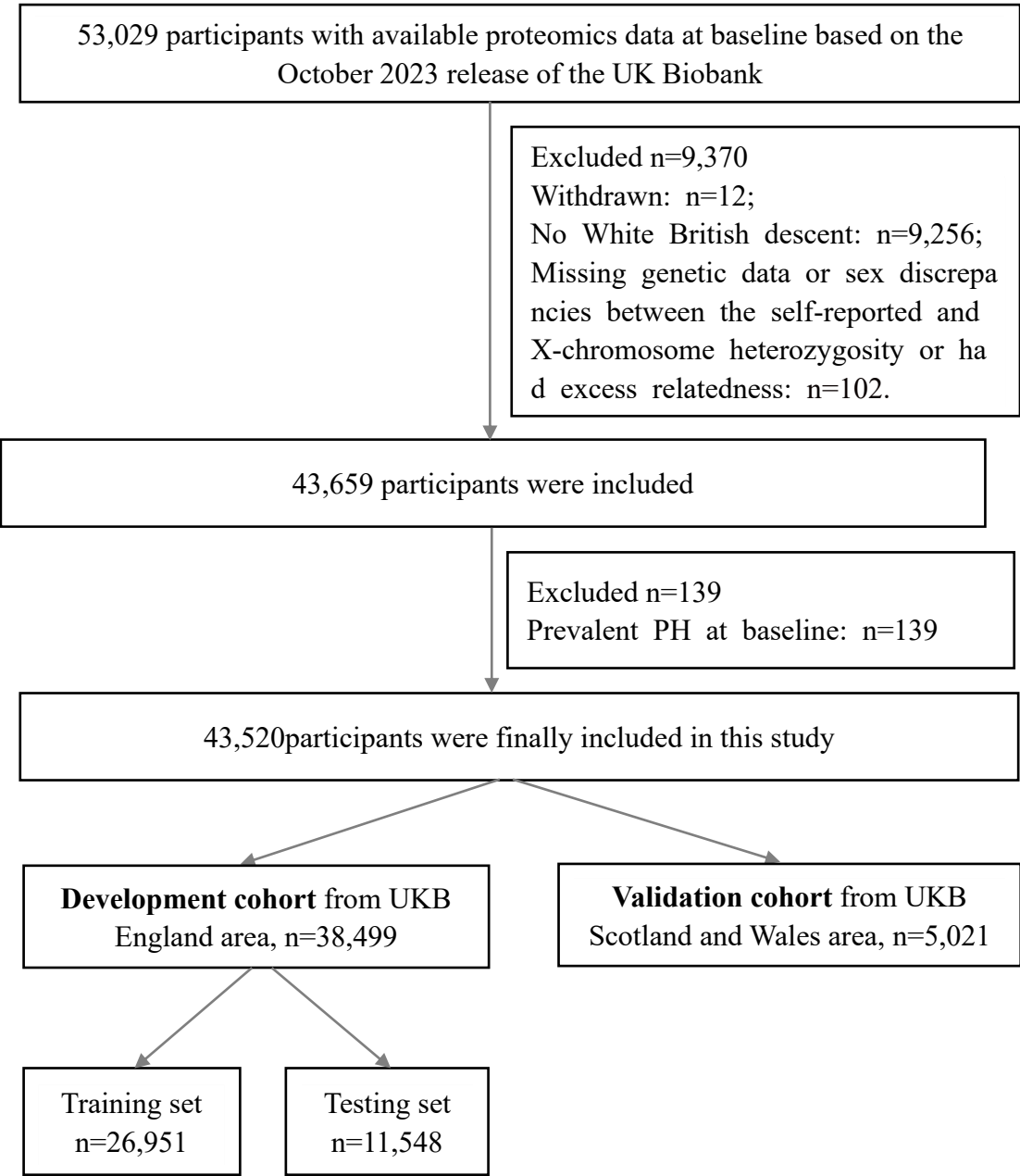


Figure S1. Flow chart of the participants in the current analysis.

