

PREVICTUS PROJECT

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Congreso RICORS Junio 2025



PREVICTUS PROJECT

Objectives: To perform an algorithm with multi-omic data to predict Hemorrhagic Transformation after rtPA or mechanical thrombectomy.

Secondary objectives: To use these multi-omic data to understand the biological pathways associated with stroke risk and stroke outcome in order to find new treatments for stroke.

530 SUBJECTS WITH:

PROTEOMIC DATA (3.000 Proteins)

1900 SUBJECTS WITH:

GENOMIC DATA (8M Genetic Variations)

PREVICTUS PROJECT

Participants:



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How can we explore the data?

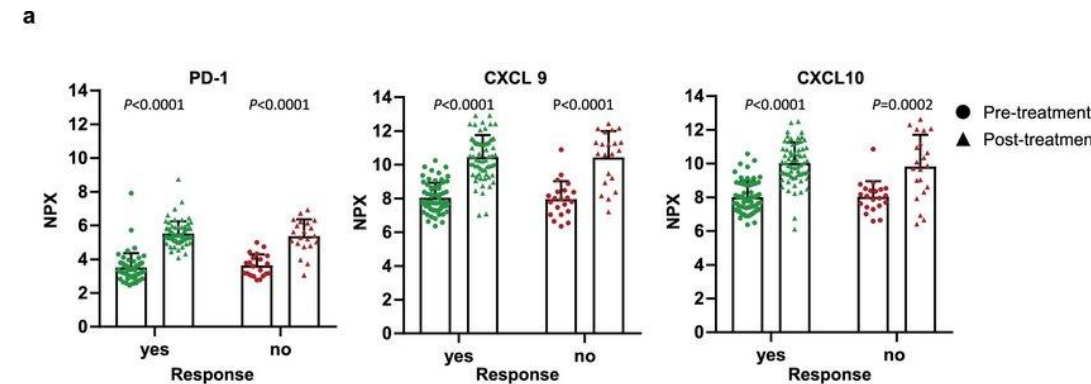
DATA

Proteomic Olink® Explore 3072

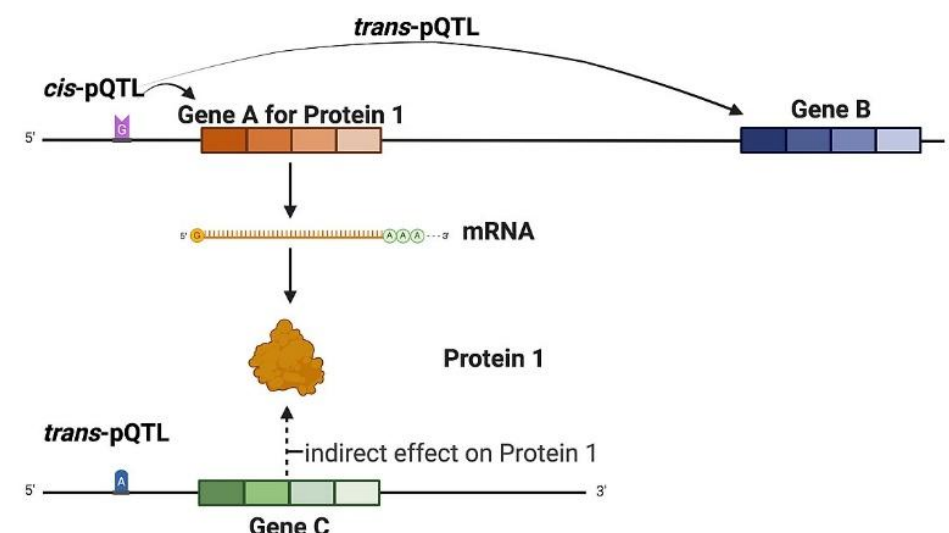
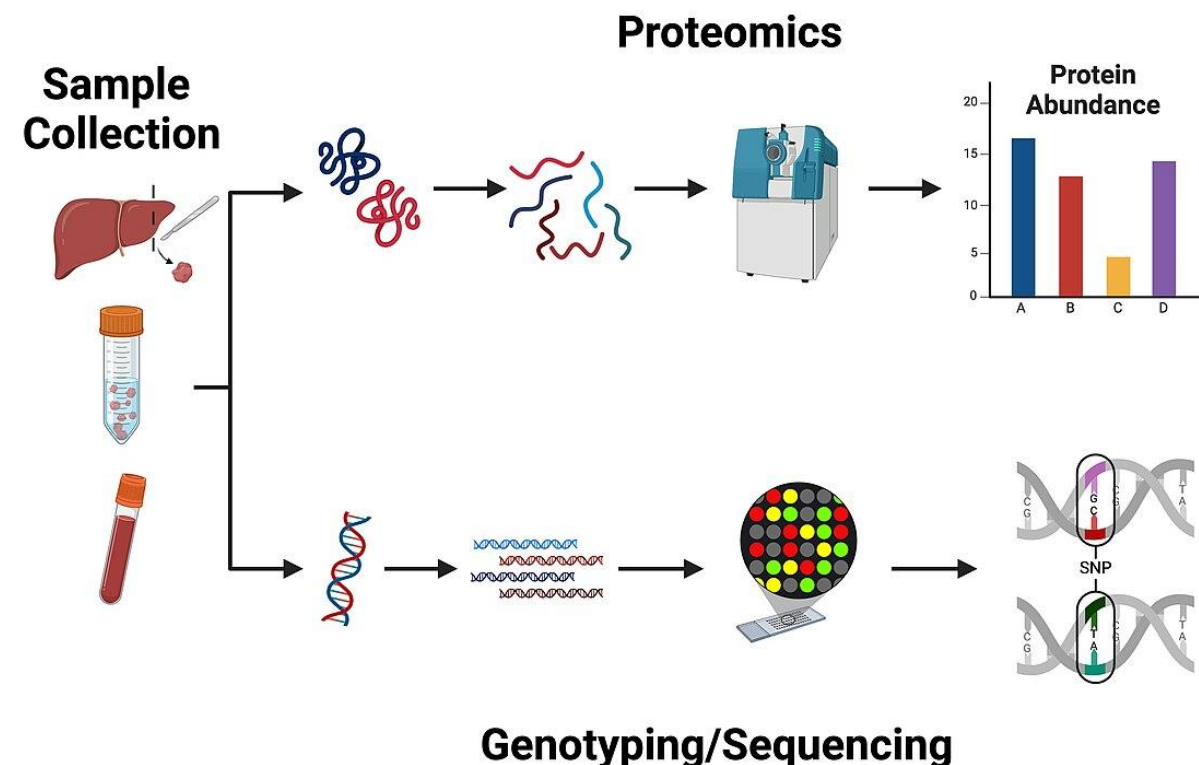
Genotyping Array

