

Novel FFPE Processing Method for Proteome Analysis Suggests Prolactin Induced Protein as Hormone Induced Cytoskeleton Remodeling Spatial Biomarker

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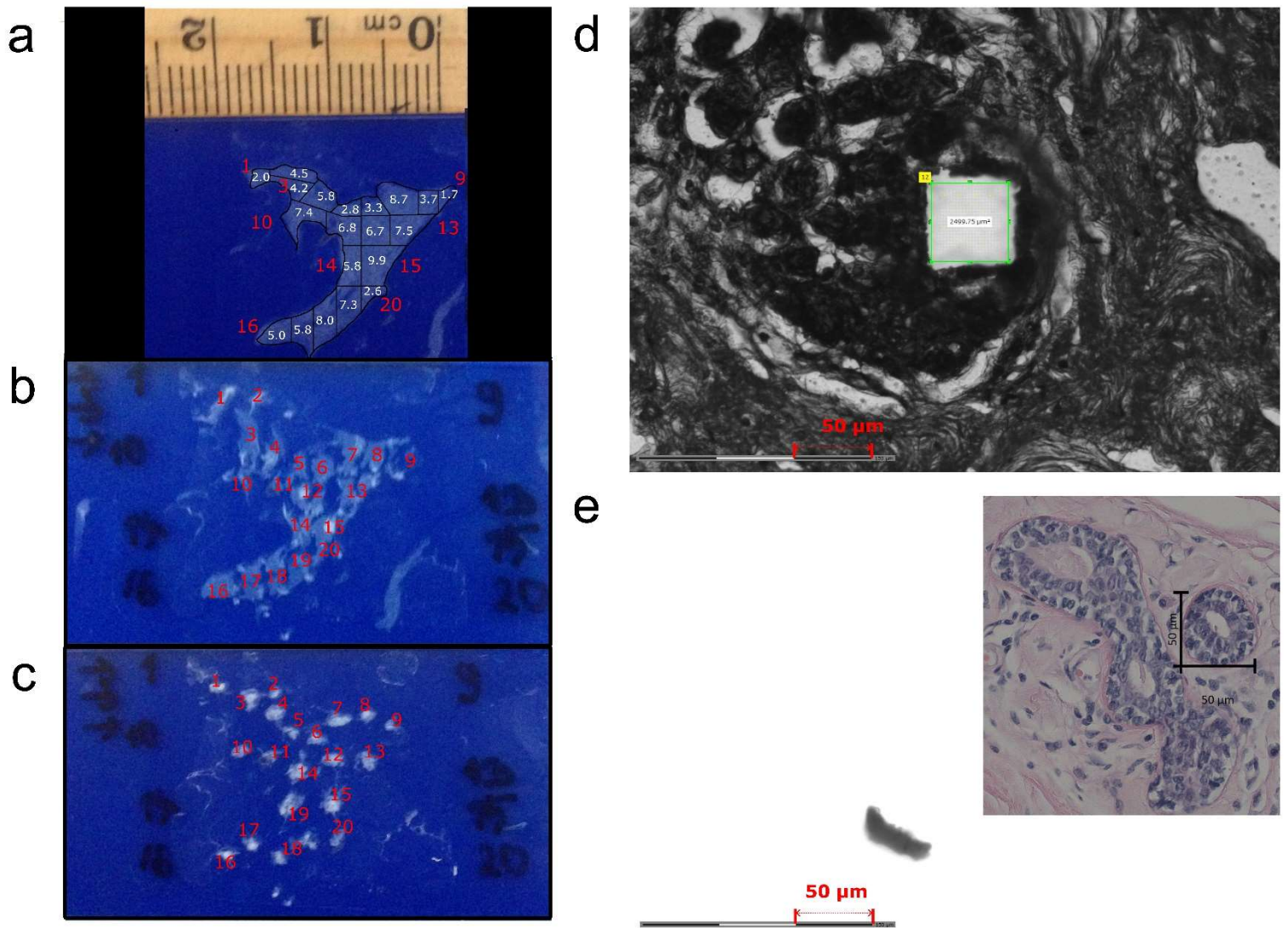
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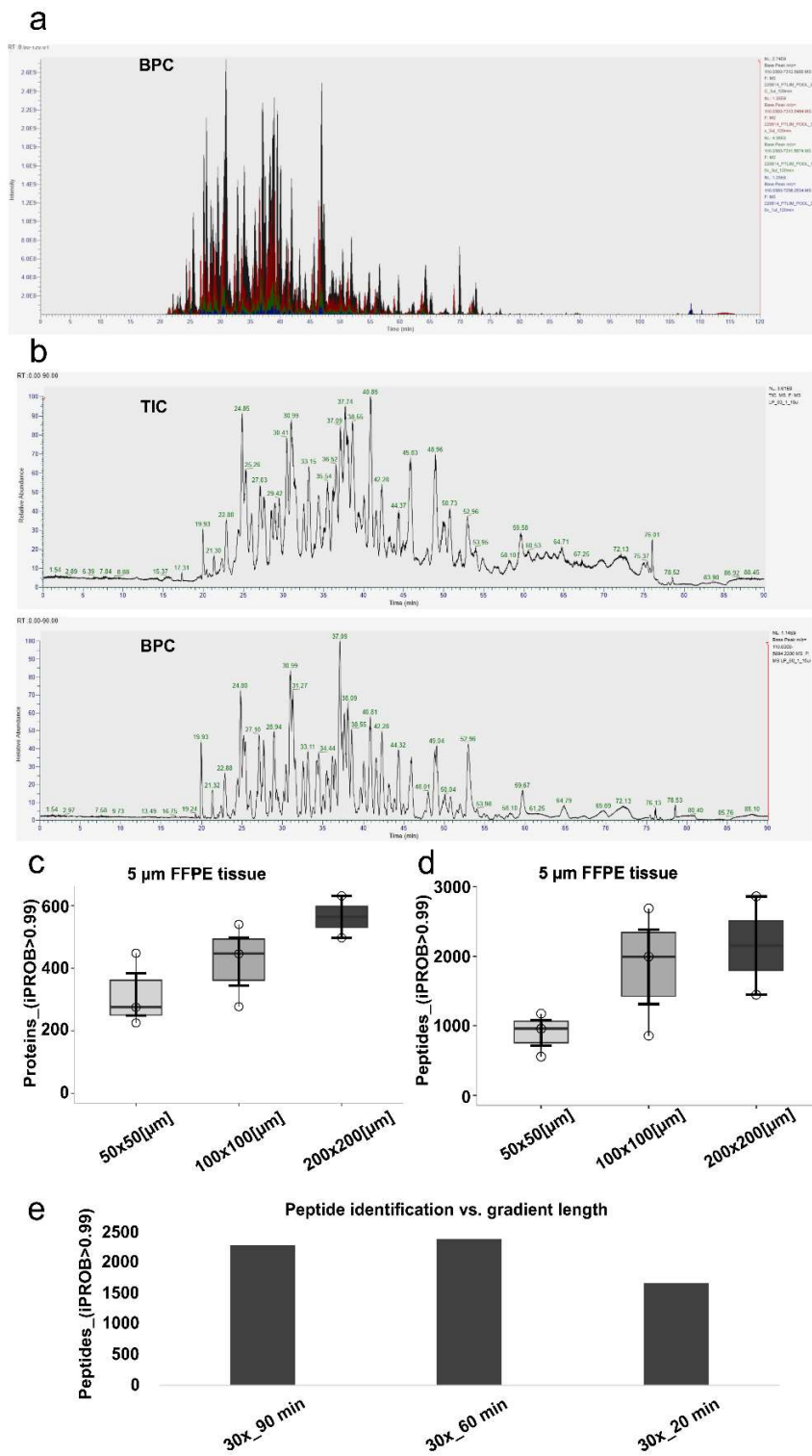
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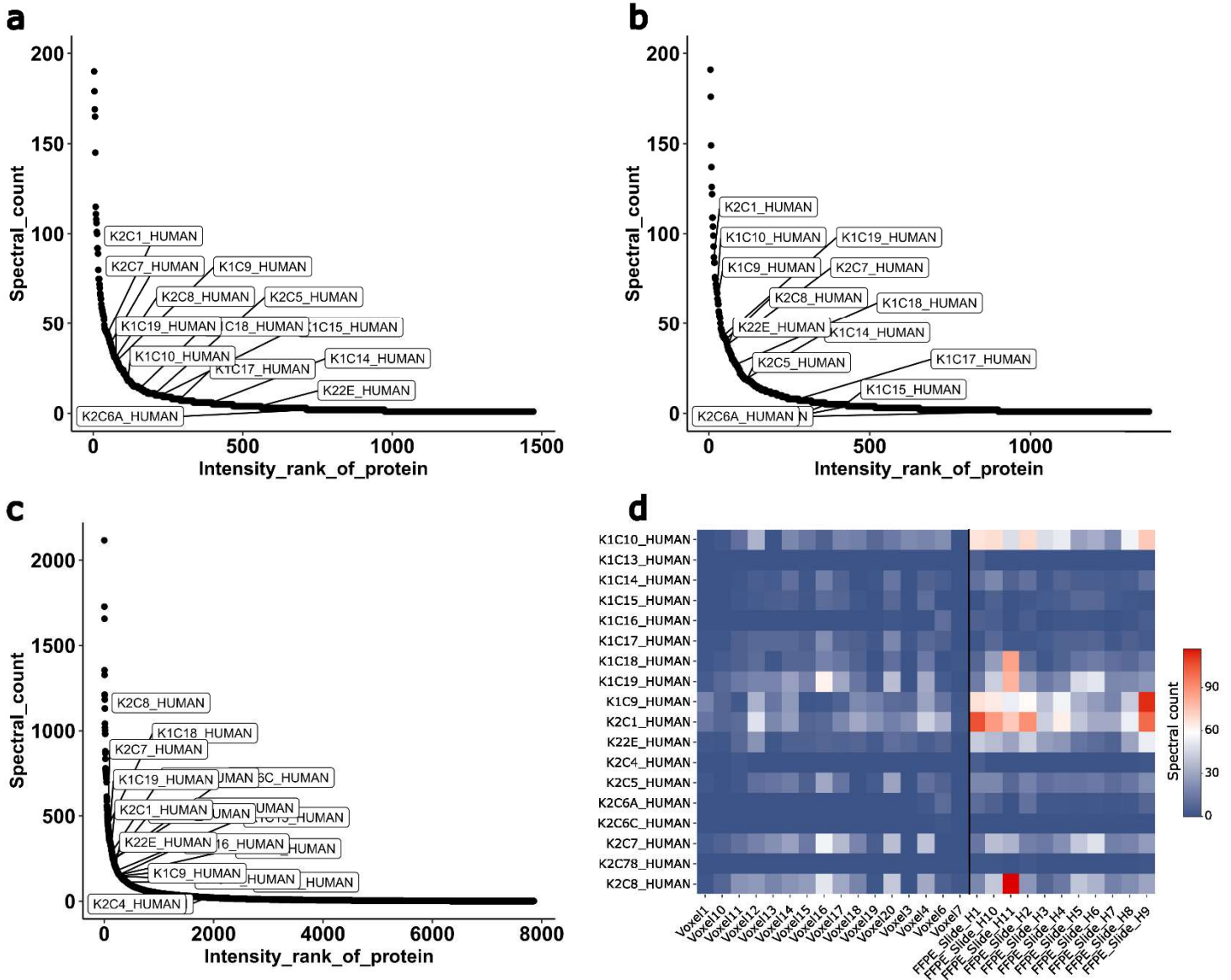
SUPPLEMENTARY INFORMATION



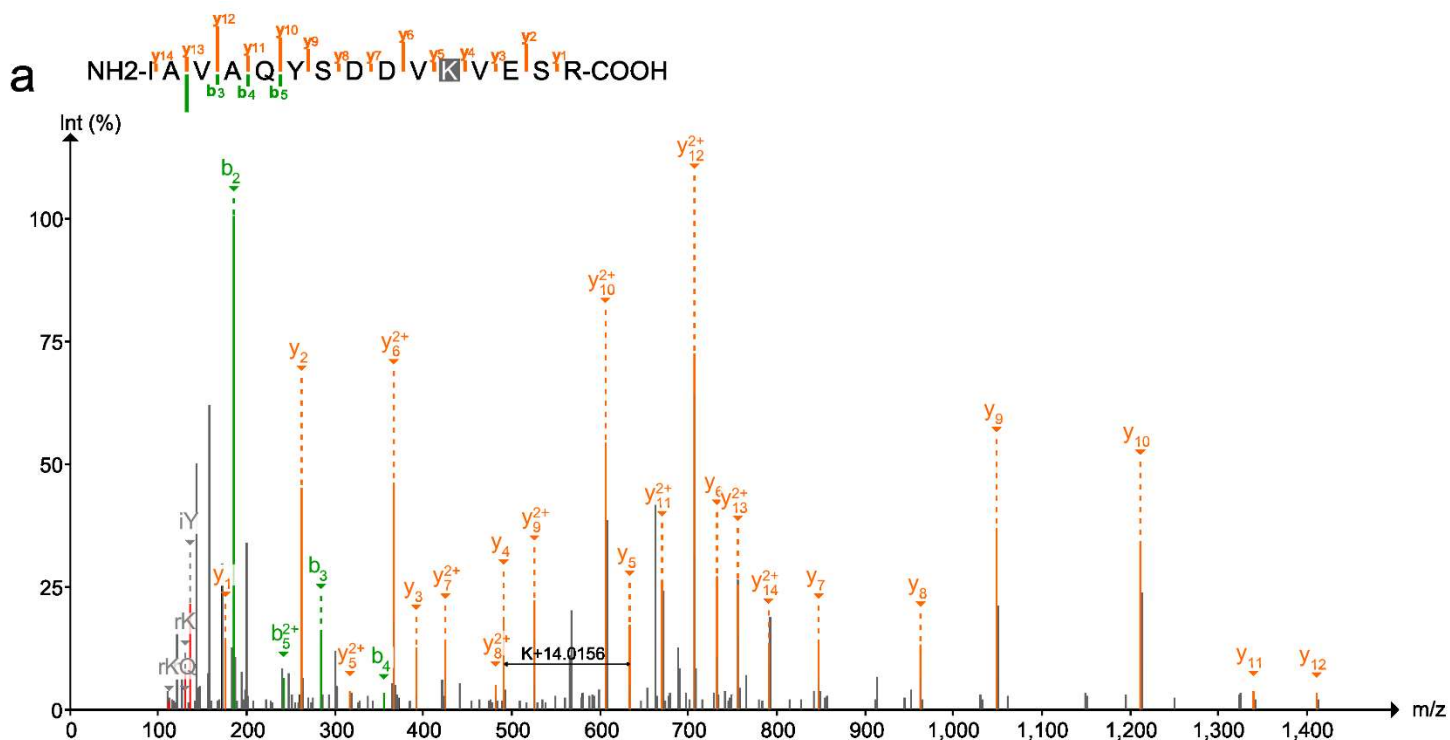
Supplementary figure 1 Workflow of glass mounted BFPT macrodissection into 20 voxels by a razor and laser capture microdissection (LCM) of formalin fixed paraffin embedded (FFPE) breast glandular tissue voxel. a) An outline of 20 macrodissected FFPE voxels ranging from approx. 2 mm² up to 10 mm² area. White numbers depict area of voxel in mm² while red numbers show the assigned number of the voxel matching across the manuscript text. b) Separating individual voxels with a razor knife c) Scraping of FFPE tissue into stacks prior adding 3 µl of lysis buffer and transfer into a glass insert with a pipette. d) Hematoxylin stained 5 µm thick breast FFPE tissue slide after dissecting 50 µm lateral size FFPE voxel using LCM. e) LCM cut breast glandular FFPE tissue of 50 µm lateral size from Supplementary figure 1D after transferring into the adhesive cap of LCM tube and an example of a color image of hematoxylin stained mammary acini of 50 µm lateral size to estimate the cell count.