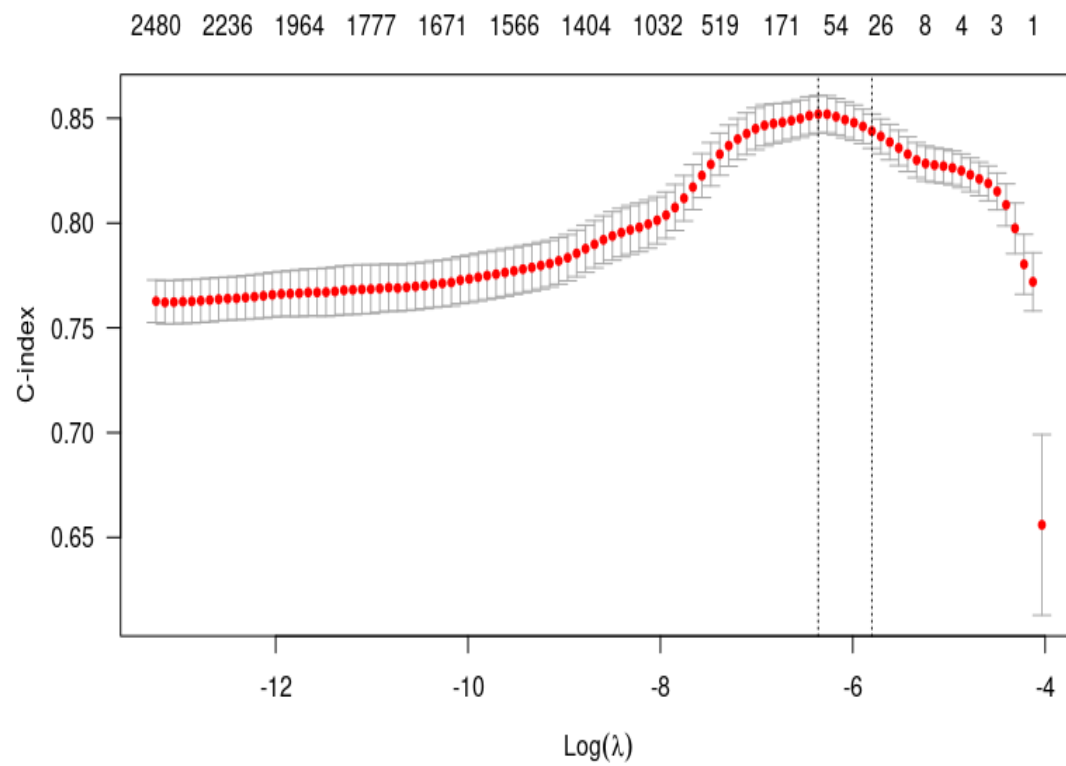


Figure S2. Cross-validation for selecting penalization strength for fitting protein pulmonary hypertension (PH) risk prediction models.

The figure shows how the penalization strength λ for fitting the protein risk score using all the protein measurements, age and sex, which is selected based on the C-index in ten-fold cross-validation. The red dots represent the mean C-index for each λ that was used and the bars represent one standard deviation in each direction for the cross-validations. The top x-axis shows how the number of nonzero coefficients changes with the penalization strength.

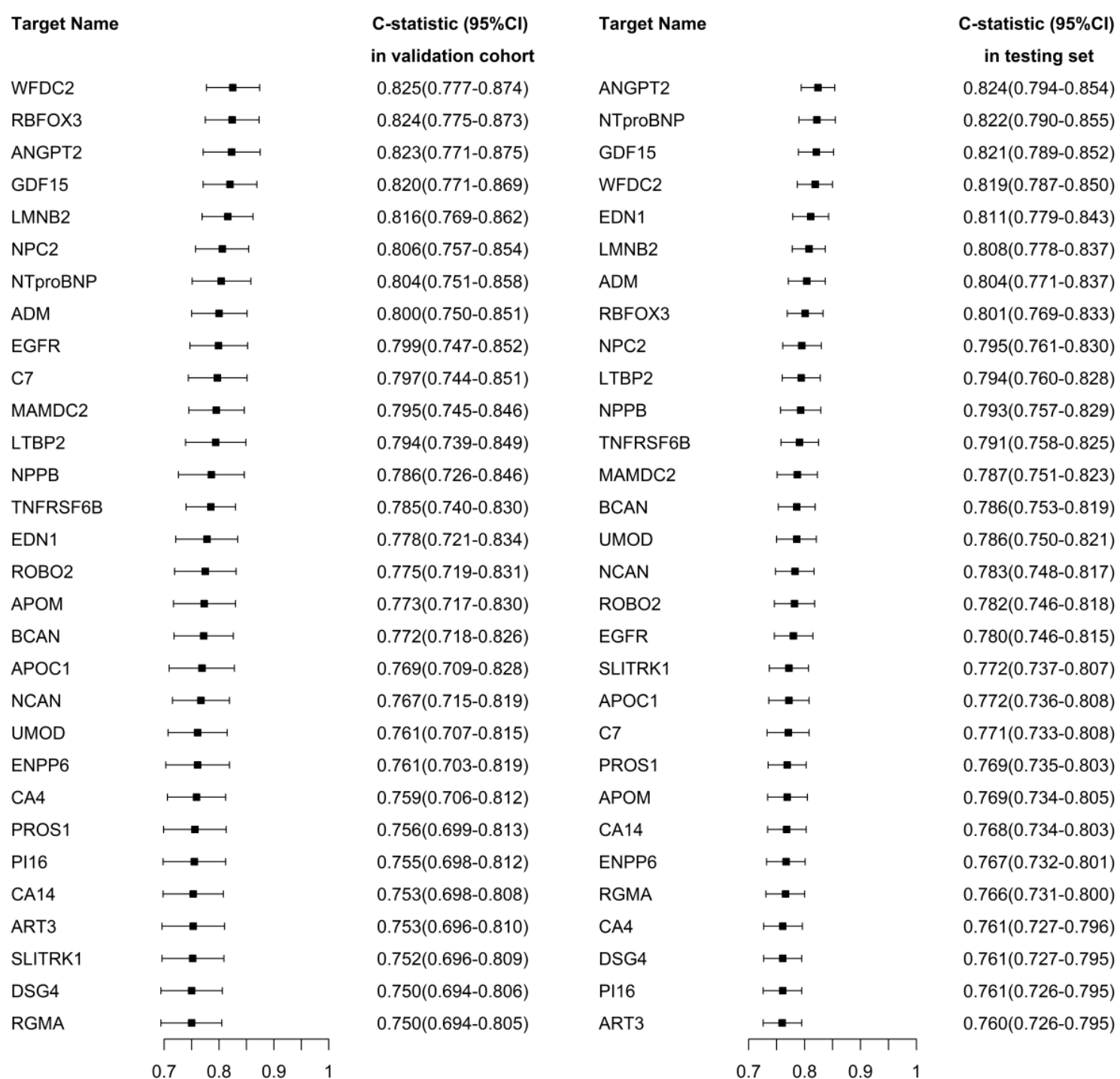


Figure S3. The C-index of individual protein for pulmonary hypertension (PH) risk prediction in internal testing and external validation cohort.

C-index was estimated as the model of age, sex and each individual protein.