Clinical variables

Proteomic analysis



Integrate genomics and proteomics



1. Identify proteins altered in acute-phase stroke patients.
2. Identify proteins associated with the mRs3

☐ PROTEOME-WIDE ANALYSIS

3. Develop a protein signature to predict the risk of severe hemorrhages after treatment.

☐ PROTEOMIC-CLINICAL SCORE
BASED ON MACHINE LEARNING

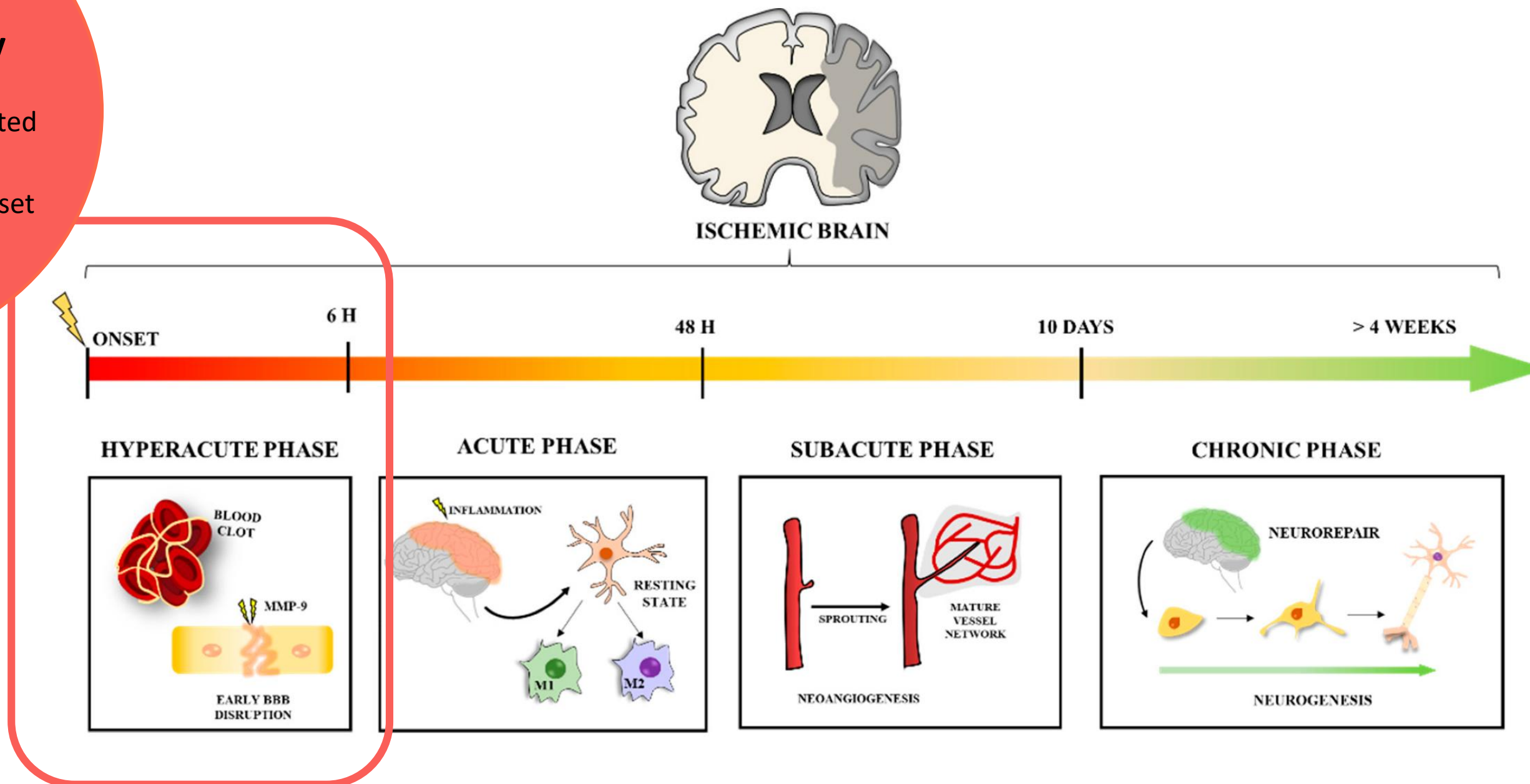
4. Integrate genomics and proteomics to identify genetic variants that regulate protein levels in the acute phase of stroke.

☐ CONTEXT SPECIFIC PROTEIN
QUANTITATIVE TRAIT LOCI (pQTL)
ANALYSIS

PROTEOME-WIDE ANALYSIS IN THE HYPERACUTE PHASE OF THE STROKE

IS have been treated with **reperfusion therapy**

IS plasma samples was collected during the first **6 hours** from symptom onset and before treatment.

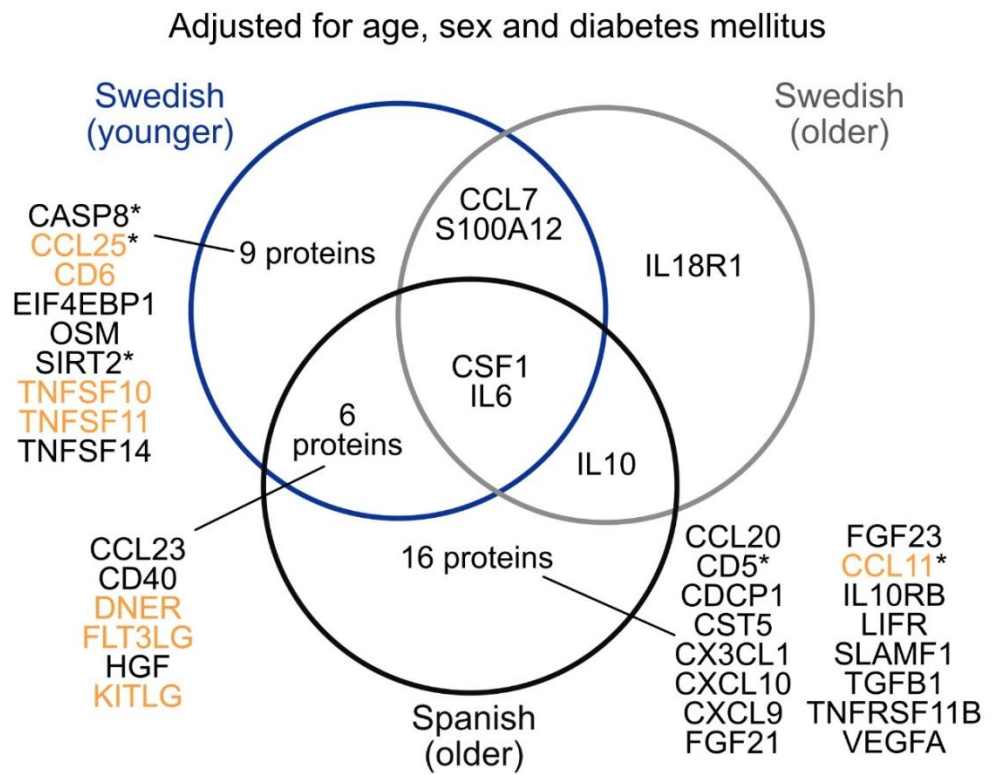
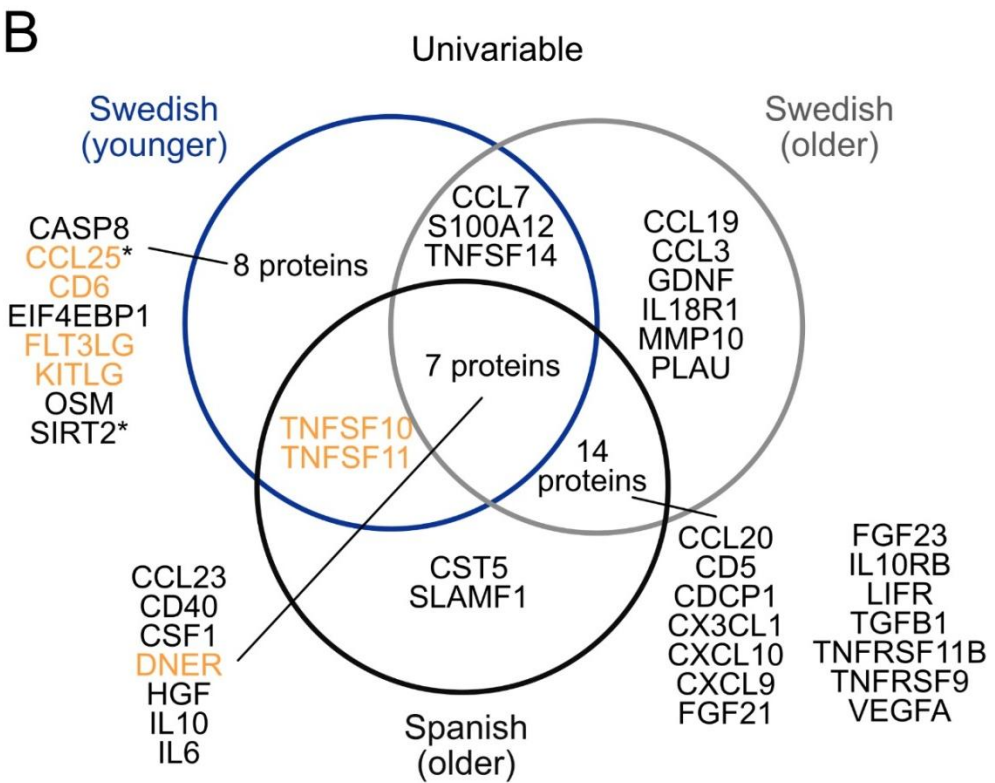