Supplementary figure 2 Mass spectrometry quality control of In-insert processed BFPT samples and detection limit. a) Base peak chromatograms (BPC) at various dilutions of average macrodissected formalin fixed paraffin embedded breast tissue slide (BFPT) sample. The black color refers to BPC acquired from 1/10 of the total extracted material per average macrodissected BFPT voxel. The red color refers to BPC acquired from 1/30 of the total extracted material per average macrodissected BFPT voxel. The green color refers to BPC acquired from 1/300 of the total extracted material per average macrodissected BFPT voxel and the blue color refers to BPC acquired from 1/1800 of the total extracted material per average macrodissected BFPT voxel. b) Total ion current chromatograms (TIC) and BPC referring to In-insert processed 50 μm lateral size LCM microdissected BFPT voxel. c) Number of protein group identifications in 50, 100 and 200 μm lateral size LCM microdissected hematoxylin stained BFPT voxels. d) Number of peptide identifications in 50, 100 and 200 μm lateral size LCM microdissected hematoxylin stained BFPT voxels. In c) and d) the error bars show standard error and the box extends from the lower to upper quartile, the line shows median. Actual values from the measurements are shown as individual circles. e) Testing the effect of gradient length on tryptic peptide identification on 30x diluted pool representing average macrodissected voxel. Gradients of 90, 60 and 20 min in length were tested. Gradients of 60 min does not show compromised tryptic peptide identification, which might be particularly important for high throughput In-insert spatial FFPE tissue analyses.



Supplementary figure 3 Benchmarking keratin spectral counts from In-insert data to two independent mass spectrometry breast formalin fixed paraffin embedded tissue (FFPE) datasets. a) Illustrates the keratin spectral count in a formalin fixed paraffin embedded breast tissue (BFPT) voxels processed by In-insert method. b) Illustrates the keratin spectral count in BFPT slides processed by the protocol published by Weke et al. ¹. c) Shows total keratin spectral count in the publicly available dataset of FFPE breast cancer tissue labelled by tandem mass tag (TMT) approach ². d) A keratin spectral count heatmap comparing the spectral count of keratins in healthy BFPT slides from 6 donors, prepared by the method described by Weke et al. with the keratin spectral count in 17 BFPT voxels prepared using the In-insert method from a single donor's healthy BFPT slide ¹. Higher spectral count keratins are shown in shades of red, while low spectral count keratins are shown in shades of blue.

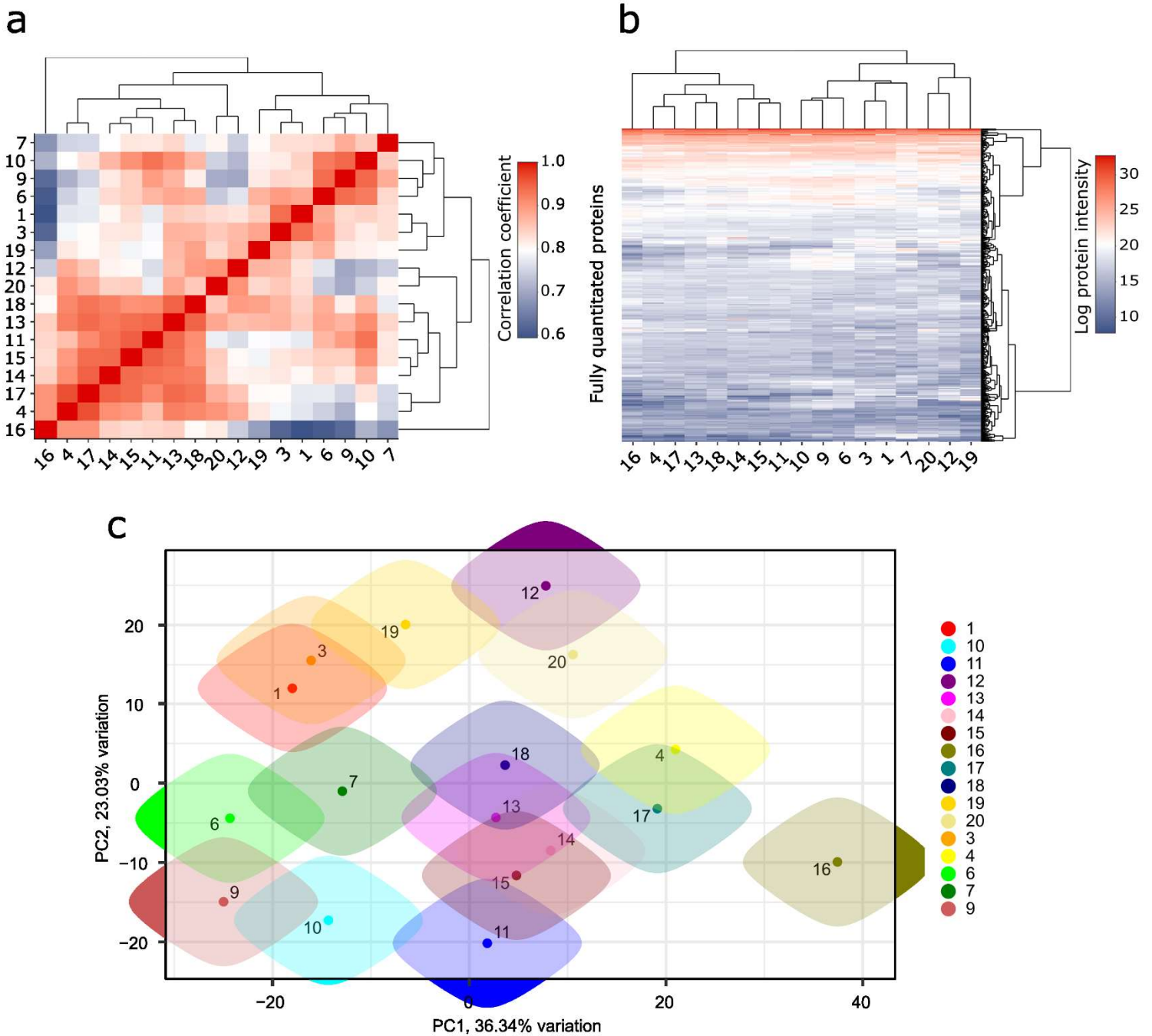


b

Type	Index	AA	Original Mass	New Defined
Mod	11	K	+14.0156	+14.0156

	b	b++	AA	y	y++	
1	114.0913	57.54931	I			15
2	185.1285	93.06787	A	1580.791	790.8994	14
3	284.1969	142.6021	V	1509.754	755.3808	13
4	355.234	178.1206	A	1410.686	705.8466	12
5	483.2926	242.1499	Q	1339.649	670.328	11
6	646.3559	323.6816	Y	1211.59	606.2987	10
7	733.3879	367.1976	S	1048.527	524.7671	9
8	848.4149	424.7111	D	961.4949	481.2511	8
9	963.4418	482.2245	D	846.4679	423.7376	7
10	1062.51	531.7587	V	731.441	366.2241	6
11	1204.621	602.814	K	632.3726	316.6899	5
12	1303.689	652.3482	V	490.262	245.6346	4
13	1432.732	716.8695	E	391.1936	196.1004	3
14	1519.764	760.3855	S	262.151	131.5791	2
15			R	175.119	88.06311	1

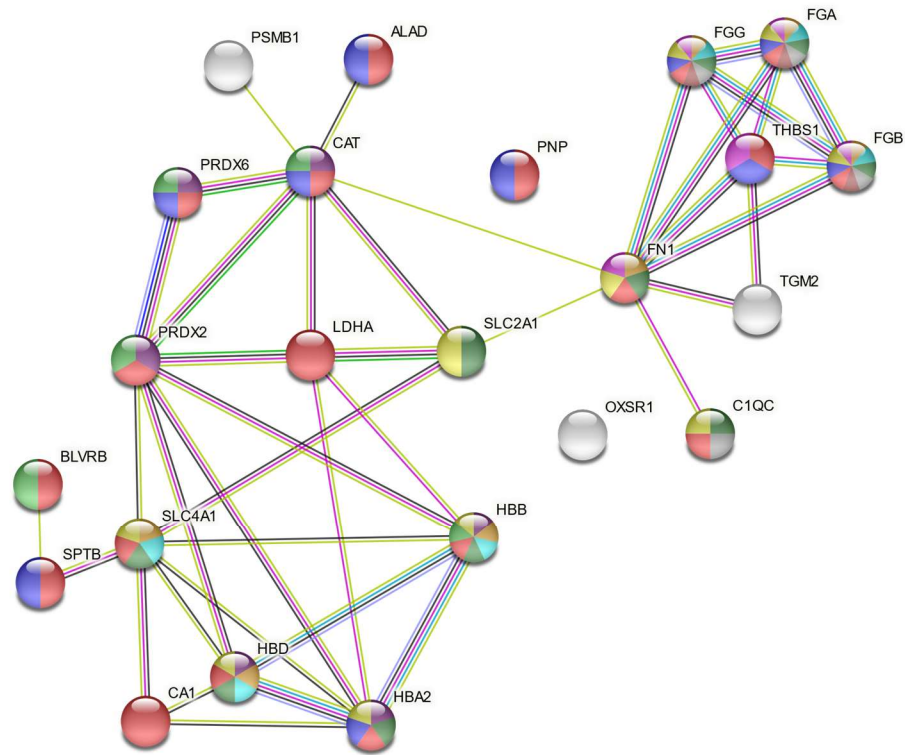
Supplementary figure 4 Annotated spectrum and fragmentation evidence of a lysine methylated miscleaved peptide. a) The fragmentation spectrum of the NH₂-I(AVAQYSDDV(K)methylated (+14.0156 Da)VESR-COOH peptide shows the detection of y and b fragment ion series on Exploris480. The delta m/z between product ions y₄ and y₅ corresponds to a mass of 142.1106 Da, which represents mass of lysine minus the mass of water molecule plus mass of methyl modification (14.0156 Da). b) Fragmentation evidence of the NH₂-I(AVAQYSDDV(K)methylated (+14.0156 Da)VESR-COOH peptide is provided. Detected b fragment ions are highlighted in blue and y fragment ions are highlighted in orange. The bold fragment ions are proving the evidence of the methylated lysine in the peptide sequence.



Supplementary figure 5 Evaluation of data independent (DIA) quantitation accuracy and reproducibility within formalin fixed paraffin embedded breast tissue voxels subjected to In-insert method processing. a) Correlation heatmap illustrates favorable correlation coefficients for quantitative data, particularly among the neighboring voxels. Notably some voxels retrieved from edge of slide exhibit greater variation, displaying lower correlation coefficients compared to other voxels. b) Protein intensity heatmap demonstrates relatively similar patterns of quantitated protein intensities across voxels, further supporting observations from correlation heatmap. c) The Principal Analysis plot (PCA) plot highlights the clustering of voxels with similar protein intensity profiles, while voxels with distinct profiles are positioned farther apart, displaying higher proteotype dissimilarity.

	log10 protein intensity (quantile normalized)																
Voxel	10	11	12	13	14	15	16	17	18	19	20	3	4	6	7	9	1
PNPH_HUMAN	16.43	12.21	9.79	14.11	10.44	10.02	11.36	9.94	9.87	9.14	13.00	16.82	15.54	10.48	13.13	19.66	13.84
CAH1_HUMAN	19.08	14.63	11.24	17.68	14.16	10.97	12.65	8.49	8.98	10.10	14.61	18.54	17.85	11.93	15.64	19.22	16.32
ANGT_HUMAN	15.87	18.62	16.68	11.32	15.44	15.60	16.07	8.62	13.33	14.49	10.30	11.65	14.54	11.42	18.30	16.30	18.79
B3AT_HUMAN	19.48	15.56	12.69	16.87	14.58	13.31	14.02	11.09	11.42	8.97	14.37	19.67	18.72	13.35	15.27	18.68	18.21
CFAI_HUMAN	14.29	16.76	14.69	11.21	13.45	13.20	13.48	10.77	10.91	13.58	12.56	11.01	12.93	9.23	17.60	14.91	17.63
GTR1_HUMAN	19.08	15.75	10.95	14.73	14.35	12.54	13.11	12.66	10.38	10.00	15.16	19.00	17.98	11.87	17.25	21.71	18.77
SPTB1_HUMAN	17.91	11.69	9.88	12.22	11.18	11.01	11.61	8.43	9.55	8.52	10.12	17.25	15.80	9.42	12.16	19.35	14.38
PIP_HUMAN	16.71	15.07	13.55	15.46	12.62	16.67	12.52	10.73	11.57	13.60	22.40	11.72	17.81	13.66	17.77	16.84	19.43
TGM2_HUMAN	15.26	12.99	8.17	10.34	10.71	7.77	7.70	8.90	8.17	10.44	14.73	15.02	14.06	8.22	15.48	13.48	13.08
THOC4_HUMAN	13.01	16.25	11.87	17.45	14.69	9.81	9.85	11.62	10.22	16.46	19.21	15.40	15.96	14.00	17.38	19.08	15.84
PGRP2_HUMAN	15.20	17.87	16.46	11.22	13.98	14.57	16.13	9.76	10.89	13.85	11.76	11.48	15.49	9.70	18.32	15.67	18.46

Supplementary table 1 A table of fully quantitated proteins with the highest standard error (SE) of protein intensity across 17 investigated formalin fixed paraffin embedded breast tissue (BFPT) voxels retrieved by applying the filter_data function of the SpatiaHeatmap R package. A cut-off on SE of the summed protein intensity was set ($SE > 0.18$) to filter the most spatially changed proteins across the BFPT voxels. Bolded are the proteins that were selected for further investigation.