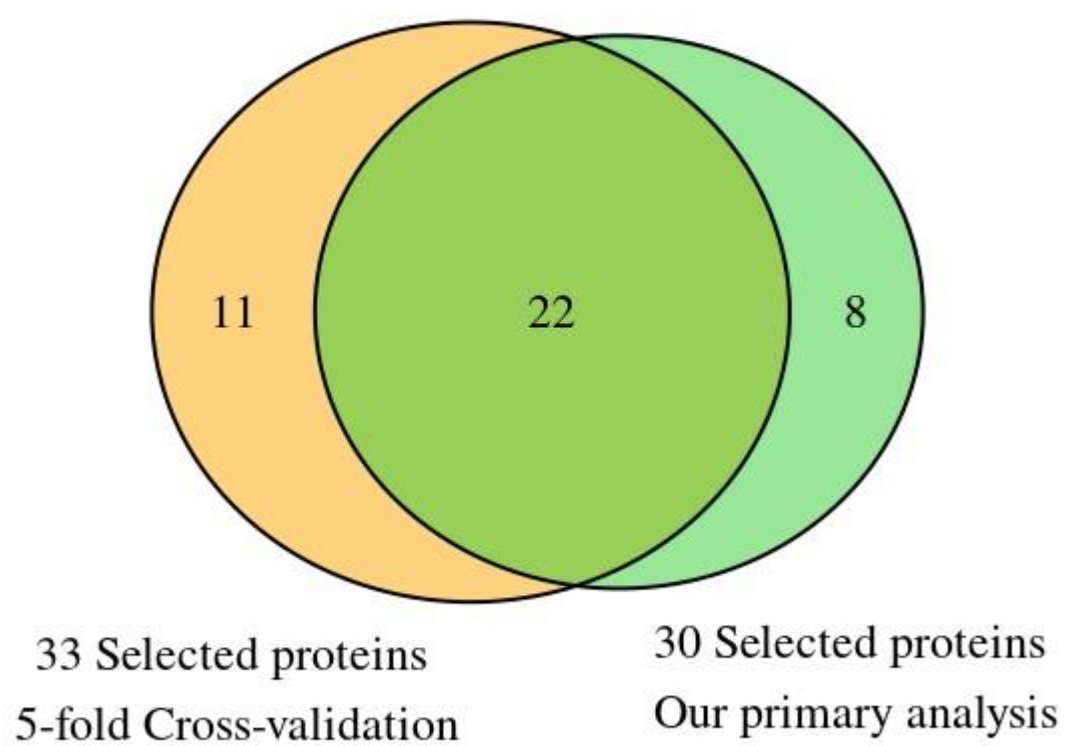


Figure S4. Venn diagram of protein panels comparison

Numbers in overlapping and non-overlapping regions indicate the count of shared or unique proteins. The intersection contains 22 proteins common to both panels.

Table S1. 30 proteins selected by LASSO model to create a protein risk score for pulmonary hypertension (PH).

Rank	Target Name	Target Full Name	UniProt	Protein panel	Coefficient/weight
1	ANGPT2	Angiopoietin-2	O15123	Oncology	0.450868308
2	GDF15	Growth/differentiation factor 15	Q99988	Cardiometabolic	0.392308546
3	NTproBNP	N-terminal prohormone of brain natriuretic peptide	NTproBNP	Cardiometabolic	0.384955313
4	NPC2	NPC intracellular cholesterol transporter 2	P61916	Cardiometabolic II	0.354777062
5	PROS1	Vitamin K-dependent protein S	P07225	Inflammation II	-0.249816275
6	ROBO2	Roundabout homolog 2	Q9HCK4	Neurology	0.22764408
7	CA4	Carbonic anhydrase 4	P22748	Cardiometabolic	-0.201884131
8	SLITRK1	SLIT and NTRK-like protein 1	Q96PX8	Inflammation II	-0.180065316
9	BCAN	Brevican core protein	Q96GW7	Neurology	-0.16179613
10	LTBP2	Latent-transforming growth factor beta-binding protein 2	Q14767	Cardiometabolic	0.156045966
11	WFDC2	WAP four-disulfide core domain protein 2	Q14508	Oncology	0.149656731
12	PI16	Peptidase inhibitor 16	Q6UXB8	Inflammation II	-0.119679793
13	ART3	Ecto-ADP-ribosyltransferase 3	Q13508	Cardiometabolic	-0.097578043
14	C7	Complement component C7	P10643	Inflammation II	0.0949396
15	APOM	Apolipoprotein M	O95445	Cardiometabolic	-0.086628696
16	TNFRSF6B	Tumor necrosis factor receptor superfamily member 6B	O95407	Neurology	0.082111108
17	EDN1	Endothelin-1	P05305	Cardiometabolic II	0.078557891
18	MAMDC2	MAM domain-containing protein 2	Q7Z304	Cardiometabolic II	0.068772993
19	APOC1	Apolipoprotein C-I	P02654	Inflammation II	-0.067444609
20	LMNB2	Lamin-B2	Q03252	Neurology II	0.057477046
21	NCAN	Neurocan core protein	O14594	Neurology	-0.057391824
22	DSG4	Desmoglein-4	Q86SJ6	Oncology	-0.046343691
23	CA14	Carbonic anhydrase 14	Q9ULX7	Oncology	-0.03734981
24	RGMA	Repulsive guidance molecule A	Q96B86	Neurology	-0.036279621
25	UMOD	Uromodulin	P07911	Cardiometabolic	-0.030209516
26	RBFOX3	RNA binding protein fox-1 homolog 3	A6NFN3	Neurology II	0.021249675
27	ADM	Pro-adrenomedullin	P35318	Oncology	0.015907939
28	ENPP6	Glycerophosphocholine cholinephosphodiesterase ENPP6	Q6UWR7	Cardiometabolic II	-0.005982494
29	NPPB	Natriuretic peptides B	P16860	Cardiometabolic	0.004291881
30	EGFR	Epidermal growth factor receptor	P00533	Cardiometabolic	-0.002002305

Table S2. 33 proteins selected by LASSO model to create a protein risk score for pulmonary hypertension (PH) through 5-fold cross-validation approach.