PROTEOMIC STUDY IDENTIFIES INFLAMMATORY PLASMA PROTEINS ASSOCIATED WITH 3-MONTH FUNCTIONAL OUTCOME AFTER ISCHEMIC STROKE



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	Swedish (younger)	Swedish (older)	Spanish (older)
n	534	482	379
Poor outcome (mRS>2)	119 (22%)	161 (33%)	210 (55%)
Age, median [IQR], years	58 [52-64]	69 [56-78]	74 [62-86]
Male sex, n (%)	340 (64)	294 (61)	198 (52)
Diabetes mellitus, n (%)	100 (19)	61 (13)	93 (25)
Hypertension, n (%)	320 (60)	209 (43)	275 (73)
Time to blood draw, median	4 days	2 days	6 hours
Thrombectomy or IV thrombolysis, n (%)	0 (0)		379 (100)
NIHSS, acute or after recanalization therapy, median [IQR]	3 [2-7]	2 [1-6]	6 [2-14]

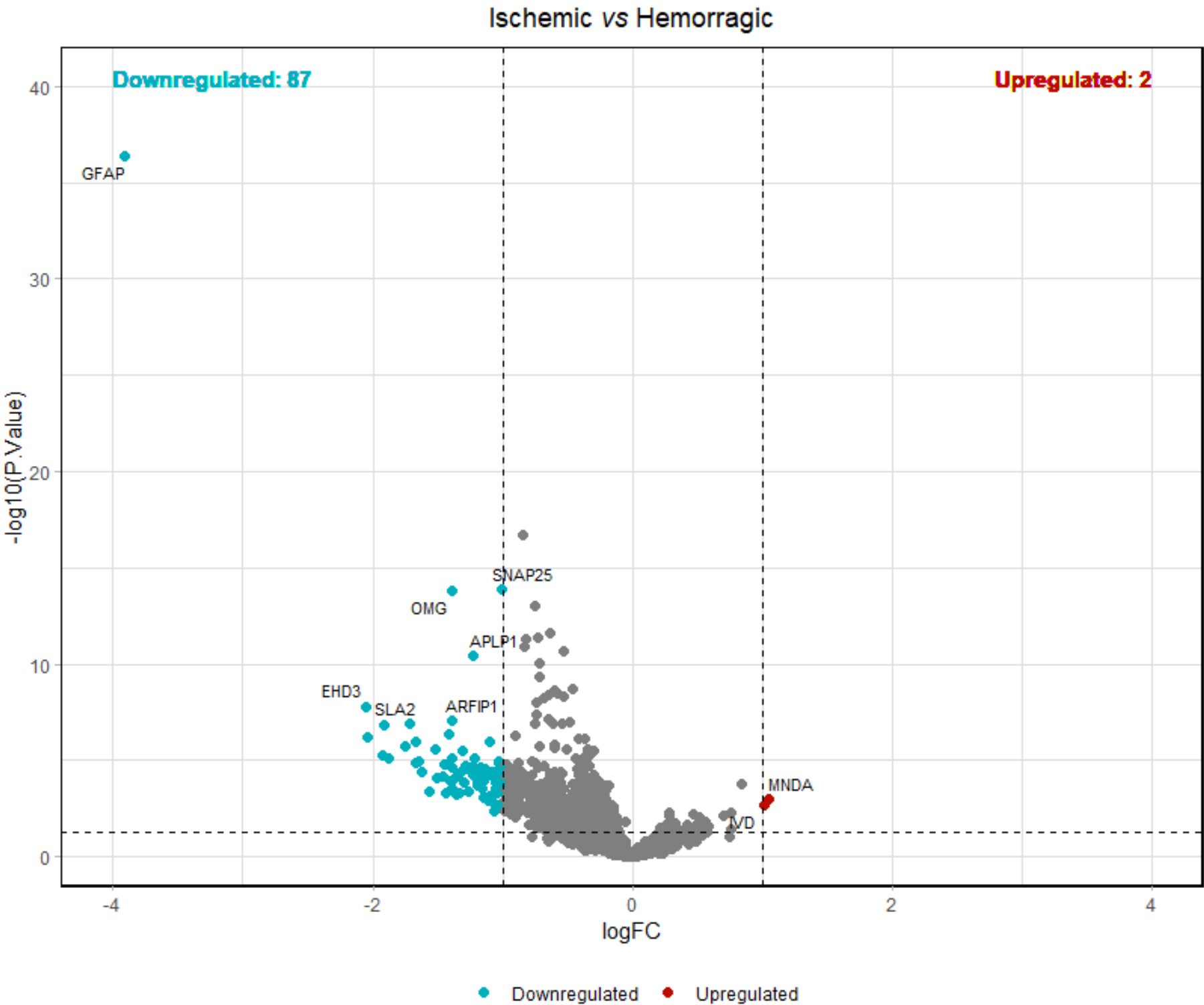


Black = OR >1 and FDR <0.05 Orange = OR <1 and FDR < 0.05
* Inconsistent directions across cohorts