Colour in STRING map	Type of analysis	term ID	term description	observed gene count	background gene count	strength	false discovery rate	matching proteins in the network (labels)
DARK VIOLET	GO Process	GO:0042744	Hydrogen peroxide catabolic process	6	28	2.26	2.18E-08	CAT,HBA2,PRDX2,HBB,PRDX6,HBD
	GO Process	GO:0045055	Regulated exocytosis	11	697	1.13	4.96E-07	CAT,THBS1,PSMB1,FGB,FGA,HBB,FGG,PRDX6,PNP,ALAD
	GO Process	GO:0010035	Response to inorganic substance	10	538	1.2	7.17E-07	CAT,HBA2,THBS1,PRDX2,FGB,FGA,HBB,FGG,ALAD,LDHA
	GO Process	GO:0006950	Response to stress	18	3485	0.64	1.09E-06	CAT,HBA2,THBS1,PSMB1,SLC4A1,PRDX2,FGB,FGA,OXSRI,HBB,FGG,PRDX6,CA1,C1QC,HBD,ALAD,SLC2A1,LDHA
	GO Process	GO:0016192	Vesicle-mediated transport	14	1805	0.82	2.05E-06	CAT,HBA2,THBS1,PSMB1,FGB,FGA,HBB,FGG,PRDX6,PNP,TGM2,ALAD,SPTB
	GO Process	GO:0042221	Response to chemical	19	4333	0.57	2.05E-06	CAT,HBA2,THBS1,PSMB1,PRDX2,FGB,FGA,OXSRI,HBB,FGG,PRDX6,PNP,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	GO Process	GO:0098869	Cellular oxidant detoxification	6	90	1.75	2.05E-06	CAT,HBA2,PRDX2,HBB,PRDX6,HBD
	GO Process	GO:0009636	Response to toxic substance	7	219	1.43	4.77E-06	CAT,HBA2,PRDX2,HBB,PRDX6,HBD,ALAD
	GO Process	GO:0006979	Response to oxidative stress	8	393	1.24	8.15E-06	CAT,HBA2,PRDX2,OXSRI,HBB,PRDX6,ALAD,LDHA
	GO Process	GO:0006810	Transport	18	4353	0.55	1.28E-05	CAT,HBA2,THBS1,PSMB1,SLC4A1,FGB,FGA,HBB,FGG,PRDX6,PNP,TGM2,HBD,ALAD,SLC2A1,CA1,SPTB
	GO Process	GO:0030193	Regulation of blood coagulation	5	80	1.73	2.64E-05	THBS1,PRDX2,FGB,FGA,FGG

	GO Process	GO:0050896	Response to stimulus	22	8046	0.37	2.68E-05	CAT,HBA2,THBS1,PSMB1,SLC4A1,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,C1QC,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	GO Process	GO:0070887	Cellular response to chemical stimulus	15	2919	0.64	3.15E-05	CAT,HBA2,THBS1,PSMB1,PRDX2,FGB,OXSR1,HBB,FGG,PRDX6,FN1,HBD,ALAD,SLC2A1,CA1
	GO Process	GO:0050878	Regulation of body fluid levels	8	509	1.13	3.81E-05	THBS1,SLC4A1,PRDX2,FGB,FGA,HBB,FGG,HBD
	GO Process	GO:0001775	Cell activation	10	1075	0.9	7.32E-05	CAT,PSMB1,PRDX2,FGB,FGA,HBB,FGG,PRDX6,PNP,ALAD
	GO Process	GO:2001237	Negative regulation of extrinsic apoptotic signaling pathway	5	106	1.6	7.59E-05	THBS1,PRDX2,FGB,FGA,FGG
	GO Process	GO:0070527	Platelet aggregation	4	42	1.91	0.0001	FGB,FGA,HBB,FGG
	GO Process	GO:0015701	Bicarbonate transport	4	43	1.9	0.00011	HBA2,SLC4A1,HBB,CA1
	GO Process	GO:0002576	Platelet degranulation	5	129	1.52	0.00018	THBS1,FGB,FGA,FGG,FN1
	GO Process	GO:2000351	Regulation of endothelial cell apoptotic process	4	50	1.83	0.00018	THBS1,FGB,FGA,FGG
	GO Process	GO:0031639	Plasminogen activation	3	11	2.37	0.0002	FGB,FGA,FGG
GOLD	GO Process	GO:0042060	Wound healing	7	439	1.13	0.0002	SLC4A1,FGB,FGA,HBB,FGG,FN1,HBD
	GO Process	GO:0002376	Immune system process	13	2481	0.65	0.00026	CAT,THBS1,PSMB1,SLC4A1,PRDX2,FGB,FGA,HBB,PRDX6,FN1,PNP,C1QC,ALAD
	GO Process	GO:1902041	Regulation of extrinsic apoptotic signaling pathway via death domain receptors	4	59	1.76	0.00028	THBS1,FGB,FGA,FGG
	GO Process	GO:0030155	Regulation of cell adhesion	8	712	0.98	0.00032	THBS1,PRDX2,FGB,FGA,FGG,FN1,PNP,TGM2
	GO Process	GO:0010941	Regulation of cell death	11	1696	0.74	0.00034	CAT,HBA2,THBS1,PRDX2,FGB,FGA,HBB,FGG,FN1,TGM2,LDHA
CYAN	GO Process	GO:0007596	Blood coagulation	6	303	1.23	0.00036	SLC4A1,FGB,FGA,HBB,FGG,HBD
	GO Process	GO:0008152	Metabolic process	21	8298	0.33	0.00037	CAT,HBA2,THBS1,PSMB1,BLVRB,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	GO Process	GO:0034116	Positive regulation of heterotypic cell-cell adhesion	3	16	2.2	0.00037	FGB,FGA,FGG
	GO Process	GO:0044237	Cellular metabolic process	20	7513	0.35	0.00055	CAT,HBA2,THBS1,PSMB1,BLVRB,PRDX2,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	GO Process	GO:0001666	Response to hypoxia	6	342	1.17	0.00057	CAT,THBS1,PSMB1,ALAD,SLC2A1,LDHA
	GO Process	GO:0042730	Fibrinolysis	3	20	2.11	0.00059	FGB,FGA,FGG
	GO Process	GO:0000302	Response to reactive oxygen species	5	198	1.33	0.00075	CAT,HBA2,PRDX2,HBB,LDHA
	GO Process	GO:0010038	Response to metal ion	6	367	1.14	0.00079	CAT,THBS1,FGB,FGA,FGG,ALAD
	GO Process	GO:0051649	Establishment of localization in cell	12	2375	0.63	0.00084	CAT,THBS1,PSMB1,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,ALAD,SPTB
	GO Process	GO:0010810	Regulation of cell-substrate adhesion	5	212	1.3	0.00096	THBS1,FGB,FGA,FGG,FN1
	GO Process	GO:0072378	Blood coagulation, fibrin clot formation	3	26	1.99	0.001	FGB,FGA,FGG
	GO Process	GO:0006955	Immune response	10	1588	0.73	0.0011	CAT,THBS1,PSMB1,FGB,FGA,HBB,PRDX6,PNP,C1QC,ALAD
	GO Process	GO:0051641	Cellular localization	13	2967	0.57	0.0011	CAT,THBS1,PSMB1,SLC4A1,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,ALAD,SPTB
	GO Process	GO:0002443	Leukocyte mediated immunity	7	641	0.97	0.0012	CAT,PSMB1,HBB,PRDX6,PNP,C1QC,ALAD
	GO Process	GO:2000352	Negative regulation of endothelial cell apoptotic process	3	29	1.94	0.0013	FGB,FGA,FGG
	GO Process	GO:0045785	Positive regulation of cell adhesion	6	423	1.08	0.0014	FGB,FGA,FGG,FN1,PNP,TGM2
	GO Process	GO:0045907	Positive regulation of vasoconstriction	3	32	1.9	0.0016	FGB,FGA,FGG
	GO Process	GO:0002252	Immune effector process	8	969	0.85	0.0017	CAT,PSMB1,PRDX2,HBB,PRDX6,PNP,C1QC,ALAD

	GO Process	GO:0018149	Peptide cross-linking	3	34	1.88	0.0019	THBS1, FN1, TGM2
	GO Process	GO:0042542	Response to hydrogen peroxide	4	119	1.46	0.0021	CAT, HBA2, HBB, LDHA
	GO Process	GO:0051716	Cellular response to stimulus	18	6489	0.37	0.0021	CAT, HBA2, THBS1, PSMB1, PRDX2, FGB, FGA, OXSR1, HBB, FGG, PRDX6, FN1, TGM2, HBD, ALAD, SLC2A1, CA1, SPTB
	GO Process	GO:0032101	Regulation of response to external stimulus	8	1013	0.83	0.0022	THBS1, PSMB1, PRDX2, FGB, FGA, OXSR1, FGG, TGM2
	GO Process	GO:0071345	Cellular response to cytokine stimulus	8	1013	0.83	0.0022	THBS1, PSMB1, FGB, OXSR1, FGG, FN1, ALAD, CA1
	GO Process	GO:0010811	Positive regulation of cell-substrate adhesion	4	124	1.44	0.0023	FGB, FGA, FGG, FN1
	GO Process	GO:1900026	Positive regulation of substrate adhesion-dependent cell spreading	3	38	1.83	0.0024	FGB, FGA, FGG
	GO Process	GO:0007160	Cell-matrix adhesion	4	127	1.43	0.0025	FGB, FGA, FGG, FN1
	GO Process	GO:1902042	Negative regulation of extrinsic apoptotic signaling pathway via death domain receptors	3	39	1.82	0.0025	FGB, FGA, FGG
	GO Process	GO:0043312	Neutrophil degranulation	6	484	1.02	0.0026	CAT, PSMB1, HBB, PRDX6, PNP, ALAD
	GO Process	GO:0062197	Cellular response to chemical stress	5	293	1.16	0.0031	CAT, PRDX2, OXSR1, PRDX6, SLC2A1
	GO Process	GO:0051592	Response to calcium ion	4	150	1.36	0.0038	THBS1, FGB, FGA, FGG
	GO Process	GO:0065008	Regulation of biological quality	14	4042	0.47	0.0041	THBS1, PSMB1, SLC4A1, PRDX2, FGB, FGA, HBB, FGG, PRDX6, FN1, TGM2, HBD, SLC2A1, SPTB
	GO Process	GO:0010770	Positive regulation of cell morphogenesis involved in differentiation	4	159	1.33	0.0046	FGB, FGA, FGG, FN1
	GO Process	GO:0042981	Regulation of apoptotic process	9	1550	0.69	0.0047	CAT, THBS1, PRDX2, FGB, FGA, FGG, FN1, TGM2, LDHA
	GO Process	GO:0043152	Induction of bacterial agglutination	2	6	2.45	0.0047	FGB, FGA
	GO Process	GO:0030198	Extracellular matrix organization	5	338	1.1	0.0051	THBS1, FGB, FGA, FGG, FN1
	GO Process	GO:0010033	Response to organic substance	12	3011	0.53	0.0054	CAT, THBS1, PSMB1, PRDX2, FGB, OXSR1, FGG, FN1, ALAD, SLC2A1, CA1, LDHA
	GO Process	GO:0009056	Catabolic process	10	2042	0.62	0.0058	CAT, HBA2, PSMB1, BLVRB, PRDX2, HBB, PRDX6, PNP, HBD, LDHA
	GO Process	GO:0043066	Negative regulation of apoptotic process	7	893	0.82	0.0063	CAT, THBS1, PRDX2, FGB, FGA, FGG, FN1
	GO Process	GO:0032102	Negative regulation of response to external stimulus	5	367	1.06	0.0069	THBS1, PRDX2, FGB, FGA, FGG
	GO Process	GO:0045321	Leukocyte activation	7	929	0.81	0.0078	CAT, PSMB1, PRDX2, HBB, PRDX6, PNP, ALAD
	GO Process	GO:0044248	Cellular catabolic process	9	1758	0.64	0.0105	CAT, HBA2, PSMB1, BLVRB, PRDX2, HBB, PRDX6, PNP, HBD
	GO Process	GO:0033197	Response to vitamin e	2	11	2.19	0.0107	CAT, ALAD
	GO Process	GO:0090276	Regulation of peptide hormone secretion	4	215	1.2	0.0118	FGB, FGA, FGG, SLC2A1
	GO Process	GO:0048584	Positive regulation of response to stimulus	10	2257	0.58	0.0119	CAT, THBS1, PSMB1, PRDX2, FGB, FGA, OXSR1, FGG, TGM2, C1QC
	GO Process	GO:0022407	Regulation of cell-cell adhesion	5	424	1	0.0122	PRDX2, FGB, FGA, FGG, PNP
	GO Process	GO:0009605	Response to external stimulus	10	2310	0.57	0.0143	CAT, THBS1, PRDX2, FGB, FGA, C1QC, ALAD, SLC2A1, LDHA, SPTB
	GO Process	GO:1902533	Positive regulation of intracellular signal transduction	7	1041	0.76	0.0143	CAT, THBS1, PRDX2, FGB, FGA, FGG, TGM2
	GO Process	GO:0043408	Regulation of mapk cascade	6	725	0.85	0.0153	THBS1, PRDX2, FGB, FGA, FGG, FN1
	GO Process	GO:0051258	Protein polymerization	3	87	1.47	0.0153	FGB, FGA, FGG
	GO Process	GO:0045595	Regulation of cell differentiation	9	1874	0.61	0.0157	THBS1, PSMB1, PRDX2, FGB, FGA, FGG, FN1, PNP, C1QC