Rank	Target Name	Target Full Name	UniProt	Protein panel	Coefficient/weight
1	PROS1	Vitamin K-dependent protein S	P07225	Inflammation II	-0.457050006
2	ANGPT2	Angiopoietin-2	O15123	Oncology	0.429640115
3	CA4	Carbonic anhydrase 4	P22748	Cardiometabolic	-0.397231008
4	NTproBNP	N-terminal prohormone of brain natriuretic peptide	NTproBNP	Cardiometabolic	0.352441713
5	EDN1	Endothelin-1	P05305	Cardiometabolic II	0.306705619
6	WFDC2	WAP four-disulfide core domain protein 2	Q14508	Oncology	0.278094264
7	GDF15	Growth/differentiation factor 15	Q99988	Cardiometabolic	0.272929508
8	RBFOX3	RNA binding protein fox-1 homolog 3	A6NFN3	Neurology II	0.249200229
9	CA14	Carbonic anhydrase 14	Q9ULX7	Oncology	-0.218188175
10	ROBO2	Roundabout homolog 2	Q9HCK4	Neurology	0.209762467
11	SLITRK1	SLIT and NTRK-like protein 1	Q96PX8	Inflammation II	-0.176139384
12	LTBP2	Latent-transforming growth factor beta-binding protein 2	Q14767	Cardiometabolic	0.171704096
13	C7	Complement component C7	P10643	Inflammation II	0.154758277
14	ADM	Pro-adrenomedullin	P35318	Oncology	0.138668374
15	NCAN	Neurocan core protein	O14594	Neurology	-0.118620566
16	LRRN1	Leucine-rich repeat neuronal protein 1	Q6UXK5	Inflammation	-0.111724892
17	CCL18	C-C motif chemokine 18	P55774	Cardiometabolic	0.08679569
18	NPC2	NPC intracellular cholesterol transporter 2	P61916	Cardiometabolic II	0.083624524
19	TNFRSF6B	Tumor necrosis factor receptor superfamily member 6B	O95407	Neurology	0.079198507
20	ART3	Ecto-ADP-ribosyltransferase 3	Q13508	Cardiometabolic	-0.066259192
21	REN	Renin	P00797	Cardiometabolic	0.065721706
22	BCAN	Brevican core protein	Q96GW7	Neurology	-0.063196906
23	RGMA	Repulsive guidance molecule A	Q96B86	Neurology	-0.062504993
24	UMOD	Uromodulin	P07911	Cardiometabolic	-0.059682027
25	LAMP3	Lysosome-associated membrane glycoprotein 3	Q9UQV4	Inflammation	0.054703271
26	YAP1	Transcriptional coactivator YAP1	P46937	Neurology II	0.034423243
27	PRRT3	Proline-rich transmembrane protein 3	Q5FWE3	Cardiometabolic II	-0.033379757
28	FHIP2A	FHF complex subunit HOOK interacting protein 2A	Q5W0V3	Cardiometabolic II	0.028685606
29	APOC1	Apolipoprotein C-I	P02654	Inflammation II	-0.019915369
30	AGER	Advanced glycosylation end product-specific receptor	Q15109	Inflammation	-0.019440142
31	CCL3	C-C motif chemokine 3	P10147	Inflammation	0.016938832
32	CSRP3	Cysteine and glycine-rich protein 3	P50461	Cardiometabolic II	0.003567185
33	EDA2R	Tumor necrosis factor receptor superfamily member 27	Q9HAV5	Oncology	0.001378469

Table S3. Key data for all GWAS sources.

Dataset	Variables	Sample size	Ancestry
UK biobank	Exposures	54,219	European
FinnGen	Outcome	125 cases	European
		162,837 controls	

Table S4. Functional and pathway enrichment analyses for selected proteins in the protein risk scores for pulmonary hypertension (PH).