Ischemic vs Hemorrhagic

T-Test Analysis (FDR, P-Value Adjusted)

P.value	* 0.05	** 0.01	*** 0.001
Proteins	553	276	79

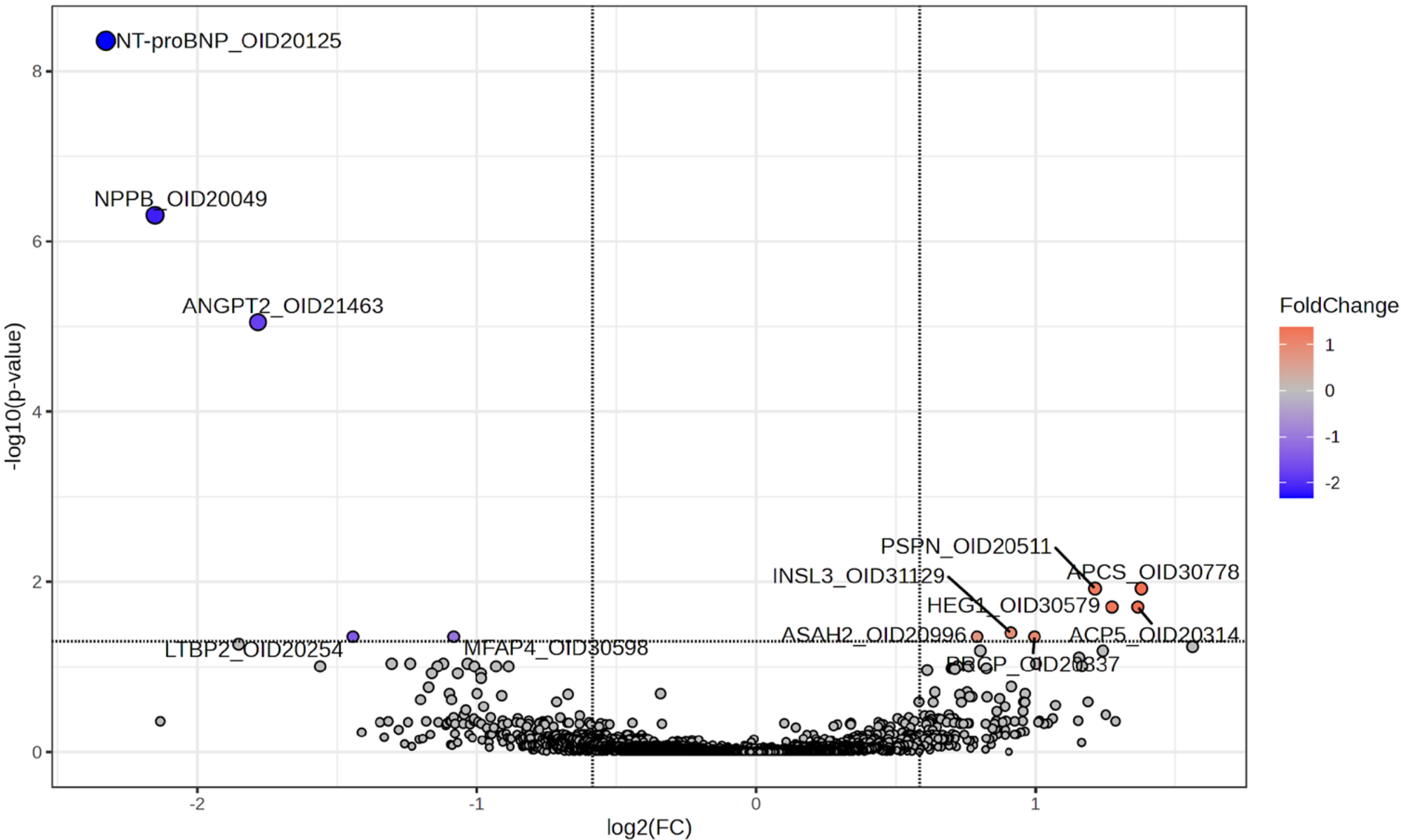


Top 20 Differential expression protein analysis								
(logFC > 0.6 logFC < -0.6 p < 0.05)								
Assay	Panel	UniProt	logFC	CI.L	CI.R	t	P.Value	adj.P.Val
GFAP	Oncology	P14136	-3.907459	-4.449042	-3.3658751	-14.185025	4.176838e-37	1.057158e-33
SNAP25	Neurology_II	P60880	-1.006607	-1.253250	-0.7599643	-8.024039	1.219526e-14	3.084180e-11
OMG	Oncology	P23515	-1.391737	-1.733971	-1.0495025	-7.995304	1.490354e-14	3.767616e-11
APLP1	Cardiometabolic	P51693	-1.231856	-1.586975	-0.8767363	-6.820037	3.491115e-11	8.801100e-08
EHD3	Cardiometabolic_II	Q9NZN3	-2.053637	-2.752745	-1.3545293	-5.775383	1.572789e-08	3.949274e-05
ARFIP1	Neurology_II	P53367	-1.394417	-1.897531	-0.8913019	-5.449124	9.000321e-08	2.257280e-04
SLA2	Neurology_II	Q9H6Q3	-1.714807	-2.341795	-1.0878185	-5.377209	1.307702e-07	3.273177e-04
LDLRAP1	Neurology_II	Q5SW96	-1.910247	-2.610797	-1.2096969	-5.361070	1.421294e-07	3.556078e-04
SH2B3	Oncology	Q9UQQ2	-1.408357	-1.947710	-0.8690038	-5.133822	4.494975e-07	1.124193e-03
DAPP1	Inflammation	Q9UN19	-2.036054	-2.828035	-1.2440734	-5.054473	6.655777e-07	1.663279e-03
LYN	Oncology	P07948	-1.101025	-1.538152	-0.6638980	-4.952116	1.096265e-06	2.736279e-03
DNM1	Oncology_II	Q05193	-1.673075	-2.337767	-1.0083841	-4.948764	1.114173e-06	2.779861e-03
GRAP2	Cardiometabolic	O75791	-1.753233	-2.467214	-1.0392517	-4.827853	1.986814e-06	4.951141e-03
MAP4K5	Neurology	Q9Y4K4	-1.514690	-2.140329	-0.8890517	-4.759939	2.735457e-06	6.808552e-03
ITPA	Cardiometabolic_II	Q9BY32	-1.313123	-1.857677	-0.7685684	-4.740949	2.989341e-06	7.434491e-03
SERPINH1	Oncology_II	P50454	-1.928227	-2.752065	-1.1043897	-4.601694	5.680167e-06	1.410953e-02
AKT2	Neurology_II	P31751	-1.874836	-2.686570	-1.0631019	-4.540992	7.477450e-06	1.855155e-02
NCK2	Inflammation	O43639	-1.215995	-1.742719	-0.6892717	-4.538896	7.548344e-06	1.871989e-02
IRAK4	Inflammation	Q9NWZ3	-1.394511	-1.998899	-0.7901233	-4.536361	7.634994e-06	1.892715e-02
TMEM132A	Cardiometabolic_II	Q24JP5	-1.031151	-1.487913	-0.5743893	-4.438475	1.181487e-05	2.926544e-02
UFD1	Oncology_II	Q92890	-1.641900	-2.369227	-0.9145735	-4.438317	1.182311e-05	2.927402e-02
ABRAXAS2	Cardiometabolic_II	Q15018	-1.034553	-1.493698	-0.5754087	-4.430009	1.226505e-05	3.034373e-02
STAT5B	Oncology	P51692	-1.671306	-2.417649	-0.9249636	-4.402699	1.383197e-05	3.419264e-02
PMVK	Neurology	Q15126	-1.451370	-2.105670	-0.7970696	-4.361162	1.658788e-05	4.093889e-02
OPHN1	Neurology_II	O60890	-1.284743	-1.868702	-0.7007836	-4.325485	1.936757e-05	4.776043e-02