	GO Process	GO:0048518	Positive regulation of biological process	16	6112	0.35	0.0174	CAT,HBA2,THBS1,PSMB1,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,C1QC,LDHA
	GO Process	GO:0015711	Organic anion transport	5	465	0.96	0.0175	HBA2,SLC4A1,HBB,SLC2A1,CA1
	GO Process	GO:0045921	Positive regulation of exocytosis	3	92	1.44	0.0175	FGB,FGA,FGG
	GO Process	GO:0002224	Toll-like receptor signaling pathway	3	100	1.41	0.0219	FGB,FGA,FGG
	GO Process	GO:0090277	Positive regulation of peptide hormone secretion	3	100	1.41	0.0219	FGB,FGA,FGG
	GO Process	GO:1903706	Regulation of hemopoiesis	5	493	0.94	0.0223	THBS1,PSMB1,PRDX2,PNP,C1QC
	GO Process	GO:0009628	Response to abiotic stimulus	7	1147	0.72	0.0238	CAT,THBS1,PSMB1,OXSR1,ALAD,SLC2A1,LDHA
	GO Process	GO:0022409	Positive regulation of cell-cell adhesion	4	272	1.1	0.0249	FGB,FGA,FGG,PNP
	GO Process	GO:0050794	Regulation of cellular process	21	10932	0.21	0.0249	CAT,HBA2,THBS1,PSMB1,SLC4A1,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,C1QC,ALAD,SLC2A1,CA1,LDHA,SPTB
	GO Process	GO:0065007	Biological regulation	22	12171	0.19	0.0249	CAT,HBA2,THBS1,PSMB1,SLC4A1,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,C1QC,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	GO Process	GO:0048522	Positive regulation of cellular process	15	5579	0.36	0.025	CAT,HBA2,THBS1,PSMB1,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,LDHA
	GO Process	GO:1901700	Response to oxygen-containing compound	8	1567	0.64	0.025	CAT,HBA2,THBS1,PRDX2,HBB,ALAD,SLC2A1,LDHA
	GO Process	GO:0090066	Regulation of anatomical structure size	5	516	0.92	0.026	FGB,FGA,FGG,FN1,SPTB
	GO Process	GO:0009725	Response to hormone	6	849	0.78	0.0315	CAT,THBS1,FGB,ALAD,SLC2A1,LDHA
	GO Process	GO:0042325	Regulation of phosphorylation	8	1626	0.62	0.0315	THBS1,SLC4A1,PRDX2,FGB,FGA,OXSR1,FGG,FN1
	GO Process	GO:0070372	Regulation of erk1 and erk2 cascade	4	292	1.07	0.0315	FGB,FGA,FGG,FN1
	GO Process	GO:0043410	Positive regulation of mapk cascade	5	543	0.89	0.0319	THBS1,PRDX2,FGB,FGA,FGG
	GO Process	GO:0010288	Response to lead ion	2	23	1.87	0.0331	CAT,ALAD
	GO Process	GO:0051241	Negative regulation of multicellular organismal process	7	1231	0.68	0.0334	THBS1,PRDX2,FGB,FGA,FGG,FN1,C1QC
	GO Process	GO:0009967	Positive regulation of signal transduction	8	1654	0.61	0.0341	CAT,THBS1,PSMB1,PRDX2,FGB,FGA,FGG,TGM2
	GO Process	GO:0030194	Positive regulation of blood coagulation	2	28	1.78	0.0457	THBS1,PRDX2
	GO Process	GO:0007155	Cell adhesion	6	925	0.74	0.0458	THBS1,FGB,FGA,HBB,FGG,FN1
	GO Process	GO:0050708	Regulation of protein secretion	4	333	1.01	0.0469	FGB,FGA,FGG,SLC2A1
	GO Process	GO:1901564	Organonitrogen compound metabolic process	14	5244	0.36	0.0478	CAT,THBS1,PSMB1,BLVRB,FGB,FGA,OXSR1,FGG,FN1,PNP,TGM2,ALAD,LDHA,SPTB
	GO Function	GO:0005201	Extracellular matrix structural constituent	5	119	1.55	0.00093	THBS1,FGB,FGA,FGG,FN1
	GO Function	GO:0005344	Oxygen carrier activity	3	14	2.26	0.00093	HBA2,HBB,HBD
	GO Function	GO:0030492	Hemoglobin binding	3	9	2.45	0.00093	SLC4A1,HBB,HBD
	GO Function	GO:0042802	Identical protein binding	12	1896	0.73	0.00093	CAT,THBS1,SLC4A1,OXSR1,FGG,PRDX6,FN1,PNP,TGM2,ALAD,SLC2A1,LDHA
	GO Function	GO:0019825	Oxygen binding	3	36	1.85	0.0081	HBA2,HBB,HBD
	GO Function	GO:0004601	Peroxidase activity	3	41	1.79	0.0098	CAT,PRDX2,PRDX6
	GO Function	GO:0020037	Heme binding	4	134	1.4	0.0098	CAT,HBA2,HBB,HBD
	GO Function	GO:0031721	Hemoglobin alpha binding	2	5	2.53	0.0098	HBB,HBD
	GO Function	GO:0051920	Peroxiredoxin activity	2	7	2.39	0.0139	PRDX2,PRDX6
	GO Function	GO:0005198	Structural molecule activity	6	635	0.91	0.0203	THBS1,FGB,FGA,FGG,FN1,SPTB

	GO Component	GO:0005615	Extracellular space	22	3195	0.77	9.67E-14	CAT,HBA2,THBS1,PSMB1,SLC4A1,BLVRB,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,C1QC,HBD,ALAD,SLC2A1,CA1,LDHA
	GO Component	GO:0070062	Extracellular exosome	20	2099	0.91	9.67E-14	CAT,HBA2,THBS1,PSMB1,SLC4A1,BLVRB,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,ALAD,SLC2A1,CA1,LDHA
DARK GREEN	GO Component	GO:0072562	Blood microparticle	10	115	1.87	9.67E-14	HBA2,SLC4A1,FGB,FGA,HBB,FGG,FN1,C1QC,HBD,SLC2A1
	GO Component	GO:0005577	Fibrinogen complex	5	8	2.73	4.14E-10	THBS1,FGB,FGA,FGG,FN1
	GO Component	GO:0034774	Secretory granule lumen	10	324	1.42	4.14E-10	CAT,THBS1,PSMB1,FGB,FGA,FGG,PRDX6,FN1,PNP,ALAD
	GO Component	GO:0030141	Secretory granule	11	845	1.04	1.23E-07	CAT,THBS1,PSMB1,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,ALAD
	GO Component	GO:0031093	Platelet alpha granule lumen	5	68	1.8	2.42E-06	THBS1,FGB,FGA,FGG,FN1
	GO Component	GO:0062023	Collagen-containing extracellular matrix	7	396	1.18	2.90E-05	THBS1,FGB,FGA,FGG,FN1,TGM2,C1QC
	GO Component	GO:1904813	ficolin-1-rich granule lumen	5	125	1.53	3.64E-05	CAT,PSMB1,HBB,PNP,ALAD
	GO Component	GO:0031410	Cytoplasmic vesicle	13	2386	0.67	4.18E-05	CAT,HBA2,THBS1,PSMB1,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,ALAD,SLC2A1
	GO Component	GO:0031838	Haptoglobin-hemoglobin complex	3	11	2.37	4.18E-05	HBA2,HBB,HBD
	GO Component	GO:0005833	Hemoglobin complex	3	12	2.33	4.92E-05	HBA2,HBB,HBD
	GO Component	GO:0005829	Cytosol	16	5193	0.42	0.0014	CAT,HBA2,PSMB1,BLVRB,PRDX2,OXSR1,HBB,PRDX6,PNP,TGM2,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	GO Component	GO:0005938	Cell cortex	5	292	1.16	0.0014	SLC4A1,FGB,FGA,SLC2A1,SPTB
	GO Component	GO:0098552	Side of membrane	6	531	0.98	0.0018	THBS1,SLC4A1,FGB,FGA,FGG,SPTB
	GO Component	GO:0005737	Cytoplasm	22	11428	0.21	0.0047	CAT,HBA2,THBS1,PSMB1,SLC4A1,BLVRB,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	GO Component	GO:0030863	Cortical cytoskeleton	3	96	1.42	0.0125	SLC4A1,SLC2A1,SPTB
	GO Component	GO:0071682	Endocytic vesicle lumen	2	20	1.93	0.0176	HBA2,HBB
	GO Component	GO:0005788	Endoplasmic reticulum lumen	4	308	1.04	0.0249	THBS1,FGA,FGG,FN1
	GO Component	GO:0009897	External side of plasma membrane	4	331	1.01	0.0315	THBS1,FGB,FGA,FGG
	GO Component	GO:0012505	Endomembrane system	13	4542	0.39	0.0315	CAT,THBS1,PSMB1,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,TGM2,ALAD,SLC2A1
	STRING clusters	CL:21831	Hemoglobin complex, and glycophorin a	4	19	2.25	5.72E-05	HBA2,SLC4A1,HBB,HBD
	STRING clusters	CL:19735	COVID-19, thrombosis and anticoagulation	3	6	2.63	0.00018	FGB,FGA,FGG
	STRING clusters	CL:21835	Hemoglobin complex	3	5	2.71	0.00018	HBA2,HBB,HBD
	STRING clusters	CL:13062	Glutathione metabolism, and Antioxidant	3	56	1.66	0.0154	CAT,PRDX2,PRDX6
	STRING clusters	CL:19706	Mixed, incl. complement and coagulation cascades, and lipoprotein particle	4	182	1.27	0.0196	FGB,FGA,FGG,C1QC
	STRING clusters	CL:13136	Mixed, incl. thioredoxin peroxidase activity, and superoxide dismutase activity	2	11	2.19	0.0273	CAT,PRDX2

GREY	KEGG	hsa04610	Complement and coagulation cascades	4	82	1.62	0.00097	FGB,FGA,FGG,C1QC
	KEGG	hsa05144	Malaria	3	46	1.74	0.0042	HBA2,THBS1,HBB
BROWN	KEGG	hsa04611	Platelet activation	3	122	1.32	0.0458	FGB,FGA,FGG
	Reactome	HSA-354194	GRB2:SOS provides linkage to MAPK signaling for Integrins	4	15	2.36	1.20E-05	FGB,FGA,FGG,FN1
	Reactome	HSA-372708	p130Cas linkage to MAPK signaling for integrins	4	15	2.36	1.20E-05	FGB,FGA,FGG,FN1
	Reactome	HSA-216083	Integrin cell surface interactions	5	85	1.7	3.22E-05	THBS1,FGB,FGA,FGG,FN1
	Reactome	HSA-168249	Innate Immune System	10	1025	0.92	4.30E-05	CAT,PSMB1,FGB,FGA,HBB,FGG,PRDX6,PNP,C1QC,ALAD
	Reactome	HSA-6802948	Signaling by high-kinase activity BRAF mutants	4	36	1.98	4.64E-05	FGB,FGA,FGG,FN1
	Reactome	HSA-1247673	Erythrocytes take up oxygen and release carbon dioxide	3	8	2.5	5.36E-05	SLC4A1,HBB,CA1
	Reactome	HSA-5674135	MAP2K and MAPK activation	4	40	1.93	5.36E-05	FGB,FGA,FGG,FN1
	Reactome	HSA-9656223	Signaling by RAF1 mutants	4	41	1.92	5.36E-05	FGB,FGA,FGG,FN1
	Reactome	HSA-114608	Platelet degranulation	5	127	1.52	5.83E-05	THBS1,FGB,FGA,FGG,FN1
	Reactome	HSA-6802946	Signaling by moderate kinase activity BRAF mutants	4	45	1.88	5.83E-05	FGB,FGA,FGG,FN1
	Reactome	HSA-6802955	Paradoxical activation of RAF signaling by kinase inactive BRAF	4	45	1.88	5.83E-05	FGB,FGA,FGG,FN1
	Reactome	HSA-9649948	Signaling downstream of RAS mutants	4	45	1.88	5.83E-05	FGB,FGA,FGG,FN1
	Reactome	HSA-168256	Immune System	12	1956	0.72	6.42E-05	CAT,PSMB1,FGB,FGA,HBB,FGG,PRDX6,PNP,C1QC,ALAD,CA1
	Reactome	HSA-1237044	Erythrocytes take up carbon dioxide and release oxygen	3	12	2.33	7.69E-05	SLC4A1,HBB,CA1
	Reactome	HSA-5673001	RAF/MAP kinase cascade	6	274	1.27	7.69E-05	PSMB1,FGB,FGA,FGG,FN1,SPTB
	Reactome	HSA-6802952	Signaling by BRAF and RAF fusions	4	65	1.72	0.00012	FGB,FGA,FGG,FN1
	Reactome	HSA-5686938	Regulation of TLR by endogenous ligand	3	19	2.13	0.00019	FGB,FGA,FGG
	Reactome	HSA-140875	Common Pathway of Fibrin Clot Formation	3	22	2.06	0.00027	FGB,FGA,FGG
	Reactome	HSA-109582	Hemostasis	7	605	0.99	0.00036	THBS1,FGB,FGA,HBB,FGG,FN1,HBD
	Reactome	HSA-3299685	Detoxification of Reactive Oxygen Species	3	37	1.84	0.001	CAT,PRDX2,PRDX6
	Reactome	HSA-6798695	Neutrophil degranulation	6	473	1.03	0.0011	CAT,PSMB1,HBB,PRDX6,PNP,ALAD
	Reactome	HSA-1643685	Disease	9	1548	0.69	0.0024	THBS1,PSMB1,SLC4A1,PRDX2,FGB,FGA,FGG,FN1,SLC2A1
	Reactome	HSA-5663202	Diseases of signal transduction by growth factor receptors and second messengers	5	392	1.04	0.0053	PSMB1,FGB,FGA,FGG,FN1
	Reactome	HSA-8957275	Post-translational protein phosphorylation	3	107	1.38	0.0174	FGA,FGG,FN1
	Reactome	HSA-381426	Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	3	124	1.31	0.0259	FGA,FGG,FN1
	Reactome	HSA-189445	Metabolism of porphyrins	2	27	1.8	0.0308	BLVRB,ALAD
	Reactome	HSA-3000170	Syndecan interactions	2	27	1.8	0.0308	THBS1,FN1
	WikiPathways	WP15	Selenium micronutrient network	7	86	1.84	6.75E-09	CAT,HBA2,PRDX2,FGB,FGA,HBB,FGG