Categories	Term	Count	<i>P</i> value	FDR	Matching proteins
GO-CC					
GOTERM_CC_DIRECT	extracellular region	21	0.000	0.000	APOM, NPC2, ADM, EDN1, ANGPT2, PI16, LTBP2, NCAN, ART3, C7, WFDC2, MAMDC2, BCAN, NPPB, ENPP6, SLITRK1, TNFRSF6B, APOC1, GDF15, PROS1
GOTERM_CC_DIRECT	extracellular space	17	0.000	0.000	NPC2, ADM, UMOD, EDN1, ANGPT2, PI16, LTBP2, NCAN, C7, WFDC2, BCAN, NPPB, TNFRSF6B, EGFR, GDF15, PROS1
GOTERM_CC_DIRECT	anchored component of membrane	6	0.000	0.000	CA4, UMOD, ENPP6, RGMA, ART3, BCAN
GOTERM_CC_DIRECT	side of membrane	5	0.000	0.000	UMOD, ENPP6, RGMA, ART3, BCAN
GOTERM_CC_DIRECT	extracellular exosome	12	0.000	0.002	NPC2, CA4, ROBO2, UMOD, ENPP6, LTBP2, ART3, C7, WFDC2, GDF15, PROS1
GOTERM_CC_DIRECT	Golgi lumen	4	0.000	0.006	UMOD, NCAN, BCAN, PROS1
GOTERM_CC_DIRECT	lysosomal lumen	3	0.008	0.096	NPC2, NCAN, BCAN
GOTERM_CC_DIRECT	membrane attack complex	2	0.011	0.113	C7
GOTERM_CC_DIRECT	cell surface	5	0.013	0.113	CA4, ROBO2, UMOD, RGMA, EGFR
GOTERM_CC_DIRECT	perineuronal net	2	0.014	0.113	NCAN, BCAN
GOTERM_CC_DIRECT	endoplasmic reticulum	6	0.022	0.165	NPC2, UMOD, RGMA, MAMDC2, APOC1, PROS1
GOTERM_CC_DIRECT	very-low-density lipoprotein particle	2	0.029	0.196	APOM, APOC1
GOTERM_CC_DIRECT	high-density lipoprotein particle	2	0.037	0.232	APOM, APOC1
GOTERM_CC_DIRECT	extracellular matrix	3	0.051	0.279	LTBP2, NCAN, BCAN
GOTERM_CC_DIRECT	basolateral plasma membrane	3	0.052	0.279	UMOD, EGFR, CA14
GOTERM_CC_DIRECT	plasma membrane	13	0.057	0.290	CA4, ROBO2, ENPP6, ANGPT2, RGMA, SLITRK1, DSG4, ART3, C7, EGFR, CA14, PROS1
GO-BP					
GOTERM_BP_DIRECT	cholesterol efflux	3	0.001	0.370	APOM, NPC2, APOC1
GOTERM_BP_DIRECT	regulation of urine volume	2	0.006	0.806	ADM, UMOD
GOTERM_BP_DIRECT	regulation of blood pressure	3	0.007	0.806	NPPB, EDN1, UMOD
GOTERM_BP_DIRECT	BMP signaling pathway	3	0.009	0.806	RGMA, DSG4, GDF15
GOTERM_BP_DIRECT	body fluid secretion	2	0.010	0.806	NPPB, EDN1
GOTERM_BP_DIRECT	positive regulation of renal sodium excretion	2	0.019	0.806	NPPB, EDN1
GOTERM_BP_DIRECT	renal sodium ion absorption	2	0.019	0.806	EDN1, UMOD
GOTERM_BP_DIRECT	central nervous system development	3	0.020	0.806	ROBO2, NCAN, BCAN
GOTERM_BP_DIRECT	response to lipopolysaccharide	3	0.021	0.806	EDN1, ADM, UMOD
GOTERM_BP_DIRECT	negative regulation of blood coagulation	2	0.021	0.806	EDN1, PROS1
GOTERM_BP_DIRECT	positive regulation of urine volume	2	0.021	0.806	NPPB, EDN1
GOTERM_BP_DIRECT	high-density lipoprotein particle remodeling	2	0.024	0.806	APOM, APOC1
GOTERM_BP_DIRECT	complement activation, alternative pathway	2	0.027	0.806	C7
GOTERM_BP_DIRECT	glycosaminoglycan catabolic process	2	0.031	0.806	NCAN, BCAN
GOTERM_BP_DIRECT	positive regulation of heart rate	2	0.031	0.806	EDN1, ADM
GOTERM_BP_DIRECT	lipoprotein metabolic process	2	0.032	0.806	APOM, APOC1
GOTERM_BP_DIRECT	cytolysis	2	0.034	0.806	C7
GOTERM_BP_DIRECT	cell-cell adhesion	3	0.034	0.806	ROBO2, DSG4, EGFR
GOTERM_BP_DIRECT	glial cell differentiation	2	0.035	0.806	NCAN, BCAN
GOTERM_BP_DIRECT	complement activation	2	0.042	0.884	C7
GOTERM_BP_DIRECT	lipid metabolic process	3	0.043	0.884	UMOD, ENPP6, APOC1
GOTERM_BP_DIRECT	positive regulation of axonogenesis	2	0.047	0.922	ROBO2, SLITRK1
GOTERM_BP_DIRECT	positive regulation of neuroblast proliferation	2	0.054	0.974	NCAN, BCAN
GOTERM_BP_DIRECT	one-carbon metabolic process	2	0.054	0.974	CA4, CA14
GOTERM_BP_DIRECT	animal organ regeneration	2	0.058	1.000	ADM, ANGPT2
GOTERM_BP_DIRECT	hair follicle development	2	0.062	1.000	DSG4, EGFR
GOTERM_BP_DIRECT	glycosaminoglycan biosynthetic process	2	0.062	1.000	NCAN, BCAN

Supplemental Materials

GOTERM_BP_DIRECT	response to activity	2	0.072	1.000	EDN1, ANGPT2
GOTERM_BP_DIRECT	cell surface receptor signaling pathway	3	0.086	1.000	NPPB, EDN1, EGFR
GO-MF					
GOTERM_MF_DIRECT	hormone activity	3	0.012	0.484	NPPB, EDN1, ADM
GOTERM_MF_DIRECT	calcium ion binding	5	0.024	0.484	UMOD, DSG4, LTBP2, NCAN, PROS1
GOTERM_MF_DIRECT	carbonate dehydratase activity	2	0.025	0.484	CA4, CA14
GOTERM_MF_DIRECT	peptidase inhibitor activity	2	0.028	0.484	PI16, WFDC2
GOTERM_MF_DIRECT	hydro-lyase activity	2	0.031	0.484	CA4, CA14
GOTERM_MF_DIRECT	hyaluronic acid binding	2	0.036	0.484	NCAN, BCAN
GOTERM_MF_DIRECT	endopeptidase inhibitor activity	2	0.070	0.799	WFDC2, PROS1
KEGG					
KEGG_PATHWAY	HIF-1 signaling pathway	3	0.019	0.824	EDN1, ANGPT2, EGFR
KEGG_PATHWAY	vascular smooth muscle contraction	3	0.028	0.824	NPPB, EDN1, ADM
KEGG_PATHWAY	nitrogen metabolism	2	0.033	0.824	CA4, CA14
KEGG_PATHWAY	cholesterol metabolism	2	0.096	1.000	NPC2, APOC1

Abbreviation: FDR, false discovery rate. GO-CC, Gene Ontology cellular component; GO-BP, Gene Ontology biological process; GO-MF, Gene Ontology molecular function; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Table S5. The key proteins in the protein-protein interaction (PPI) network.