Atherothrombotic vs Cardioembolic

AT/CES Comparative



5 Down - 7 UP

Top 12 Differentially Expressed Proteins

Name ↑↓	FC ↑↓	log2(FC) ↑↓	p.adjusted ↑↓	-log10(p) ↑↓
NT-proBNP_OID20125	0.19928	-2.3271	4.3961E-9	8.3569
NPPB_OID20049	0.22515	-2.151	4.9245E-7	6.3076
ANGPT2_OID21463	0.29062	-1.7828	8.9132E-6	5.05
APCS_OID30778	2.6005	1.3788	0.012004	1.9207
PSPN_OID20511	2.3177	1.2127	0.012004	1.9207
ACP5_OID20314	2.5778	1.3661	0.019772	1.7039
HEG1_OID30579	2.4179	1.2738	0.019772	1.7039
INSL3_OID31129	1.8815	0.91187	0.039609	1.4022
LTBP2_OID20254	0.36789	-1.4427	0.044147	1.3551
MFAP4_OID30598	0.47235	-1.0821	0.044147	1.3551
PRCP_OID20337	1.9945	0.99602	0.044147	1.3551
ASA2_OID20996	1.7301	0.79083	0.044147	1.3551



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01 | Proteomics of stroke risk

Plasma collections of 686 patients

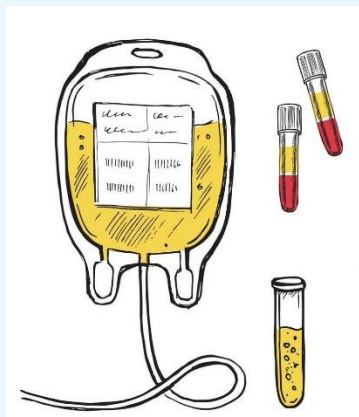


ISQUEMIC STROKE (IS) →
498

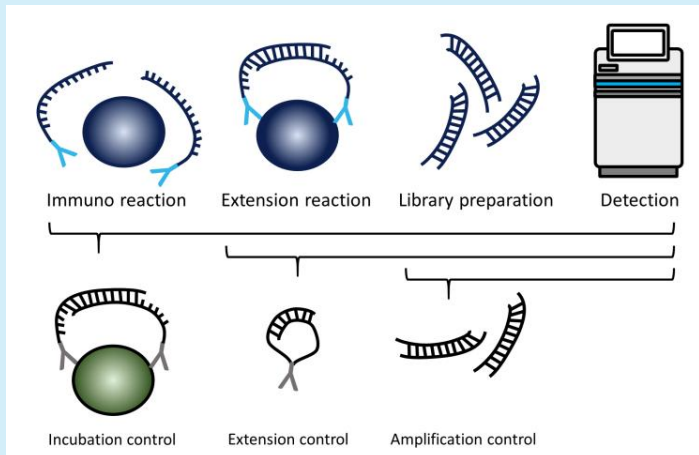
POPULATION CONTROLS →
50

DISCOVERY REPLICATION

- 398 IS cases
- 39 controls
- 100 IS cases
- 13 controls



OLINK Explore to analyse 3,072 proteins



Analysis Plan

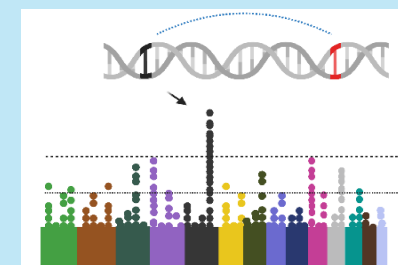
PROTEOME-WIDE ANALYSIS

Linear regression with Limma
 $NPX \sim IS\ risk + sex + age$

PROTEINS SELECTION

Proteins q-value ≤ 0.05 and consistent
logFC across both cohorts

MR and
COLOCALIZATION
with GIGASTROKE



STROKE RISK?

Cox in **UKBB** data
Proteins q-value ≤ 0.05

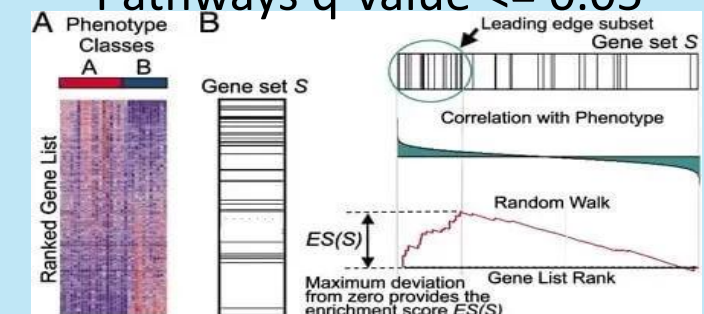


PHARMACOLOGICAL REPOSITIONING ANALYSIS

GSEA (Gene Set
Enrichment Analysis)