	WikiPathways	WP176	Folate metabolism	6	69	1.87	8.35E-08	CAT,HBA2,FGB,FGA,HBB,FGG
	WikiPathways	WP3888	VEGFA-VEGFR2 signaling pathway	9	428	1.25	1.77E-07	PRDX2,FGB,FGA,FGG,PRDX6,PNP,HBD,LDHA
	WikiPathways	WP4927	COVID-19, thrombosis and anticoagulation	3	7	2.56	2.86E-05	FGB,FGA,FGG
	WikiPathways	WP272	Blood clotting cascade	3	23	2.05	0.00049	FGB,FGA,FGG
	WikiPathways	WP2806	Complement system	4	97	1.55	0.00062	THBS1,FGB,FGA,FGG
	WikiPathways	WP4136	Fibrin complement receptor 3 signaling pathway	3	41	1.79	0.0018	FGB,FGA,FGG
	WikiPathways	WP2456	HIF1A and PPARG regulation of glycolysis	2	8	2.33	0.005	SLC2A1,LDHA
	WikiPathways	WP4629	Aerobic glycolysis	2	12	2.15	0.009	SLC2A1,LDHA
	WikiPathways	WP1946	Cori cycle	2	17	2	0.0151	SLC2A1,LDHA
	WikiPathways	WP4206	Hereditary leiomyomatosis and renal cell carcinoma pathway	2	20	1.93	0.0185	SLC2A1,LDHA
	WikiPathways	WP2911	miRNA targets in ECM and membrane receptors	2	22	1.89	0.0202	THBS1,PNP
	WikiPathways	WP2884	NRF2 pathway	3	143	1.25	0.0334	BLVRB,PRDX6,SLC2A1
	WikiPathways	WP453	Inflammatory response pathway	2	30	1.75	0.0334	THBS1,PNP
	WikiPathways	WP3614	Photodynamic therapy-induced HIF-1 survival signaling	2	37	1.66	0.043	SLC2A1,LDHA
	Monarch HPO	HP:0011900	Hypofibrinogenemia	5	22	2.29	1.10E-06	SLC4A1,FGB,FGA,FGG,SPTB
	Monarch HPO	HP:0001871	Abnormality of blood and blood-forming tissues	12	1216	0.92	1.13E-05	CAT,SLC4A1,FGB,FGA,HBB,FGG,PNP,HBD,ALAD,SLC2A1,SPTB
	Monarch HPO	HP:0001878	Hemolytic anemia	6	102	1.7	1.13E-05	SLC4A1,HBB,PNP,ALAD,SLC2A1,SPTB
	Monarch HPO	HP:0004936	Venous thrombosis	5	65	1.82	3.20E-05	SLC4A1,FGB,FGA,HBB,FGG
	Monarch HPO	HP:0001928	Abnormality of coagulation	6	171	1.47	7.34E-05	SLC4A1,FGB,FGA,HBB,FGG,SPTB
	Monarch HPO	HP:0012223	Splenic rupture	3	4	2.8	7.34E-05	FGB,FGA,FGG
	Monarch HPO	HP:0002715	Abnormality of the immune system	12	1700	0.78	0.00012	CAT,SLC4A1,FGB,FGA,HBB,FGG,PNP,C1QC,ALAD,SLC2A1,LDHA,SPTB
	Monarch HPO	HP:0001877	Abnormal erythrocyte morphology	8	556	1.09	0.00015	CAT,SLC4A1,HBB,PNP,HBD,ALAD,SLC2A1,SPTB
	Monarch HPO	HP:0001923	Reticulocytosis	4	38	1.95	0.00015	SLC4A1,HBB,SLC2A1,SPTB
	Monarch HPO	HP:0005525	Spontaneous hemolytic crises	3	7	2.56	0.00015	SLC4A1,SLC2A1,SPTB
	Monarch HPO	HP:0100763	Abnormality of the lymphatic system	8	577	1.07	0.00015	SLC4A1,FGB,FGA,HBB,FGG,PNP,SLC2A1,SPTB
	Monarch HPO	HP:0000225	Gingival bleeding	4	45	1.88	0.00021	CAT,FGB,FGA,FGG
	Monarch HPO	HP:0001903	Anemia	7	426	1.15	0.00025	SLC4A1,HBB,PNP,HBD,ALAD,SLC2A1,SPTB
	Monarch HPO	HP:0004447	Poikilocytosis	4	48	1.85	0.00025	SLC4A1,HBB,SLC2A1,SPTB
	Monarch HPO	HP:0025066	Decreased mean corpuscular volume	3	10	2.41	0.00025	SLC4A1,HBB,SPTB
	Monarch HPO	HP:0400008	Menometrorrhagia	3	10	2.41	0.00025	FGB,FGA,FGG
	Monarch HPO	HP:0004446	Stomatocytosis	3	13	2.29	0.00041	SLC4A1,SLC2A1,SPTB
	Monarch HPO	HP:0001342	Cerebral hemorrhage	4	61	1.75	0.00046	FGB,FGA,FGG,PNP
	Monarch HPO	HP:0001939	Abnormality of metabolism/homeostasis	12	2167	0.67	0.00063	CAT,SLC4A1,FGB,FGA,HBB,FGG,PNP,ALAD,SLC2A1,LDHA,SPTB
	Monarch HPO	HP:0025546	Abnormal mean corpuscular hemoglobin concentration	3	16	2.2	0.00063	SLC4A1,HBB,SPTB
	Monarch HPO	HP:0100724	Hypercoagulability	3	19	2.13	0.00089	SLC4A1,HBB,SPTB

	Monarch HPO	EFO:0004747	Protein measurement	18	5855	0.42	0.00095	CAT,PSMB1,SLC4A1,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,C1QC,HBD,SLC2A1,CA1,LDHA,SPTB
	Monarch HPO	HP:0001978	Extramedullary hematopoiesis	3	20	2.11	0.00095	SLC4A1,HBB,SPTB
	Monarch HPO	EFO:0004272	Anemia (phenotype)	5	189	1.35	0.00097	CAT,SLC4A1,HBB,HBD,SPTB
	Monarch HPO	HP:0005268	Miscarriage	3	21	2.08	0.001	FGB,FGA,FGG
	Monarch HPO	HP:0012379	Abnormal enzyme/coenzyme activity	5	198	1.33	0.0011	CAT,SLC4A1,HBB,ALAD,LDHA
	Monarch HPO	EFO:0004503	Hematological measurement	16	4594	0.47	0.0012	SLC4A1,BLVRB,PRDX2,FGB,FGA,OXSR1,HBB,FGG,FN1,TGM2,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	Monarch HPO	HP:0002904	Hyperbilirubinemia	4	89	1.58	0.0012	SLC4A1,HBB,SLC2A1,SPTB
	Monarch HPO	HP:0001744	Splenomegaly	6	383	1.12	0.0013	SLC4A1,FGA,HBB,PNP,SLC2A1,SPTB
	Monarch HPO	HP:0100659	Abnormal cerebral vascular morphology	6	381	1.13	0.0013	FGB,FGA,HBB,FGG,FN1,PNP
	Monarch HPO	HP:0001935	Microcytic anemia	3	28	1.96	0.0017	CAT,HBB,HBD
	Monarch HPO	HP:0011277	Abnormality of the urinary system physiology	8	931	0.86	0.0019	SLC4A1,FGA,HBB,FN1,PNP,C1QC,ALAD,LDHA
	Monarch HPO	HP:0002597	Abnormality of the vasculature	10	1673	0.71	0.0022	CAT,SLC4A1,FGB,FGA,HBB,FGG,FN1,PNP,SLC2A1,SPTB
	Monarch HPO	HP:0001386	Joint swelling	3	35	1.86	0.0027	FGB,FGA,FGG
	Monarch HPO	HP:0004364	Abnormal circulating nitrogen compound concentration	6	447	1.06	0.0027	SLC4A1,HBB,PNP,SLC2A1,LDHA,SPTB
	Monarch HPO	HP:0012649	Increased inflammatory response	8	984	0.84	0.0027	CAT,SLC4A1,FGA,HBB,PNP,C1QC,LDHA,SPTB
	Monarch HPO	HP:0003111	Abnormal blood ion concentration	5	277	1.19	0.0037	SLC4A1,HBB,ALAD,SLC2A1,LDHA
	Monarch HPO	HP:0000980	Pallor	4	135	1.4	0.0042	SLC4A1,HBB,SLC2A1,SPTB
	Monarch HPO	HP:0002012	Abnormality of the abdominal organs	8	1069	0.8	0.0042	SLC4A1,FGB,FGA,HBB,FGG,PNP,SLC2A1,SPTB
	Monarch HPO	HP:0004444	Spherocytosis	2	5	2.53	0.0057	SLC4A1,SPTB
	Monarch HPO	HP:0001743	Abnormality of the spleen	4	152	1.35	0.006	FGB,FGA,HBB,FGG
	Monarch HPO	EFO:0004528	Mean corpuscular hemoglobin concentration	6	545	0.97	0.0063	SLC4A1,OXSR1,HBB,SLC2A1,CA1,SPTB
	Monarch HPO	HP:0001081	Cholelithiasis	3	52	1.69	0.0068	SLC4A1,HBB,SPTB
	Monarch HPO	EFO:0004623	Fibrinogen measurement	3	54	1.67	0.0069	FGB,FGA,FGG
	Monarch HPO	HP:0004870	Chronic hemolytic anemia	2	6	2.45	0.0069	HBB,SPTB
	Monarch HPO	HP:0008341	Distal renal tubular acidosis	2	6	2.45	0.0069	SLC4A1,FN1
	Monarch HPO	HP:0010972	Anemia of inadequate production	4	160	1.33	0.0069	CAT,SLC4A1,HBB,HBD
	Monarch HPO	HP:0012211	Abnormal renal physiology	6	558	0.96	0.0069	SLC4A1,FGA,HBB,FN1,C1QC,LDHA
	Monarch HPO	HP:0004297	Abnormality of the biliary system	4	164	1.32	0.007	SLC4A1,FGA,HBB,SPTB
	Monarch HPO	HP:0025142	Constitutional symptom	7	864	0.84	0.0074	CAT,SLC4A1,HBB,ALAD,SLC2A1,LDHA,SPTB
	Monarch HPO	HP:0002027	Abdominal pain	4	172	1.3	0.008	SLC4A1,HBB,ALAD,SPTB
	Monarch HPO	HP:0045040	Abnormal lactate dehydrogenase level	3	58	1.64	0.008	SLC4A1,HBB,LDHA
	Monarch HPO	EFO:0010700	Reticulocyte measurement	7	887	0.83	0.0083	SLC4A1,BLVRB,OXSR1,ALAD,SLC2A1,CA1,SPTB
	Monarch HPO	HP:0000952	Jaundice	4	175	1.29	0.0083	SLC4A1,HBB,SLC2A1,SPTB
	Monarch HPO	HP:0000079	Abnormality of the urinary system	9	1657	0.66	0.0091	SLC4A1,FGA,HBB,FN1,PNP,C1QC,ALAD,SLC2A1,LDHA
	Monarch HPO	HP:0004804	Congenital hemolytic anemia	2	8	2.33	0.0091	SLC4A1,SPTB
	Monarch HPO	HP:0001046	Intermittent jaundice	2	9	2.28	0.0101	SLC4A1,SPTB

	Monarch HPO	HP:0001930	Nonspherocytic hemolytic anemia	2	9	2.28	0.0101	SLC4A1,HBB
	Monarch HPO	HP:0004445	Elliptocytosis	2	9	2.28	0.0101	SLC4A1,SPTB
	Monarch HPO	HP:0003110	Abnormality of urine homeostasis	6	638	0.9	0.0103	FGA,HBB,FN1,PNP,ALAD,LDHA
	Monarch HPO	EFO:0010701	Mean reticulocyte volume	5	408	1.02	0.013	SLC4A1,OXSRI,SLC2A1,CA1,SPTB
	Monarch HPO	HP:0001892	Abnormal bleeding	5	411	1.01	0.0133	CAT,FGB,FGA,FGG,FN1
	Monarch HPO	HP:0000421	Epistaxis	3	78	1.51	0.0144	FGB,FGA,FGG
	Monarch HPO	EFO:0005192	Red blood cell distribution width	6	713	0.85	0.017	SLC4A1,OXSRI,HBB,HBD,SLC2A1,SPTB
	Monarch HPO	HP:0001723	Restrictive cardiomyopathy	2	13	2.12	0.017	SLC4A1,SPTB
	Monarch HPO	HP:0005502	Increased red cell osmotic fragility	2	13	2.12	0.017	SLC4A1,SPTB
	Monarch HPO	HP:0025143	Chills	2	13	2.12	0.017	SLC4A1,SPTB
	Monarch HPO	HP:0001927	Acanthocytosis	2	14	2.08	0.0185	SLC4A1,SPTB
	Monarch HPO	HP:0025548	Increased mean corpuscular hemoglobin concentration	2	14	2.08	0.0185	SLC4A1,SPTB
	Monarch HPO	HP:0000707	Abnormality of the nervous system	12	3470	0.47	0.0214	CAT,SLC4A1,FGB,FGA,HBB,FGG,FN1,PNP,ALAD,SLC2A1,LDHA,SPTB
	Monarch HPO	HP:0040186	Maculopapular exanthema	2	16	2.03	0.0225	SLC4A1,SPTB
	Monarch HPO	HP:0003270	Abdominal distention	3	100	1.41	0.0252	SLC4A1,ALAD,SPTB
	Monarch HPO	HP:0200042	Skin ulcer	3	100	1.41	0.0252	SLC4A1,HBB,SPTB
	Monarch HPO	HP:0001997	Gout	2	18	1.98	0.0261	SLC4A1,SPTB
	Monarch HPO	HP:0000988	Skin rash	3	103	1.39	0.0263	SLC4A1,FGA,SPTB
	Monarch HPO	HP:0000124	Renal tubular dysfunction	3	109	1.37	0.0303	SLC4A1,HBB,FN1
	Monarch HPO	HP:0002239	Gastrointestinal hemorrhage	3	111	1.36	0.0316	FGB,FGA,FGG
	Monarch HPO	EFO:0007986	Reticulocyte count	5	527	0.91	0.0326	SLC4A1,BLVRB,ALAD,CA1,SPTB
	Monarch HPO	HP:0011842	Abnormal skeletal morphology	10	2573	0.52	0.0344	SLC4A1,FGB,FGA,HBB,FGG,FN1,PNP,ALAD,SLC2A1,SPTB
	Monarch HPO	HP:0000790	Hematuria	3	118	1.34	0.0365	FGA,HBB,FN1
	Monarch HPO	HP:0002240	Hepatomegaly	5	544	0.89	0.0365	SLC4A1,FGA,HBB,SLC2A1,SPTB
	Monarch HPO	EFO:0004509	Hemoglobin measurement	7	1228	0.69	0.0372	SLC4A1,OXSRI,HBB,HBD,SLC2A1,CA1,SPTB
	Monarch HPO	HP:0003470	Paralysis	3	122	1.32	0.0383	SLC4A1,ALAD,SLC2A1
	Monarch HPO	EFO:0004526	Mean corpuscular volume	6	872	0.77	0.0387	SLC4A1,OXSRI,HBB,SLC2A1,CA1,SPTB
	Monarch HPO	HP:0003265	Neonatal hyperbilirubinemia	2	24	1.85	0.0387	SLC4A1,SPTB
	Monarch HPO	HP:0003326	Myalgia	3	127	1.3	0.0414	SLC4A1,LDHA,SPTB
	Monarch HPO	HP:0000118	Phenotypic abnormality	14	5134	0.37	0.0437	CAT,SLC4A1,FGB,FGA,HBB,FGG,FN1,PNP,C1QC,HBD,ALAD,SLC2A1,LDHA,SPTB
	Monarch HPO	HP:0002725	Systemic lupus erythematosus	2	26	1.82	0.0437	PNP,C1QC
	Monarch HPO	HP:0001433	Hepatosplenomegaly	3	136	1.27	0.0481	SLC4A1,HBB,SLC2A1
	DISEASES	DOID:589	Congenital hemolytic anemia	6	55	1.97	3.00E-07	HBA2,SLC4A1,HBB,HBD,SLC2A1,SPTB
	DISEASES	DOID:74	Hematopoietic system disease	9	409	1.27	5.76E-07	HBA2,SLC4A1,FGB,FGA,HBB,FGG,HBD,SLC2A1,SPTB
	DISEASES	DOID:2236	Congenital afibrinogenemia	3	3	2.93	2.05E-05	FGB,FGA,FGG
	DISEASES	DOID:10241	Thalassemia	3	14	2.26	0.00059	HBA2,HBB,HBD
	DISEASES	DOID:5378	Hemoglobin d disease	2	2	2.93	0.0043	HBB,HBD