Rank	Key nodes (Protein)	Degree Centrality (DC)	Closeness Centrality (CC)	Betweenness Centrality (BC)
1	EDN1	10	0.09039548	5
2	EGFR	8	0.08988764	10.666667
3	GDF15	8	0.08988764	3.3333333
4	ADM	8	0.08938547	1.6666666
5	ANGPT2	6	0.08938547	1.3333334
6	NPPB	6	0.08888889	0
7	CA4	4	0.06666667	2
8	NCAN	4	0.06666667	2
9	SLITRK1	2	0.0625	0
10	ROBO2	2	0.0625	0
11	PROS1	2	0.066390045	0
12	UMOD	2	0.08743169	0
13	RBFOX3	2	0.066390045	0
14	CA14	2	0.066390045	0
15	BCAN	2	0.066390045	0
16	APOM	2	0.0625	0
17	APOC1	2	0.0625	0

Degree Centrality (DC), it simply counts the number of links a node to others in the network. A higher DC value indicates that the node has more direct connections or interactions with other nodes in the network.

Closeness Centrality (CC), it measures how close a node is to all others in the network. A higher CC value indicates that the node is located closer to others in the network, enabling faster communication and interactions.

Betweenness Centrality (BC), it measures how often a node lies on the shortest path between others in the network. A higher BC value indicates that the node plays a more significant role in connecting different parts of the network.

Table S6. Mendelian randomization for selected proteins and the risk of pulmonary hypertension (PH).

Exposure	ID Outcome	Method	Number of snp	Odds ratio	Low 95%CI	Up 95%CI	P value
RGMA	finn-b-I9_HYPTENSPUL	Inverse variance weighted	11	2.730683	1.151214	6.477187	0.022635
NPC2	finn-b-I9_HYPTENSPUL	Inverse variance weighted	5	0.266607	0.076834	0.925097	0.037283
PI16	finn-b-I9_HYPTENSPUL	Inverse variance weighted	12	0.588049	0.292389	1.182678	0.136394
DSG4	finn-b-I9_HYPTENSPUL	Wald ratio	1	0.027429	0.000133	5.664982	0.186068
ART3	finn-b-I9_HYPTENSPUL	Inverse variance weighted	11	0.585384	0.261275	1.311549	0.19324
WFDC2	finn-b-I9_HYPTENSPUL	Inverse variance weighted	3	0.292202	0.037227	2.293577	0.241862
BCAN	finn-b-I9_HYPTENSPUL	Inverse variance weighted	4	0.474892	0.131525	1.714676	0.255615
LTBP2	finn-b-I9_HYPTENSPUL	Inverse variance weighted	5	4.956681	0.272821	90.05436	0.279254
PROS1	finn-b-I9_HYPTENSPUL	Inverse variance weighted	3	0.363518	0.033167	3.984297	0.407456
TNFRSF6B	finn-b-I9_HYPTENSPUL	Inverse variance weighted	12	0.768854	0.407842	1.449423	0.416456
APOM	finn-b-I9_HYPTENSPUL	Inverse variance weighted	7	0.515426	0.091152	2.914523	0.453372
ADM	finn-b-I9_HYPTENSPUL	Inverse variance weighted	3	0.523558	0.093374	2.935655	0.461929
NCAN	finn-b-I9_HYPTENSPUL	Inverse variance weighted	4	0.536545	0.094011	3.062203	0.483537
APOC1	finn-b-I9_HYPTENSPUL	Inverse variance weighted	7	1.805817	0.318718	10.23153	0.50422
CA4	finn-b-I9_HYPTENSPUL	Inverse variance weighted	3	1.278777	0.580348	2.817739	0.541817
EGFR	finn-b-I9_HYPTENSPUL	Inverse variance weighted	8	0.7111	0.224837	2.249024	0.561674
CA14	finn-b-I9_HYPTENSPUL	Inverse variance weighted	3	0.46407	0.024993	8.616931	0.606509
ANGPT2	finn-b-I9_HYPTENSPUL	Inverse variance weighted	5	0.742769	0.234588	2.351809	0.613069
EDN1	finn-b-I9_HYPTENSPUL	Inverse variance weighted	4	0.779148	0.25991	2.335698	0.655941
LMNB2	finn-b-I9_HYPTENSPUL	Wald ratio	1	3.705493	0.008627	1591.654	0.671969
C7	finn-b-I9_HYPTENSPUL	Inverse variance weighted	16	1.094695	0.707368	1.694109	0.684674
MAMDC2	finn-b-I9_HYPTENSPUL	Inverse variance weighted	4	1.262525	0.389732	4.089904	0.697485
GDF15	finn-b-I9_HYPTENSPUL	Inverse variance weighted	14	0.850416	0.31211	2.317158	0.751375
SLITRK1	finn-b-I9_HYPTENSPUL	Wald ratio	1	1.257198	0.11404	13.85958	0.851727
ENPP6	finn-b-I9_HYPTENSPUL	Inverse variance weighted	14	1.058332	0.575301	1.946921	0.85535
ROBO2	finn-b-I9_HYPTENSPUL	Inverse variance weighted	4	1.161614	0.168339	8.01567	0.879176
NPPB	finn-b-I9_HYPTENSPUL	Inverse variance weighted	3	1.12144	0.184472	6.817457	0.900948
UMOD	finn-b-I9_HYPTENSPUL	Inverse variance weighted	22	1.000928	0.703013	1.425091	0.995893

Supplemental Materials

Table S7. Identification of druggable targets for selected proteins of pulmonary hypertension (PH).