PATHWAYS SELECTION

Pathways q-value ≤ 0.05



PROTEOME-WIDE ANALYSIS

DISCOVERY → **383** IS cases vs. **39** population controls

REPLICATION → **100** IS cases vs. **13** population controls



Linear regression with Limma

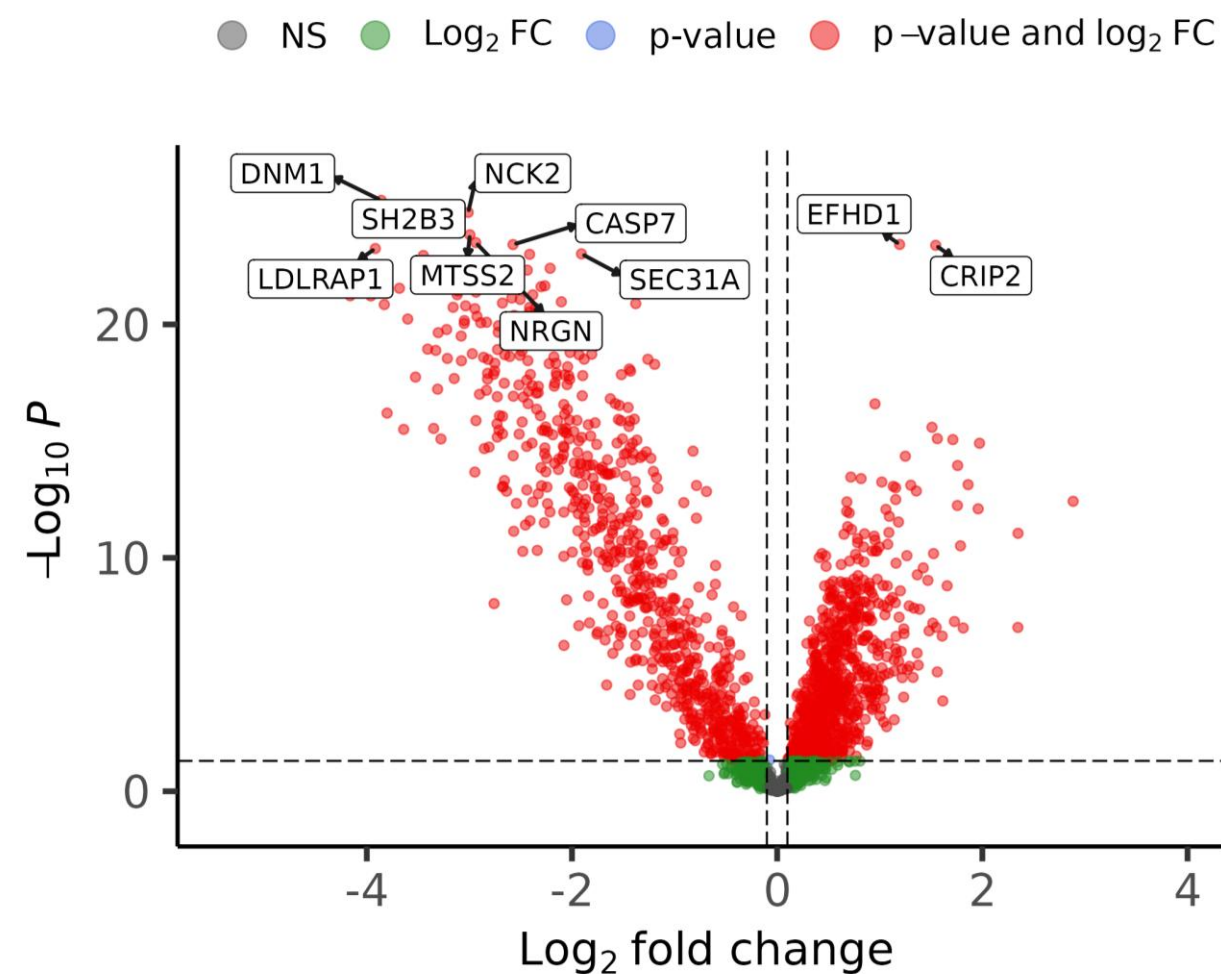
$NPX \sim IS\ risk + sex + age$

640 proteins associated with IS

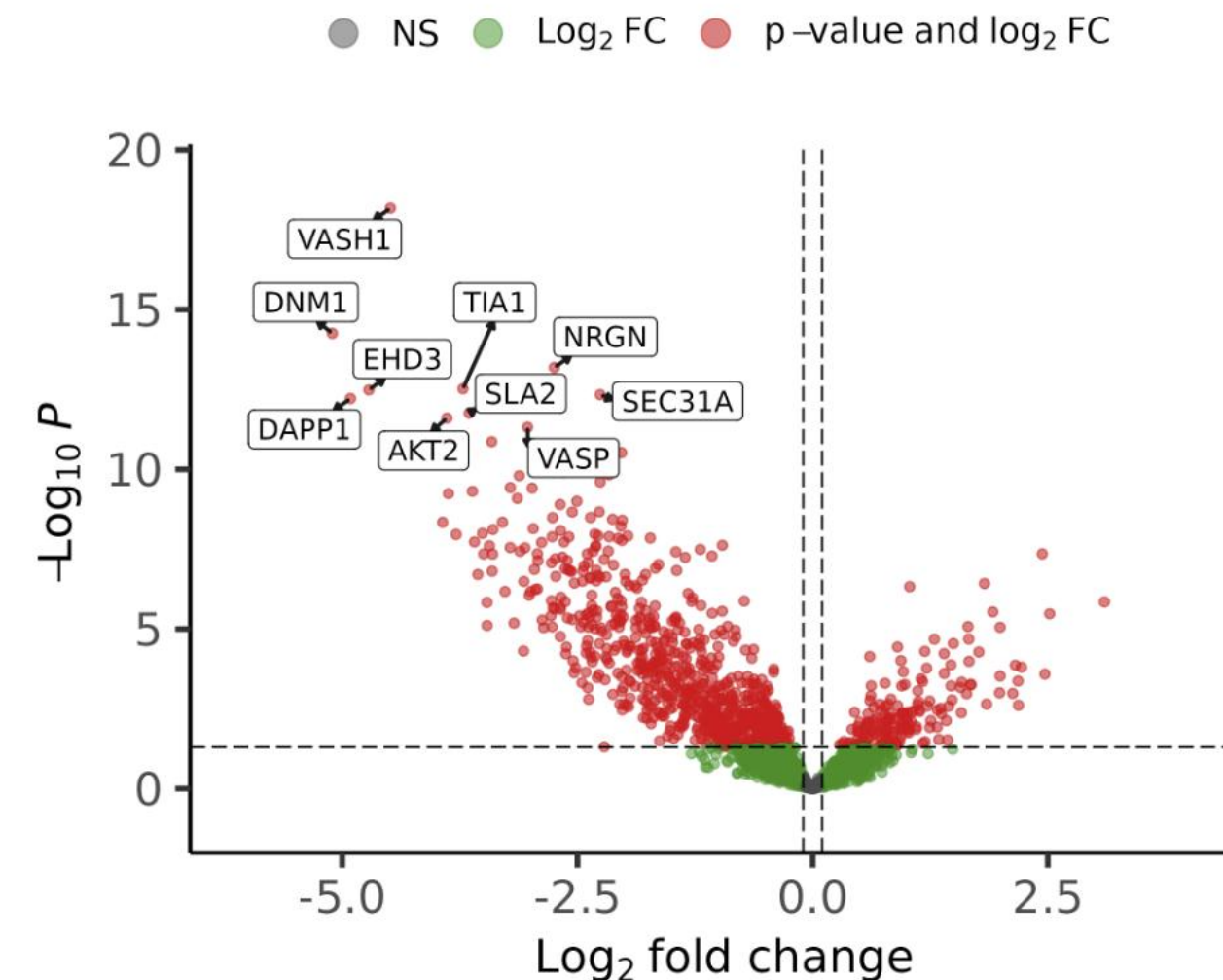
(q-value ≤ 0.05 and consistent logFC across both cohorts)