	DISEASES	DOID:4	Disease	17	5921	0.39	0.0099	CAT,HBA2,SLC4A1,FGB,FGA,HBB,FGG,FN1,PNP,TGM2,C1QC,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	DISEASES	DOID:0110031	Hemoglobin h disease	2	5	2.53	0.0121	HBA2,HBB
	DISEASES	DOID:12241	Beta thalassemia	2	6	2.45	0.0146	HBB,HBD
	DISEASES	DOID:2373	Hereditary elliptocytosis	2	8	2.33	0.0215	SLC4A1,SPTB
	DISEASES	DOID:9120	Amyloidosis	3	70	1.56	0.026	FGA,HBB,FN1
	DISEASES	DOID:0050737	Autosomal recessive disease	8	1422	0.68	0.0352	HBA2,FGB,FGA,HBB,FGG,PNP,TGM2,HBD
	DISEASES	DOID:12971	Hereditary spherocytosis	2	13	2.12	0.0352	SLC4A1,SPTB
RED	TISSUES	BTO:0000089	Blood	19	1675	0.98	6.93E-14	CAT,HBA2,THBS1,SLC4A1,BLVRB,PRDX2,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,C1QC,HBD,ALAD,CA1,LDHA,SPTB
	TISSUES	BTO:0000570	Hematopoietic system	20	2543	0.83	2.30E-12	CAT,HBA2,THBS1,SLC4A1,BLVRB,PRDX2,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,TGM2,C1QC,HBD,ALAD,CA1,LDHA,SPTB
	TISSUES	BTO:0000759	Liver	18	1882	0.91	7.11E-12	CAT,HBA2,THBS1,SLC4A1,BLVRB,PRDX2,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,TGM2,ALAD,SLC2A1,LDHA,SPTB
	TISSUES	BTO:0000345	Digestive gland	19	2645	0.79	7.92E-11	CAT,HBA2,THBS1,SLC4A1,BLVRB,PRDX2,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,TGM2,ALAD,SLC2A1,CA1,LDHA,SPTB
BLUE	TISSUES	BTO:0000132	Blood platelet	10	337	1.4	9.49E-10	CAT,HBA2,THBS1,FGB,FGA,FGG,PRDX6,PNP,ALAD,SPTB
GREEN	TISSUES	BTO:0000424	Erythrocyte	5	39	2.04	4.02E-07	CAT,BLVRB,PRDX2,HBB,PRDX6
	TISSUES	BTO:0001486	Skeletal system	12	1203	0.93	5.22E-07	HBA2,THBS1,FGB,FGA,HBB,FGG,PRDX6,FN1,TGM2,SLC2A1,LDHA,SPTB
	TISSUES	BTO:0001491	Viscus	19	5020	0.51	3.74E-06	CAT,HBA2,THBS1,SLC4A1,BLVRB,PRDX2,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,TGM2,ALAD,SLC2A1,CA1,LDHA,SPTB
	TISSUES	BTO:0000574	Hematopoietic cell	10	933	0.96	7.83E-06	CAT,SLC4A1,BLVRB,PRDX2,HBB,PRDX6,FN1,C1QC,HBD,LDHA
	TISSUES	BTO:0000562	Heart	7	695	0.93	0.0016	THBS1,FGA,HBB,FN1,TGM2,LDHA,SPTB
	TISSUES	BTO:0000284	Organism form	11	2239	0.62	0.0022	CAT,HBA2,THBS1,PSMB1,OXSR1,HBB,FN1,TGM2,ALAD,SLC2A1,LDHA
	TISSUES	BTO:0001489	Whole body	23	12619	0.19	0.0053	CAT,HBA2,THBS1,PSMB1,SLC4A1,BLVRB,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,FN1,PNP,TGM2,C1QC,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	TISSUES	BTO:0000174	Embryonic structure	10	2132	0.6	0.0085	CAT,HBA2,THBS1,PSMB1,OXSR1,HBB,FN1,TGM2,SLC2A1,LDHA
	TISSUES	BTO:0000203	Respiratory system	8	1436	0.68	0.0163	HBA2,THBS1,PSMB1,PRDX2,FN1,TGM2,SLC2A1,LDHA
	TISSUES	BTO:0000141	Bone marrow	5	478	0.95	0.02	THBS1,FGA,PRDX6,FN1,LDHA
	TISSUES	BTO:0001090	Mouth	5	482	0.95	0.02	HBA2,FN1,PNP,ALAD,SLC2A1
	TISSUES	BTO:0002731	Erythroid cell	2	16	2.03	0.02	SLC4A1,HBD
	TISSUES	BTO:0000763	Lung	7	1162	0.71	0.0241	HBA2,THBS1,PSMB1,PRDX2,FN1,TGM2,LDHA
	TISSUES	BTO:0001078	Placenta	7	1176	0.7	0.0248	HBA2,THBS1,HBB,FN1,TGM2,SLC2A1,LDHA
	TISSUES	BTO:0000421	Connective tissue	6	871	0.77	0.0316	CAT,BLVRB,PRDX2,PRDX6,FN1,SLC2A1
	TISSUES	BTO:0001176	Endothelial cell	3	133	1.28	0.0383	THBS1,FN1,TGM2
	TISSUES	BTO:0000394	Aorta endothelium	2	32	1.73	0.0492	THBS1,FN1
YELLOW	COMPARTMENTS	GOCC:0072562	Blood microparticle	10	116	1.87	2.07E-13	HBA2,SLC4A1,FGB,FGA,HBB,FGG,FN1,C1QC,HBD,SLC2A1
	COMPARTMENTS	GOCC:0005615	Extracellular space	13	985	1.05	1.18E-08	HBA2,THBS1,SLC4A1,FGB,FGA,HBB,FGG,FN1,TGM2,C1QC,HBD,SLC2A1,LDHA
VIOLET	COMPARTMENTS	GOCC:0005577	Fibrinogen complex	5	19	2.35	4.52E-08	THBS1,FGB,FGA,FGG,FN1
	COMPARTMENTS	GOCC:0030141	Secretory granule	11	704	1.12	7.43E-08	CAT,THBS1,PSMB1,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,ALAD
	COMPARTMENTS	GOCC:0031982	Vesicle	15	2051	0.79	1.86E-07	CAT,HBA2,THBS1,PSMB1,FGB,FGA,HBB,FGG,PRDX6,FN1,PNP,TGM2,ALAD,SLC2A1,LDHA

	COMPARTMENTS	GOCC:0031093	Platelet alpha granule lumen	5	68	1.8	6.59E-06	THBS1,FGB,FGA,FGG,FN1
	COMPARTMENTS	GOCC:0005737	Cytoplasm	22	7871	0.38	8.29E-06	CAT,HBA2,THBS1,PSMB1,SLC4A1,BLVRB,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,PNP,TGM2,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	COMPARTMENTS	GOCC:0031410	Cytoplasmic vesicle	12	1709	0.78	2.31E-05	CAT,HBA2,THBS1,PSMB1,FGB,FGA,HBB,FGG,PRDX6,PNP,ALAD
	COMPARTMENTS	GOCC:0034774	Secretory granule lumen	6	230	1.35	4.34E-05	THBS1,FGB,FGA,FGG,PRDX6,PNP
	COMPARTMENTS	GOCC:1904813	ficolin-1-rich granule lumen	5	125	1.53	5.26E-05	CAT,PSMB1,HBB,PNP,ALAD
	COMPARTMENTS	GOCC:0031838	Haptoglobin-hemoglobin complex	3	11	2.37	6.55E-05	HBA2,HBB,HBD
	COMPARTMENTS	GOCC:0005833	Hemoglobin complex	3	22	2.06	0.00039	HBA2,HBB,HBD
	COMPARTMENTS	GOCC:0005829	Cytosol	13	2919	0.58	0.00055	CAT,HBA2,PSMB1,BLVRB,OXSR1,HBB,PRDX6,PNP,TGM2,HBD,CA1,LDHA,SPTB
	COMPARTMENTS	GOCC:0009897	External side of plasma membrane	4	104	1.51	0.00079	THBS1,FGB,FGA,FGG
	COMPARTMENTS	GOCC:1903561	Extracellular vesicle	6	444	1.06	0.0011	THBS1,HBB,PNP,TGM2,SLC2A1,LDHA
	COMPARTMENTS	GOCC:0098552	Side of membrane	5	266	1.2	0.0013	THBS1,FGB,FGA,FGG,SPTB
	COMPARTMENTS	GOCC:0070013	Intracellular organelle lumen	12	2812	0.56	0.0021	CAT,HBA2,THBS1,PSMB1,FGB,FGA,HBB,FGG,PRDX6,PNP,ALAD
	COMPARTMENTS	GOCC:0005788	Endoplasmic reticulum lumen	4	150	1.36	0.0024	THBS1,FGA,FGG,PNP
	COMPARTMENTS	GOCC:0070062	Extracellular exosome	5	368	1.06	0.0048	THBS1,PNP,TGM2,SLC2A1,LDHA
	COMPARTMENTS	GOCC:0030863	Cortical cytoskeleton	3	71	1.56	0.0065	SLC4A1,SLC2A1,SPTB
	COMPARTMENTS	GOCC:0009986	Cell surface	5	433	0.99	0.0095	THBS1,FGB,FGA,FGG,SPTB
	COMPARTMENTS	GOCC:0071682	Endocytic vesicle lumen	2	22	1.89	0.0243	HBA2,HBB
	COMPARTMENTS	GOCC:0110165	Cellular anatomical entity	23	13853	0.15	0.0243	CAT,HBA2,THBS1,PSMB1,SLC4A1,BLVRB,PRDX2,FGB,FGA,OXSR1,HBB,FGG,PRDX6,PNP,TGM2,C1QC,HBD,ALAD,SLC2A1,CA1,LDHA,SPTB
	UniProt Keywords	KW-0360	Hereditary hemolytic anemia	5	33	2.11	4.63E-07	HBA2,SLC4A1,HBB,SLC2A1,SPTB
	UniProt Keywords	KW-0561	Oxygen transport	3	11	2.37	0.00017	HBA2,HBB,HBD
	UniProt Keywords	KW-0007	Acetylation	14	3341	0.55	0.00071	CAT,HBA2,PSMB1,SLC4A1,PRDX2,OXSR1,HBB,PRDX6,PNP,TGM2,HBD,SLC2A1,CA1,LDHA
	UniProt Keywords	KW-0575	Peroxidase	3	26	1.99	0.00086	CAT,PRDX2,PRDX6
	UniProt Keywords	KW-0225	Disease mutation	13	3145	0.55	0.0015	HBA2,SLC4A1,FGB,FGA,HBB,FGG,PNP,PNP,C1QC,ALAD,SLC2A1,LDHA,SPTB
	UniProt Keywords	KW-0349	Heme	4	121	1.45	0.0015	CAT,HBA2,HBB,HBD
	UniProt Keywords	KW-0094	Blood coagulation	3	46	1.74	0.0024	FGB,FGA,FGG
	UniProt Keywords	KW-0250	Elliptocytosis	2	8	2.33	0.0044	SLC4A1,SPTB
	UniProt Keywords	KW-0597	Phosphoprotein	19	8057	0.3	0.0044	CAT,HBA2,PSMB1,SLC4A1,BLVRB,PRDX2,FGA,OXSR1,HBB,FGG,PRDX6,PNP,PNP,TGM2,HBD,ALAD,SLC2A1,LDHA,SPTB
	UniProt Keywords	KW-0971	Glycation	2	12	2.15	0.0073	HBA2,HBB

	UniProt Keywords	KW-0049	Antioxidant	2	14	2.08	0.0087	PRDX2,PRDX6
	UniProt Keywords	KW-0560	Oxidoreductase	5	568	0.87	0.0207	CAT,BLVRB,PRDX2,PRDX6,LDHA
	Pfam	PF08702	Fibrinogen alpha/beta chain family	3	3	2.93	9.72E-05	FGB,FGA,FGG
	Pfam	PF00042	Globin	3	13	2.29	0.0014	HBA2,HBB,HBD
	Pfam	PF00147	Fibrinogen beta and gamma chains, C-terminal globular domain	3	24	2.03	0.0047	FGB,FGA,FGG
	Pfam	PF10417	C-terminal domain of 1-Cys peroxiredoxin	2	5	2.53	0.0238	PRDX2,PRDX6
	Pfam	PF08534	Redoxin	2	6	2.45	0.0253	PRDX2,PRDX6
	InterPro	IPR012290	Fibrinogen, alpha/beta/gamma chain, coiled coil domain	3	3	2.93	0.00019	FGB,FGA,FGG
	InterPro	IPR000971	Globin	3	11	2.37	0.0017	HBA2,HBB,HBD
	InterPro	IPR009050	Globin-like superfamily	3	11	2.37	0.0017	HBA2,HBB,HBD
	InterPro	IPR012292	Globin/Protoglobin	3	11	2.37	0.0017	HBA2,HBB,HBD
	InterPro	IPR020837	Fibrinogen, conserved site	3	19	2.13	0.0029	FGB,FGA,FGG
	InterPro	IPR014716	Fibrinogen, alpha/beta/gamma chain, C-terminal globular, subdomain 1	3	26	1.99	0.0057	FGB,FGA,FGG
	InterPro	IPR002181	Fibrinogen, alpha/beta/gamma chain, C-terminal globular domain	3	32	1.9	0.0087	FGB,FGA,FGG
	InterPro	IPR036056	Fibrinogen-like, C-terminal	3	32	1.9	0.0087	FGB,FGA,FGG
	InterPro	IPR024706	Peroxiredoxin, AhpC-type	2	3	2.75	0.0099	PRDX2,PRDX6
	InterPro	IPR002337	Haemoglobin, beta-type	2	4	2.63	0.0134	HBB,HBD
	InterPro	IPR000866	Alkyl hydroperoxide reductase subunit C/ Thiol specific antioxidant	2	5	2.53	0.017	PRDX2,PRDX6
	InterPro	IPR019479	Peroxiredoxin, C-terminal	2	5	2.53	0.017	PRDX2,PRDX6
	SMART	SM01212	Fibrinogen alpha/beta chain family	3	3	2.93	2.05E-05	FGB,FGA,FGG
	SMART	SM00186	Fibrinogen-related domains (FReDs)	3	27	1.98	0.002	FGB,FGA,FGG

Supplementary table 2. STRING protein interaction and functional enrichment analysis of the 23 proteins spatially most closely regulated with the respect to solute carrier family 2 (GTR1)³. The red color highlights proteins linked by the "BTO:0000089 Blood" (19 partners, FDR = 6.93e-14) term. Proteins highlighted in blue are linked by the "BTO:0000132 Blood platelet" (10 partners, FDR = 9.49e-10) term. The green color highlights protein partners linked by the "BTO:0000424 Erythrocyte" (5 partners, FDR = 4.02e-07) term. The Yellow and violet colored hits were found in the Subcellular localization (compartment) analysis which linked them via the "Blood microparticle" (10 partners, FDR = 2.07e-13) and the Fibrinogen complex (5 partners, FDR = 4.52e-08) terms. Dark green colored hits were found in the Cellular Component (Gene Ontology) analysis which linked them by the "Blood microparticle" (10 partners, FDR = 9.67e-14) term. Biochemical processes and pathways linked the 23 queries by the "Blood coagulation" (6 partners, FDR = 0.00036, cyan), "GO:0042060_WoundHealing" (7 partners, FDR = 0.00020, gold), GO:0042744_H.PeroxideCatabolicProcess (6 partners, FDR = 2.18e-08, dark violet) GO terms. While, the KEGG pathway analysis revealed enrichment of the "hsa04610_Platelet_Activation" (3 partners, FDR = 0.0458, brown) and the "Complement and coagulation cascades" (4 partners, FDR = 0.00097, grey) terms.