Target name	Target ID	Target Type	Drug name	Drugs Type	Disease
ANGPT2	T21960	Successful target	Faricimab	Approved	Neovascular age-related macular degeneration
			AMG 386	Phase 3	Neuropathic pain
			Trebananib	Phase 3	Ovarian cancer
			REGN910-3	Phase 2	Neovascular age-related macular degeneration
			RG7221	Phase 2	Colorectal cancer
			RO5520985	Phase 2	Colorectal cancer
			CVX-060	Phase 1/2	Solid tumour/cancer
			BI 836880	Phase 1	Neoplasm
			CVX-241	Phase 1	Solid tumour/cancer
			LY3127804	Phase 1	Solid tumour/cancer
			MEDI3617	Phase 1	Solid tumour/cancer
			Nesvacumab	Phase 1	Solid tumour/cancer
			REGN-910	Phase 1	Solid tumour/cancer
			Zifibancimig	Phase 1	Neovascular age-related macular degeneration
GDF15	T33245	Clinical trial target	Ponsegromab	Phase 2	Heart failure
			CIN-109	Phase 1	Obesity
			CIN-209	Preclinical	Obesity
NTproBNP	-	-	-	-	-
NPC2	-	-	-	-	-
PROS1	-	-	-	-	-
ROBO2	-	-	-	-	-
CA4	T53378	Successful target	Brinzolamide	Approved	Open-angle glaucoma
			Salicyclic acid	Approved	Seborrhoeic dermatitis
			Sulfamylon	Approved	Bacterial infection
			Curcumin	Phase 3	Solid tumour/cancer
			Coumate	Phase 2	Breast cancer

Supplemental Materials

			Sodium pyruvate	Phase 1/2	Asthma
SLITRK1	-	-	-	-	-
BCAN	-	-	-	-	-
LTBP2	-	-	-	-	-
WFDC2	-	-	-	-	-
PI16	-	-	-	-	-
ART3	-	-	-	-	-
C7	-	-	-	-	-
APOM	-	-	-	-	-
TNFRSF6B	-	-	-	-	-
EDN1	T25076	Literature-reported Target	Tetramethylpyrazine	Discontinued in Phase 2	Neurological disorder
MAMDC2	-	-	-	-	-
APOC1	-	-	-	-	-
LMNB2	-	-	-	-	-
NCAN	-	-	-	-	-
DSG4	-	-	-	-	-
CA14	T31992	Successful Target	Sulfamylon	Approved	Bacterial infection
			TRIENTINE	Approved	Inborn error of metabolism
			Curcumin	Phase 3	Solid tumour/cancer
			Coumate	Phase 2	Breast cancer
RGMA	T99313	Clinical trial target	Elezanumab	Phase 2	Multiple sclerosis
UMOD	-	-	-	-	-
RBFOX3	-	-	-	-	-
ADM	T20629	Clinical trial Target	BAY1097761	Phase 2	Respiratory distress syndrome
ENPP6	-	-	-	-	-
NPPB	T55302	Literature-reported target	-	-	Hypertension
EGFR	T59328	Successful target	Amivantamab	Approved	Non-small-cell lung cancer

Supplemental Materials

BIBW 2992	Approved	Non-small-cell lung cancer
Cetuximab	Approved	Colorectal cancer
Dacomitinib	Approved	Non-small-cell lung cancer
Epidermal growth factor	Approved	Vulnerary
Erlotinib	Approved	Non-small-cell lung cancer
Gefitinib	Approved	Solid tumour/cancer
HEGF	Approved	Diabetic foot ulcer
Lapatinib	Approved	Breast cancer
Merimepodib	Approved	Breast cancer
Necitumumab	Approved	Colorectal cancer
NERATINIB MALEATE	Approved	HER2/NEU overexpressing breast cancer
Nitroglycerin	Approved	Diabetic foot ulcer
Osimertinib	Approved	Non-small-cell lung cancer
Panitumumab	Approved	Colorectal cancer
SKI-758	Approved	Ischemia
Sorafenib	Approved	Renal cell carcinoma
Vandetanib	Approved	Solid tumour/cancer
Icotinib hydrochloride	Registered	Non-small-cell lung cancer
A140	Phase 3	Head and neck cancer
Almonertinib	Phase 3	Non-small-cell lung cancer
ASP1929	Phase 3	Head and neck cancer
Bevacizumab + Erlotinib	Phase 3	Metastatic colorectal cancer
CO-1686	Phase 3	Lung cancer
DE-766	Phase 3	Non-small-cell lung cancer
EGF816	Phase 3	Non-small-cell lung cancer
HKI-272	Phase 3	Breast cancer
Rindopepimut	Phase 3	Glioblastoma multiforme
SYM-004	Phase 3	Metastatic colorectal cancer
Zalutumumab	Phase 3	Head and neck cancer

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Indium-111	Phase 2/3	Solid tumour/cancer
Varlitinib	Phase 2/3	Metastatic biliary tract neoplasms
ABT-414	Phase 2	Glioblastoma multiforme
ASP8273	Phase 2	Non-small-cell lung cancer
BMS-599626	Phase 2	Solid tumour/cancer
BMS-690514	Phase 2	Chronic pain
CetuGEX	Phase 2	Solid tumour/cancer
CI-1033	Phase 2	Lymphoma
Depatuxizumab	Phase 2	Glioblastoma of brain
HER1-VSSP vaccine	Phase 2	Solid tumour/cancer
HM-78136B	Phase 2	Solid tumour/cancer
Matuzumab	Phase 2	Gastric adenocarcinoma
MEHD-7945A	Phase 2	Colorectal cancer
Pazopanib + Tyverb/Tykerb	Phase 2	Inflammatory breast cancer
Pelitinib	Phase 2	Lymphoma
RM-1929	Phase 2	Head and neck cancer
Tarloxotinib	Phase 2	Non-small-cell lung cancer
TT-100	Phase 2	Non-small-cell lung cancer
VATALANIB	Phase 2	Solid tumour/cancer
AFM24	Phase 1/2	Solid tumour/cancer
BDTX-189	Phase 1/2	Solid tumour/cancer
CART-EGFR	Phase 1/2	Solid tumour/cancer
EGFR CART	Phase 1/2	Colorectal cancer
EMB-01	Phase 1/2	Neoplasm
EMD 55900	Phase 1/2	Glioma
SN-32793	Phase 1/2	Non-small-cell lung cancer
Sym013	Phase 1/2	Epithelial ovarian cancer
Sym015	Phase 1/2	Solid tumour/cancer
TAK-186	Phase 1/2	Aggressive cancer