A predominant pattern of lower levels in IS cases (81%)

DISCOVERY



REPLICATION

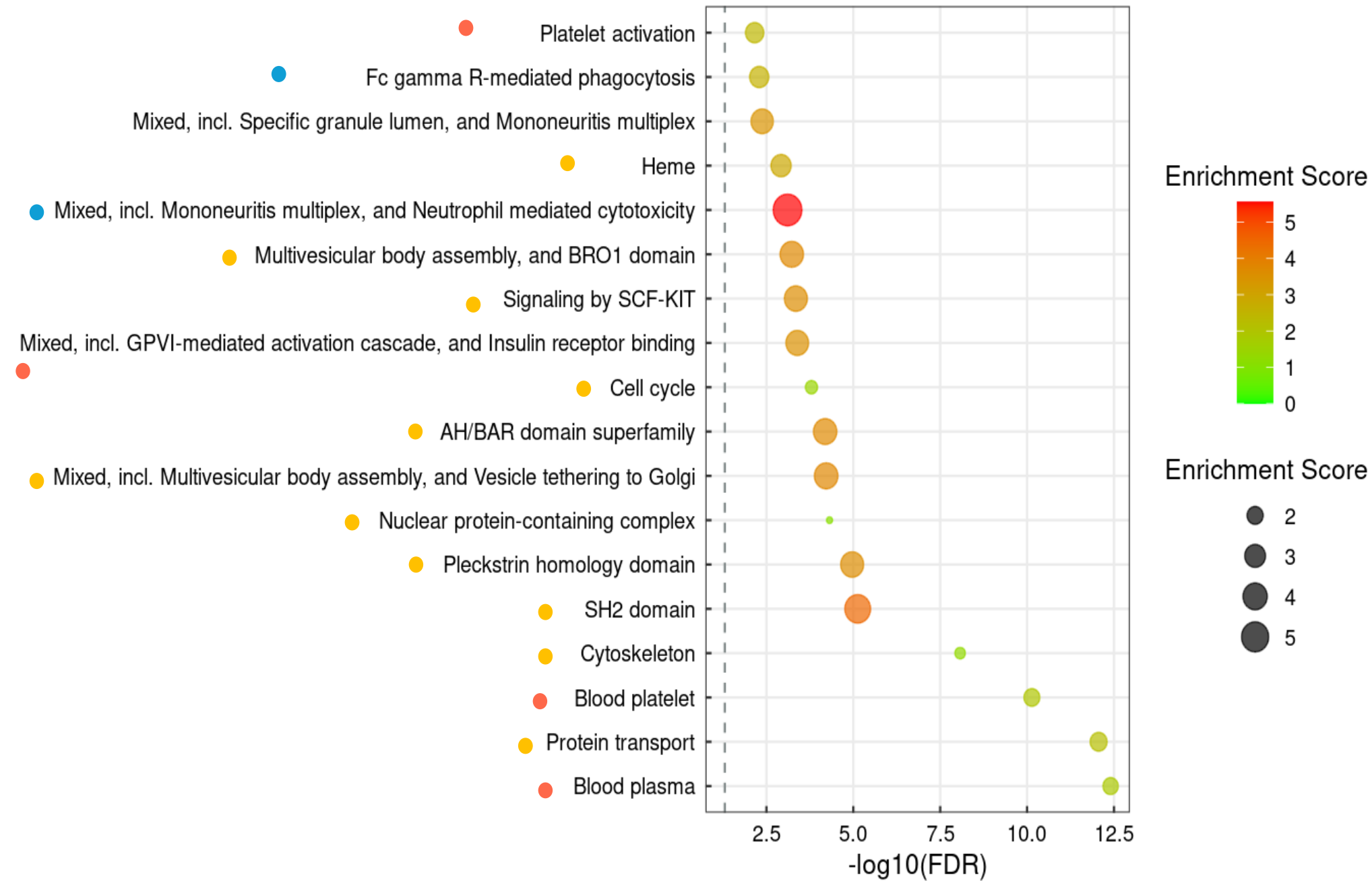


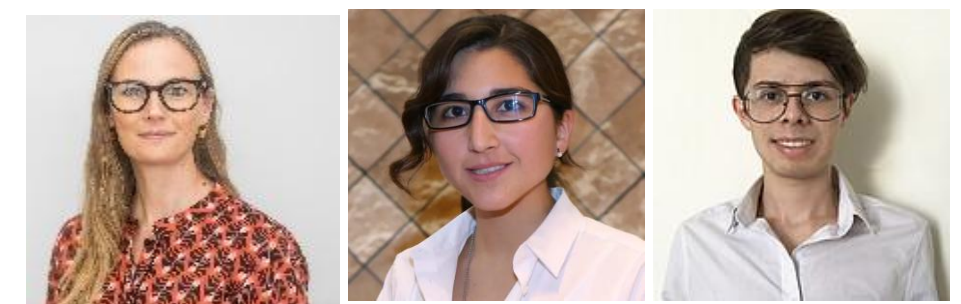
PROTEOME-WIDE ANALYSIS

DISCOVERY **383** **39**
 REPLICATION **100** **13**

Linear regression with Limma

inflammation/ immune response, platelet
 activation/blood processes cellular injury
 processes

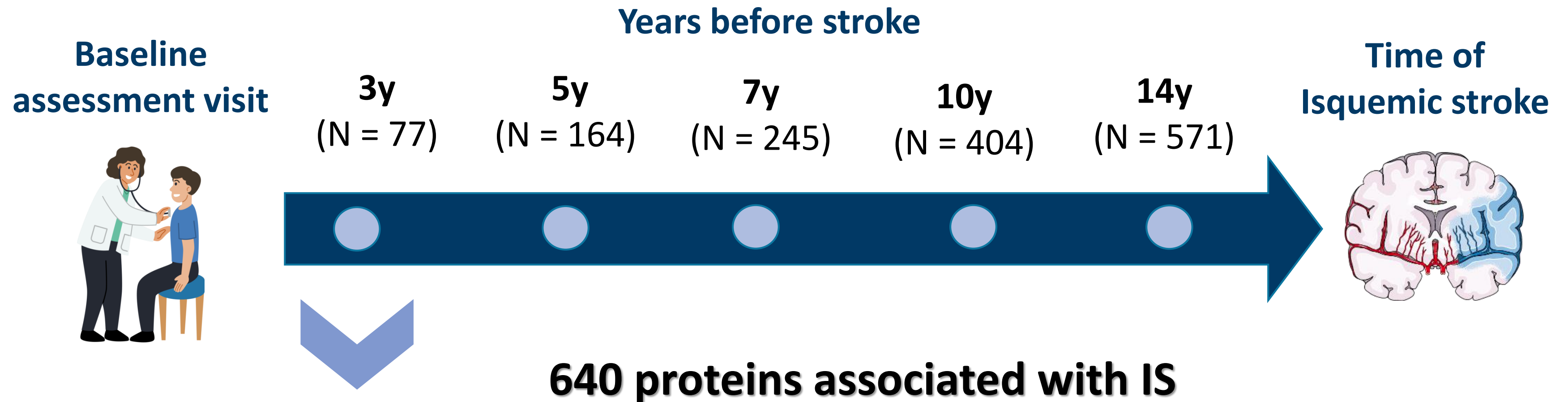




Dr Claudia Langenberg
Dr Julia Carrasco-Zanini-Sanchez
Msc Paul Vega
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COX IN UKBB DATA