Protein	PIP_HUMAN adjacency values	Protein	PIP_HUMAN adjacency values	Protein	PIP_HUMAN adjacency values	Protein	PIP_HUMAN adjacency values
ENOA_HUMAN	1.11E-08	MYH9_HUMAN	6.74E-06	CAN1_HUMAN	5.00E-05	FBN1_HUMAN	2.16E-04
HSP7C_HUMAN	1.66E-08	NONO_HUMAN	6.78E-06	KAPO_HUMAN	5.03E-05	1433E_HUMAN	2.18E-04
H10_HUMAN	1.44E-07	COGA1_HUMAN	6.88E-06	CSRP1_HUMAN	5.24E-05	GLU2B_HUMAN	2.20E-04
ABHEB_HUMAN	1.51E-07	CLH1_HUMAN	6.91E-06	LAMA5_HUMAN	5.28E-05	FCGBP_HUMAN	2.21E-04
KPYM_HUMAN	1.81E-07	ANXA4_HUMAN	7.23E-06	HNRPD_HUMAN	5.37E-05	RISC_HUMAN	2.26E-04
HNRPC_HUMAN	2.63E-07	H1X_HUMAN	7.98E-06	PDIA1_HUMAN	5.45E-05	CAN2_HUMAN	2.29E-04
OST48_HUMAN	2.70E-07	COFA1_HUMAN	8.22E-06	DUS3L_HUMAN	5.46E-05	FSCN1_HUMAN	2.43E-04
PRDX3_HUMAN	3.00E-07	PGK1_HUMAN	8.51E-06	HP1B3_HUMAN	5.69E-05	LAMB1_HUMAN	2.57E-04
BIP_HUMAN	3.31E-07	H4_HUMAN	8.74E-06	AL7A1_HUMAN	5.87E-05	ODPB_HUMAN	2.69E-04
CH60_HUMAN	4.34E-07	XRCC6_HUMAN	8.98E-06	CATD_HUMAN	6.00E-05	PCBP1_HUMAN	3.05E-04
PLEC_HUMAN	6.02E-07	ATPO_HUMAN	9.64E-06	MFAP4_HUMAN	6.19E-05	CAC1A_HUMAN	3.31E-04
CNDP2_HUMAN	7.24E-07	IQGA1_HUMAN	9.82E-06	SERA_HUMAN	6.24E-05	TMM43_HUMAN	3.55E-04
LRC47_HUMAN	8.68E-07	SSRD_HUMAN	1.06E-05	ROA3_HUMAN	6.81E-05	HLLA_HUMAN	3.56E-04
RL7_HUMAN	8.98E-07	AHNK_HUMAN	1.15E-05	DNPEP_HUMAN	6.91E-05	RPN1_HUMAN	3.78E-04
EFTU_HUMAN	9.10E-07	PRDX1_HUMAN	1.30E-05	RL6_HUMAN	7.34E-05	K2C5_HUMAN	3.79E-04
AK1A1_HUMAN	9.51E-07	CAPG_HUMAN	1.40E-05	MOES_HUMAN	7.80E-05	ACADV_HUMAN	3.93E-04
ACTN4_HUMAN	1.09E-06	GPX3_HUMAN	1.44E-05	RRBP1_HUMAN	7.83E-05	RBP2_HUMAN	3.98E-04
NUCL_HUMAN	1.30E-06	TCP4_HUMAN	1.59E-05	UBA1_HUMAN	8.16E-05	FLNA_HUMAN	4.16E-04
LASP1_HUMAN	1.32E-06	DYHC1_HUMAN	1.68E-05	CO4A2_HUMAN	8.50E-05	ENPL_HUMAN	4.35E-04
HS71A_HUMAN	1.46E-06	ATPB_HUMAN	1.78E-05	PRAF3_HUMAN	8.53E-05	DHE3_HUMAN	4.65E-04
NPM_HUMAN	1.67E-06	PDCD6_HUMAN	1.82E-05	KREM2_HUMAN	9.19E-05	CDC42_HUMAN	4.71E-04
MDHM_HUMAN	1.67E-06	RL8_HUMAN	1.87E-05	K1C19_HUMAN	9.59E-05	RL10A_HUMAN	5.17E-04
RL31_HUMAN	1.76E-06	CBR1_HUMAN	2.09E-05	GRP75_HUMAN	9.73E-05	CPNS1_HUMAN	5.19E-04
RL12_HUMAN	1.81E-06	PDIA6_HUMAN	2.11E-05	TBB5_HUMAN	9.93E-05	STT3B_HUMAN	5.55E-04
HS90A_HUMAN	1.83E-06	CH10_HUMAN	2.39E-05	PTBP1_HUMAN	1.07E-04	NCK5L_HUMAN	5.56E-04
FBLN5_HUMAN	1.88E-06	IF4H_HUMAN	2.48E-05	HCD2_HUMAN	1.19E-04	COIA1_HUMAN	5.69E-04
EF2_HUMAN	1.93E-06	SEPT2_HUMAN	2.61E-05	HCDH_HUMAN	1.20E-04	ARK72_HUMAN	5.96E-04
TINAL_HUMAN	2.01E-06	CO7A1_HUMAN	2.90E-05	PHB1_HUMAN	1.27E-04		
PYGB_HUMAN	2.02E-06	HNRPK_HUMAN	2.93E-05	RAB7A_HUMAN	1.29E-04	ANXA7_HUMAN	6.79E-04
H2AY_HUMAN	2.14E-06	RS18_HUMAN	2.96E-05	PGBM_HUMAN	1.31E-04	PEF1_HUMAN	7.06E-04
PHB2_HUMAN	2.17E-06	TERA_HUMAN	3.10E-05	LMNA_HUMAN	1.32E-04	COF1_HUMAN	7.71E-04
LMNB2_HUMAN	2.25E-06	RL13_HUMAN	3.12E-05	COX2_HUMAN	1.33E-04	IDHP_HUMAN	8.24E-04
MYL6_HUMAN	2.54E-06	BCAM_HUMAN	3.13E-05	ANXA1_HUMAN	1.36E-04	RS15_HUMAN	8.55E-04
ROA2_HUMAN	2.72E-06	FRIL_HUMAN	3.35E-05	SND1_HUMAN	1.40E-04	GDIR1_HUMAN	9.89E-04
EMIL1_HUMAN	2.93E-06	HNRH3_HUMAN	3.37E-05	ACTN1_HUMAN	1.43E-04	TAGL2_HUMAN	1.01E-03
CAP1_HUMAN	3.68E-06	PEBP1_HUMAN	3.46E-05	TPIS_HUMAN	1.47E-04	RS28_HUMAN	1.04E-03
PDIA3_HUMAN	3.78E-06	CO4A1_HUMAN	3.52E-05	H2A2B_HUMAN	1.54E-04	RTN4_HUMAN	1.07E-03
WDR1_HUMAN	3.93E-06	DPYL3_HUMAN	3.77E-05	CNN1_HUMAN	1.65E-04	COR1B_HUMAN	1.07E-03
G3P_HUMAN	4.14E-06	ANXA3_HUMAN	4.08E-05	PUR9_HUMAN	1.65E-04	CISY_HUMAN	1.13E-03
PRDX5_HUMAN	4.29E-06	TXND5_HUMAN	4.23E-05	LSM3_HUMAN	1.74E-04	TM109_HUMAN	1.22E-03
K1C18_HUMAN	4.30E-06	PLAK_HUMAN	4.46E-05	RD23B_HUMAN	1.88E-04	RSSA_HUMAN	1.25E-03
PPIA_HUMAN	4.47E-06	RHG01_HUMAN	4.48E-05	SRSF3_HUMAN	1.93E-04	SC22B_HUMAN	1.28E-03
HNRPM_HUMAN	5.19E-06	RS16_HUMAN	4.64E-05	SFPQ_HUMAN	1.93E-04	SPB6_HUMAN	1.28E-03
HNRPU_HUMAN	5.99E-06	MYH11_HUMAN	4.90E-05	GANAB_HUMAN	2.01E-04	SPTN1_HUMAN	1.28E-03
HS90B_HUMAN	6.13E-06	RS24_HUMAN	4.98E-05	SODM_HUMAN	2.13E-04	NID2_HUMAN	1.33E-03

Protein	PIP_HUMAN adjacency values	Protein	PIP_HUMAN adjacency values	Protein	PIP_HUMAN adjacency values	Protein	PIP_HUMAN adjacency values
TKT_HUMAN	1.36E-03	S20A2_HUMAN	5.32E-03	PNCB_HUMAN	1.95E-02	CO6A2_HUMAN	4.86E-02
RINI_HUMAN	1.38E-03	ANXA2_HUMAN	5.32E-03	CO5A1_HUMAN	1.98E-02	G6PI_HUMAN	4.89E-02
RACK1_HUMAN	1.42E-03	ACOH_C_HUMAN	5.58E-03	CT144_HUMAN	2.00E-02	AACT_HUMAN	5.00E-02
CO5A2_HUMAN	1.43E-03	MPCP_HUMAN	5.70E-03	HSPB1_HUMAN	2.22E-02	SRPX_HUMAN	5.07E-02
TENX_HUMAN	1.56E-03	TCPE_HUMAN	6.12E-03	CUTA_HUMAN	2.22E-02	HPT_HUMAN	5.17E-02
GSTP1_HUMAN	1.60E-03	THRB_HUMAN	6.15E-03	IF5A1_HUMAN	2.27E-02	PRDX2_HUMAN	5.29E-02
SPTB2_HUMAN	1.60E-03	CROCC_HUMAN	6.25E-03	CFAB_HUMAN	2.37E-02	CERU_HUMAN	5.38E-02
TLN1_HUMAN	1.61E-03	NB5R3_HUMAN	6.57E-03	PCOC1_HUMAN	2.43E-02	NOS1_HUMAN	5.41E-02
1433Z_HUMAN	1.79E-03	PRR12_HUMAN	7.25E-03	RT09_HUMAN	2.47E-02	IGHM_HUMAN	5.42E-02
MZB1_HUMAN	1.80E-03	PCYOX_HUMAN	7.35E-03	CO1A2_HUMAN	2.48E-02	IGJ_HUMAN	5.43E-02
TPP1_HUMAN	1.87E-03	TETN_HUMAN	7.53E-03	EHD2_HUMAN	2.65E-02	KCD12_HUMAN	5.48E-02
DPOLO_HUMAN	1.89E-03	BGH3_HUMAN	7.89E-03	FBLN1_HUMAN	2.79E-02	HEM2_HUMAN	5.58E-02
TAGL_HUMAN	2.05E-03	PA1B2_HUMAN	7.93E-03	IPSP_HUMAN	2.80E-02	OLFL3_HUMAN	5.58E-02
VAT1_HUMAN	2.09E-03	PGM1_HUMAN	8.06E-03	IGHA1_HUMAN	2.86E-02	ZA2G_HUMAN	5.63E-02
PARK7_HUMAN	2.13E-03	6PGD_HUMAN	8.16E-03	GDIB_HUMAN	2.98E-02	COCA1_HUMAN	5.69E-02
LAMC1_HUMAN	2.44E-03	ARPC4_HUMAN	8.59E-03	CO8B_HUMAN	2.99E-02	TLN2_HUMAN	5.77E-02
TALDO_HUMAN	2.45E-03	COEA1_HUMAN	8.69E-03	PSME2_HUMAN	3.06E-02	A1BG_HUMAN	5.78E-02
ALDOA_HUMAN	2.45E-03	ILEU_HUMAN	8.94E-03	RS25_HUMAN	3.11E-02	UGPA_HUMAN	5.84E-02
MYL9_HUMAN	2.45E-03	2AAA_HUMAN	9.12E-03	ALDH2_HUMAN	3.12E-02	ANXA5_HUMAN	5.90E-02
AL1A1_HUMAN	2.47E-03	ESYT1_HUMAN	9.17E-03	MYO1C_HUMAN	3.22E-02	F13A_HUMAN	6.04E-02
PPIB_HUMAN	2.61E-03	POSTN_HUMAN	9.46E-03	SDHA_HUMAN	3.27E-02	CAVN1_HUMAN	6.06E-02
CSPG2_HUMAN	2.78E-03	PGRC1_HUMAN	9.77E-03	COLA1_HUMAN	3.32E-02	TSP1_HUMAN	6.16E-02
QCR1_HUMAN	2.80E-03	TRFL_HUMAN	1.04E-02	PRDX4_HUMAN	3.33E-02	SPTB1_HUMAN	6.19E-02
VINC_HUMAN	2.83E-03	CPNE3_HUMAN	1.05E-02	SAMP_HUMAN	3.35E-02	AEBP1_HUMAN	6.20E-02
EHD4_HUMAN	2.88E-03	DPYL2_HUMAN	1.13E-02	CAV1_HUMAN	3.36E-02	CO8G_HUMAN	6.29E-02
LZTS3_HUMAN	2.90E-03	ITB1_HUMAN	1.14E-02	A2GL_HUMAN	3.41E-02	RUBIC_HUMAN	6.49E-02
FBLN3_HUMAN	3.00E-03	GELS_HUMAN	1.14E-02	ANGT_HUMAN	3.49E-02	RRAS_HUMAN	6.71E-02
ECHB_HUMAN	3.12E-03	GGT5_HUMAN	1.15E-02	HYEP_HUMAN	3.50E-02	HEMO_HUMAN	6.72E-02
PLSL_HUMAN	3.40E-03	AL9A1_HUMAN	1.16E-02	HEP2_HUMAN	3.53E-02	ITIH4_HUMAN	6.84E-02
ALDOC_HUMAN	3.40E-03	PROF1_HUMAN	1.17E-02	CO9_HUMAN	3.54E-02	LBP_HUMAN	7.37E-02
GNAI2_HUMAN	3.50E-03	SYPL1_HUMAN	1.18E-02	IPYR_HUMAN	3.58E-02	IGHA2_HUMAN	7.37E-02
NID1_HUMAN	3.57E-03	PGRC2_HUMAN	1.19E-02	CO2A1_HUMAN	3.67E-02	ALBU_HUMAN	7.38E-02
TCPG_HUMAN	3.83E-03	ILK_HUMAN	1.22E-02	S10A6_HUMAN	3.69E-02	TRFE_HUMAN	7.56E-02
ATPA_HUMAN	3.90E-03	HRG_HUMAN	1.29E-02	THIL_HUMAN	3.83E-02	KVD33_HUMAN	7.56E-02
KAP2_HUMAN	3.97E-03	CO6A3_HUMAN	1.41E-02	PEDF_HUMAN	3.87E-02	PGS1_HUMAN	7.68E-02
SERPH_HUMAN	4.04E-03	ITIH1_HUMAN	1.42E-02	ITIH2_HUMAN	3.99E-02	PGRP2_HUMAN	7.75E-02
FUBP2_HUMAN	4.12E-03	ANX11_HUMAN	1.46E-02	PLIN4_HUMAN	4.01E-02	CRYAB_HUMAN	7.93E-02
CPNE1_HUMAN	4.31E-03	LAMB2_HUMAN	1.48E-02	MUC18_HUMAN	4.09E-02	DERM_HUMAN	8.08E-02
FGD6_HUMAN	4.61E-03	VTNC_HUMAN	1.55E-02	HV349_HUMAN	4.20E-02	LITD1_HUMAN	8.15E-02
DDAH2_HUMAN	4.73E-03	PSA_HUMAN	1.59E-02	OLFL1_HUMAN	4.21E-02	PLIN1_HUMAN	8.24E-02
SBP1_HUMAN	5.11E-03	CO1A1_HUMAN	1.60E-02	DPP4_HUMAN	4.37E-02	IC1_HUMAN	8.31E-02
THIO_HUMAN	5.16E-03	SH3L1_HUMAN	1.61E-02	RS9_HUMAN	4.37E-02	HV146_HUMAN	8.38E-02
FKB1A_HUMAN	5.20E-03	PSB2_HUMAN	1.76E-02	APOB_HUMAN	4.48E-02	ANXA6_HUMAN	8.47E-02
UBE2N_HUMAN	5.20E-03	IF172_HUMAN	1.78E-02	CO6A1_HUMAN	4.54E-02	GPDA_HUMAN	8.52E-02
VIME_HUMAN	5.25E-03	CO5A3_HUMAN	1.82E-02	AMBP_HUMAN	4.80E-02	FINC_HUMAN	8.59E-02