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ZN-e4	Phase 1/2	Non-small-cell lung cancer
S-222611	Phase 1b	Malignant solid tumour
AMG 595	Phase 1	Glioblastoma multiforme
Anti-EGFR CAR T	Phase 1	Glioma
Anti-HER3/EGFR DAF	Phase 1	Metastatic epithelial tumour
AP32788	Phase 1	Non-small-cell lung cancer
AST-1306	Phase 1	Solid tumour/cancer
AZD9592	Phase 1	Aggressive cancer
BCA101	Phase 1	Solid tumour/cancer
BIBX-1382	Phase 1	Chronic lymphocytic leukaemia
Cipatinib	Phase 1	Solid tumour/cancer
CLN-081	Phase 1	Non-small-cell lung cancer
CUDC-101	Phase 1	Solid tumour/cancer
CX-904	Phase 1	Colorectal cancer
D2C7	Phase 1	Glioblastoma of brain
EGFR806-specific CAR T cell	Phase 1	Atypical teratoid/rhabdoid tumour
HER-2/HER-1 vaccine	Phase 1	Solid tumour/cancer
IMGN289	Phase 1	Solid tumour/cancer
JNJ-26483327	Phase 1	Solid tumour/cancer
LY3164530	Phase 1	Advanced cancer
MCLA-158	Phase 1	Solid tumour/cancer
MM-151	Phase 1	Solid tumour/cancer
MR1-1	Phase 1	Brain cancer
PF-05230907	Phase 1	Nontraumatic intracerebral hemorrhage
SI-B001	Phase 1	Metastatic epithelial tumour
SYN004	Phase 1	Solid tumour/cancer
¹¹¹ In-hEGF	Preclinical	Breast cancer
EGFR/IGFR tandem adnectin	Preclinical	Solid tumour/cancer

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Table S8. Performance evaluation of the primary pulmonary hypertension (PAH) risk prediction model in internal testing and external validation cohorts.

Model	C-index	Comparison to reference models		
		C-index increase (95% CI)	10-y Risk continuous	10-y Risk IDI (95% CI)
		NRI (95% CI)		
Internal testing cohort				
Reference model: Basic model (age + sex)	0.744(0.689,0.798)			
Clinical risk model*	0.811(0.766,0.855)	0.067(-0.003,0.137)	0.333(0.153,0.424)	0.004(0.002,0.024)
Protein model (age + sex + PH protein risk score)	0.871(0.831,0.910)	0.126(0.057,0.194)	0.368(0.245,0.489)	0.043(0.019,0.094)
Reference model: Clinical risk model				
Clinical risk model + PH protein risk score	0.869(0.828,0.911)	0.059(-0.002,0.119)	0.310(0.127,0.453)	0.046(0.018,0.100)
Reference model: Protein model				
PH protein risk score + Clinical risk model	0.869(0.828,0.911)	-0.002(-0.059,0.056)	0.294(0.050,0.375)	0.007(0.000,0.058)
External validation cohort				
Reference model: Basic model (age + sex)	0.732(0.652,0.813)			
Clinical risk model*	0.851(0.797,0.905)	0.118(0.021,0.215)	0.433(0.141,0.537)	0.017(0.005,0.087)
Protein model (age + sex + PH protein risk score)	0.875(0.817,0.933)	0.142(0.043,0.241)	0.414(0.202,0.560)	0.044(0.016,0.118)
Reference model: Clinical risk model				
Clinical risk model + PH protein risk score	0.911(0.866,0.956)	0.060(-0.010,0.130)	0.390(0.044,0.487)	0.043(0.006,0.156)
Reference model: Protein model				
PH protein risk score + Clinical risk model	0.911(0.866,0.956)	0.036(-0.037,0.109)	0.248(0.030,0.472)	0.016(0.001,0.116)

*Clinical risk model: age, sex, BMI, smoking status, pulse rate, prevalence of hypertension, diabetes, cardiovascular disease, chronic kidney disease and chronic respiratory disease.

Abbreviation: INI, integrated discrimination improvement; NDI, net reclassification improvement.

Table S9. Predictive performance of the pulmonary hypertension (PH) protein risk score in internal testing and external validation cohort, after excluding participants with missing data on selected proteins.

Model	HR (95%CI)	C-index
Internal testing cohort		
Protein model (age + sex + PH protein risk score)	2.70 (2.26,3.24)	0.897 (0.869,0.924)
External validation cohort		
Protein model (age + sex + PH protein risk score)	2.40 (1.81,3.18)	0.871 (0.815, 0.927)

*Adjusted for age, sex, body mass index, smoking status, pulse rate, prevalence of hypertension, diabetes, cardiovascular disease, chronic kidney disease, and chronic lung disease.

Table S10. Predictive performance of the pulmonary hypertension (PH) protein risk score using 33 proteins selected by 5-fold cross-validation approach in internal testing and external validation cohort.

PH protein risk score	HR* (95%CI)	C-index
Development cohort		
PH protein risk score	2.78 (2.60, 2.96)	0.869 (0.852, 0.886)
Validation cohort		
PH protein risk score	2.53 (2.03, 3.16)	0.881 (0.839, 0.923)

*Adjusted for age, sex, body mass index, smoking status, pulse rate, prevalence of hypertension, diabetes, cardiovascular disease, chronic kidney disease, and chronic lung disease.