- **3,000 plasma proteins across 50,000 individuals**



MODELS

→ **Simple:** sex, age, platelets

→ **Complex:** sex, age, platelets, BMI, alcohol consumption, smoking

COX IN UKBB DATA

PREVIOUS STUDIES

Stroke risk

IL16, NOS1, NOS3, MMP8

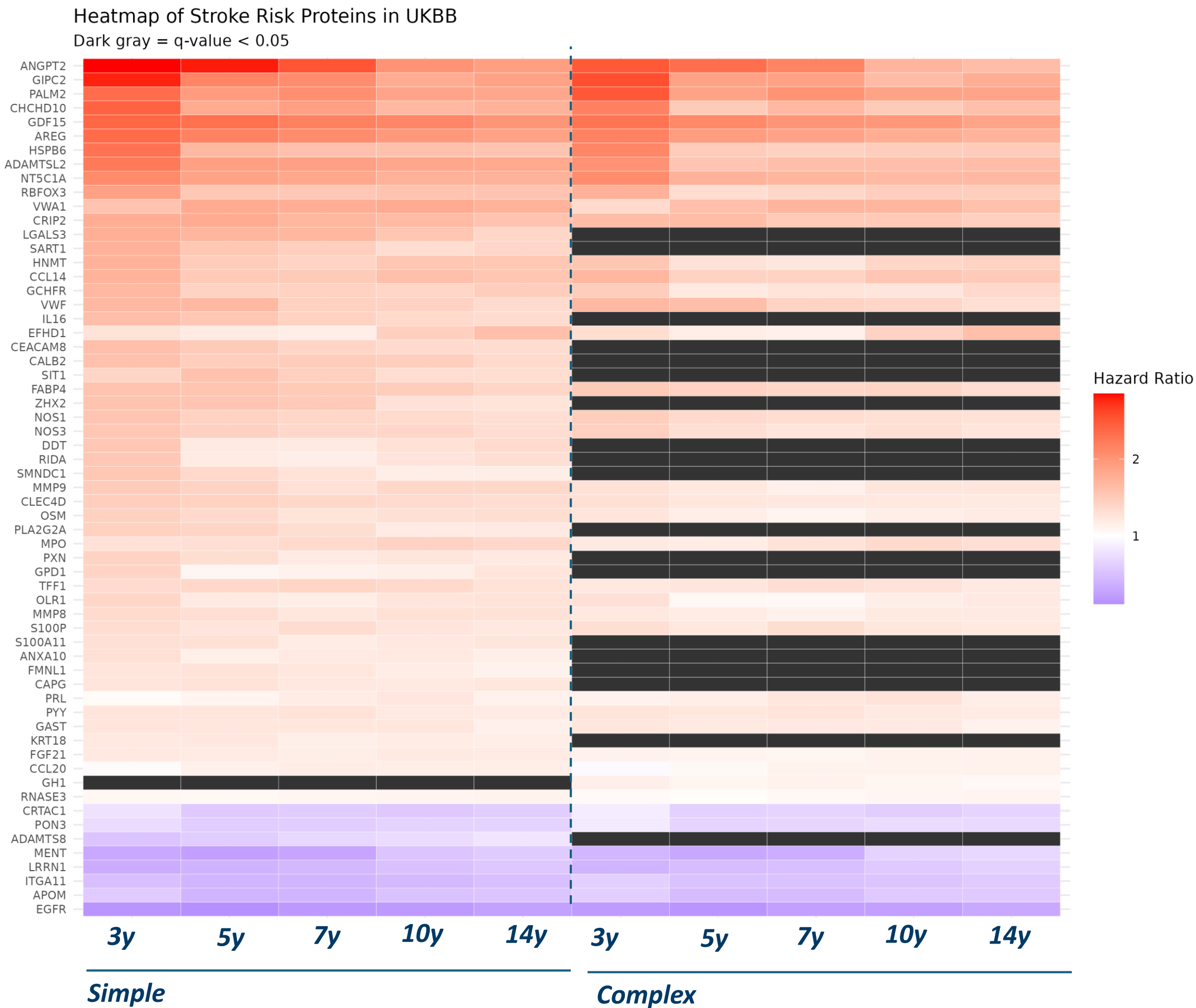
PRL, ADAMTSL2, APOM,
CCL14, CCEC4D

Stroke risk + outcome

FAB4, VWF

Outcome

MMP9, AMGP2, CRTAC1, MPO,
OSM, RNASE3





Analysis Plan

PROTEOME-WIDE ANALYSIS

BY TOAST

Linear regression with Limma
 $NPX \sim IS\ risk + sex + age$

PROTEINS SELECTION

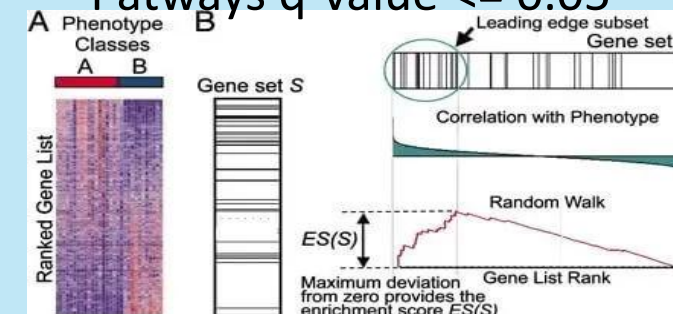
Proteins q-value ≤ 0.05 and consistent
logFC across both cohorts

GSEA (Gene Set
Enrichment Analysis)



PATHWAYS SELECTION

Pathways q-value ≤ 0.05

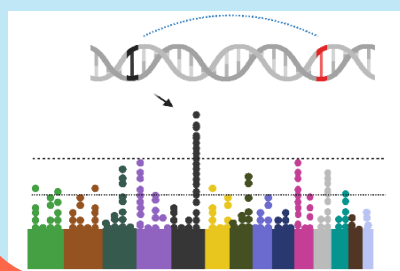


STROKE RISK?

Cox in **UKBB** data
Proteins q-value ≤ 0.05



MR and
COLOCALIZATION
with GIGASTROKE



PHARMACOLOGICAL REPOSITIONING ANALYSIS

02 | Next steps

03| Conclusions

A total of 640 proteins were associated with the acute phase of IS.

Involved in pathways related to inflammation/immune response, platelet activation/blood, and cellular injury.

61 proteins were associated with IS incidence or risk in UKBB.

Although most of the proteins associated with IS in the acute phase have lower levels in cases than in controls, those specifically associated with risk have higher levels.

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THANK YOU FOR YOUR ATTENTION

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<https://strokemics.com/>