Protein	PIP_HUMAN adjacency values	Protein	PIP_HUMAN adjacency values	Protein	PIP_HUMAN adjacency values
CATA_HUMAN	8.71E-02	GTR1_HUMAN	1.30E-01	K1C10_HUMAN	0.32
CFAD_HUMAN	8.73E-02	PGS2_HUMAN	1.34E-01	HV374_HUMAN	0.35
LEG1_HUMAN	8.80E-02	PSA3_HUMAN	1.35E-01	CD44_HUMAN	0.36
APOA4_HUMAN	8.90E-02	ACSL1_HUMAN	1.39E-01	PSA1_HUMAN	0.37
LYSC_HUMAN	8.92E-02	LEG3_HUMAN	0.14	K1C9_HUMAN	0.43
AOC3_HUMAN	8.94E-02	CO3A1_HUMAN	0.14	KVD20_HUMAN	0.43
IGKC_HUMAN	9.29E-02	MIME_HUMAN	0.15	C1QC_HUMAN	0.44
B3AT_HUMAN	9.36E-02	FAAA_HUMAN	0.15	NDK3_HUMAN	0.45
FAS_HUMAN	9.44E-02	CAH1_HUMAN	0.15	HV226_HUMAN	0.47
CO6A6_HUMAN	9.81E-02	HBD_HUMAN	0.15	CYTB_HUMAN	0.55
ANT3_HUMAN	9.82E-02	SODE_HUMAN	0.15	K2C1_HUMAN	0.55
LAMA4_HUMAN	9.86E-02	APOA2_HUMAN	0.17	PIP_HUMAN	1.00
EST1_HUMAN	9.88E-02	HV338_HUMAN	0.18		
CBPA3_HUMAN	9.95E-02	LDHB_HUMAN	0.18		
FIBB_HUMAN	9.96E-02	ECM1_HUMAN	0.19		
PRDX6_HUMAN	1.01E-01	FETUA_HUMAN	0.19		
MDHC_HUMAN	1.03E-01	PLMN_HUMAN	0.20		
HBB_HUMAN	1.03E-01	KV401_HUMAN	0.20		
ASPN_HUMAN	1.04E-01	RMC1_HUMAN	0.20		
CFAI_HUMAN	1.04E-01	LDHA_HUMAN	0.21		
CO3_HUMAN	1.04E-01	HV307_HUMAN	0.21		
APOA1_HUMAN	1.05E-01	PSB1_HUMAN	0.21		
IGHG4_HUMAN	1.05E-01	A1AG1_HUMAN	0.21		
PRELP_HUMAN	1.06E-01	LV861_HUMAN	0.22		
KV320_HUMAN	1.08E-01	FABP4_HUMAN	0.23		
VTDB_HUMAN	1.09E-01	IGHG1_HUMAN	0.23		
FA12_HUMAN	1.10E-01	FMOD_HUMAN	0.23		
APOE_HUMAN	1.10E-01	STT3A_HUMAN	0.23		
FIBG_HUMAN	1.12E-01	HV102_HUMAN	0.23		
PNPH_HUMAN	1.13E-01	LV147_HUMAN	0.23		
CAVN3_HUMAN	1.14E-01	TGM2_HUMAN	0.23		
CMA1_HUMAN	1.14E-01	THOC4_HUMAN	0.24		
LUM_HUMAN	1.15E-01	TTHY_HUMAN	0.25		
IGLL1_HUMAN	1.15E-01	BLVRB_HUMAN	0.26		
KNG1_HUMAN	1.17E-01	C4BPA_HUMAN	0.26		
A2MG_HUMAN	1.17E-01	OXSR1_HUMAN	0.26		
HBA_HUMAN	1.17E-01	A1AG2_HUMAN	0.26		
LG3BP_HUMAN	1.23E-01	IMA1_HUMAN	0.27		
A1AT_HUMAN	1.23E-01	FABP5_HUMAN	0.28		
FIBA_HUMAN	1.25E-01	IGHG2_HUMAN	0.30		
CLUS_HUMAN	1.27E-01	CATG_HUMAN	0.31		

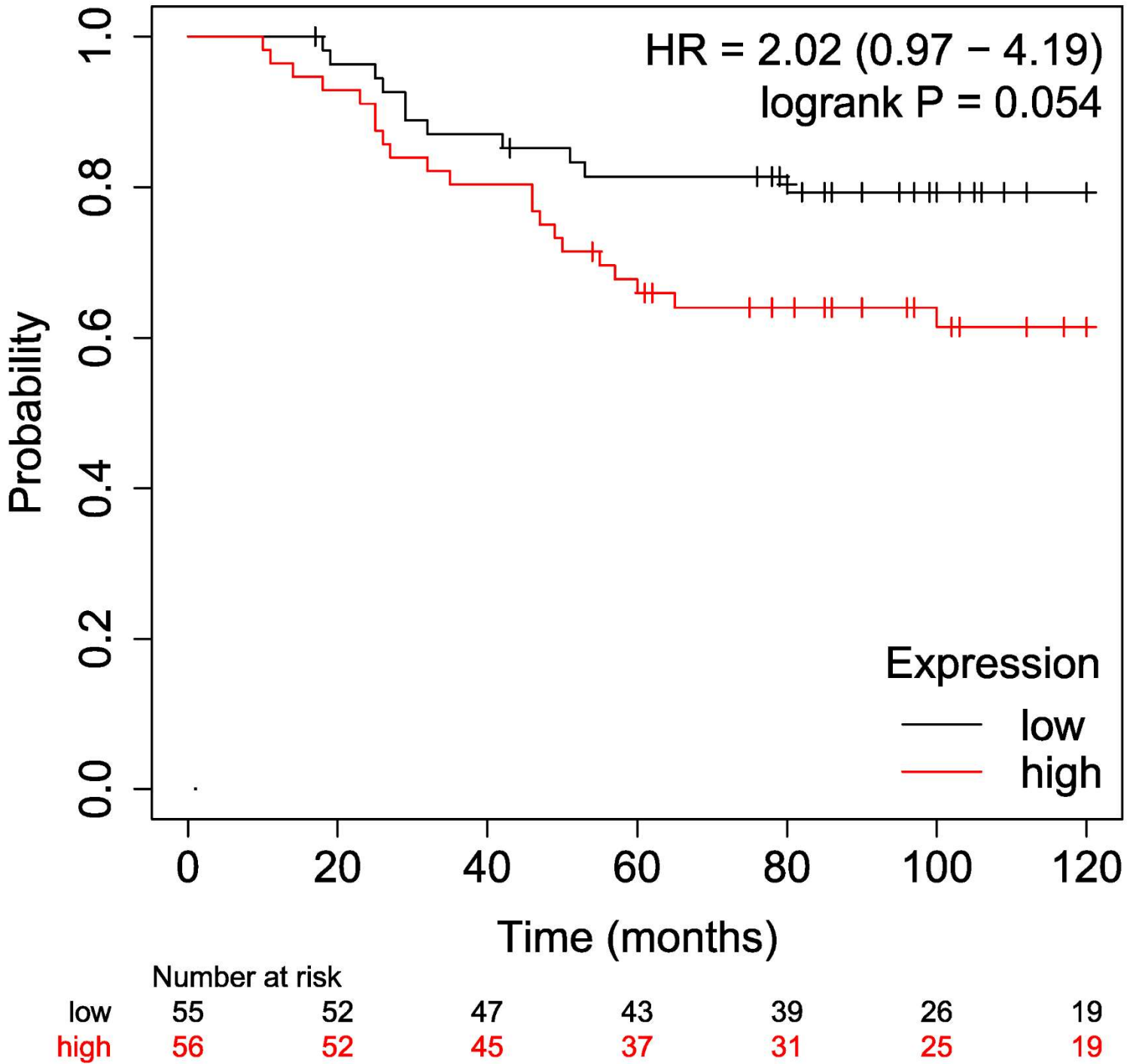
Supplementary table 3. A subset of prolactin inducible protein (PIP) spatial protein regulation adjacency values to other fully quantitated proteins (N=453) determined by adj_mod function of spatialHeatmap R package. The lower the adjacency value, the more inverse is the spatial regulation of the protein pair. In contrary, the values close to 1 show protein pairs obeying the same spatial regulation trends. The dark blue proteins (cutoff for adjacency value < 5.96e-04) showing inverse spatial regulation trends to PIP were subjected to STRING protein interaction and functional enrichment analysis. Keratins closely spatially regulated to PIP are highlighted by red color, while those with opposing regulatory trends are bolded.

Cellular_compartment_enrichment						
term ID	term description	observed gene count	background gene count	strength	false discovery rate	matching proteins in the network (labels)
GOCC:0045111	Intermediate filament cytoskeleton	4	116	2.13	1.55E-05	KRT5,PLEC,KRT19,KRT18
GOCC:0005882	Intermediate filament	3	73	2.21	0.00065	KRT5,KRT19,KRT18
GOCC:0099512	Supramolecular fiber	4	490	1.5	0.0015	KRT5,PLEC,KRT19,KRT18
GOCC:0043034	Costamere	2	13	2.78	0.0025	PLEC,KRT19
GOCC:0045095	Keratin filament	2	16	2.69	0.0031	KRT5,KRT18
GOCC:0005615	Extracellular space	4	985	1.2	0.009	KRT5,PIP,KRT19,KRT18

Cellular_component_enrichment						
term ID	term description	observed gene count	background gene count	strength	false discovery rate	matching proteins in the network (labels)
GO:0045111	Intermediate filament cytoskeleton	4	237	1.82	1.90E-04	KRT5,PLEC,KRT19,KRT18
GO:0005882	Intermediate filament	3	199	1.77	0.0091	KRT5,KRT19,KRT18
GO:0043034	Costamere	2	19	2.61	0.0091	PLEC,KRT19
GO:0070062	Extracellular exosome	5	2099	0.97	0.0091	KRT5,PIP,PLEC,KRT19, KRT18
GO:0099512	Supramolecular fiber	4	939	1.22	0.0091	KRT5,PLEC,KRT19, KRT18
GO:0045095	Keratin filament	2	92	1.93	0.0349	KRT5,KRT18

Supplementary table 4 A detailed result of Cellular compartment and component enrichment analysis of a set of proteins displaying opposing spatial regulatory trends to prolactin inducible protein (PIP) in the STRING protein interaction and functional enrichment analysis³. Summed protein intensity for highlighted term (bold) was plotted in main text figure FIG6H.

PIP (P12273)



Supplementary figure 6 A functional study of PIP relation to overall survival in breast cancer proteomic dataset. KMplot relates high and low expression of prolactin inducible protein (PIP) protein breast cancer (BC) patients (N=126) with overall survival in 120 months post diagnosis⁴. KMplot illustrates that high expression of PIP protein in BC patients leads to significantly lower overall survival (p = 0.054) if compared to overall survival in BC patients with low PIP expression within a timeline of 120 months post-diagnosis.

SUPPLEMENTARY REFERENCES

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4. Ósz, Á., Lánckzy, A. & Győrffy, B. Survival analysis in breast cancer using proteomic data from four independent datasets. *Sci. Rep.* **11**, 16787 (2021).