

The participation of the intrinsically disordered regions of the bHLH-PAS transcription factors in disease development

Marta Kolonko-Adamska ¹, Vladimir N. Uversky ^{2,3}, Beata Greb-Markiewicz ^{1,*}

¹ Department of Biochemistry, Molecular Biology and Biotechnology, Faculty of Chemistry, Wrocław University of Science and Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

² Department of Molecular Medicine, USF Health Byrd Alzheimer's Research Institute, Morsani College of Medicine, University of South Florida, Tampa, FL, United States

³ Laboratory of New Methods in Biology, Institute for Biological Instrumentation, Russian Academy of Sciences, Federal Research Center "Pushchino Scientific Center for Biological Research of the Russian Academy of Sciences", Pushchino, Moscow region, 142290 Russia

* Correspondence: beata.greb-markiewicz@pwr.edu.pl; Tel.: 0048713206226

Supplementary Materials

- 1) Results of the HuVarBase analysis of hAHR, hAHRR, hSIM1, hSIM2, hHIF2a, hNPAS4, hARNT2, and hBMAL1.
- 2) Results of the NetPhos 3.1 server phosphorylation sites prediction for hAHR, hAHRR, hSIM1, hSIM2, hHIF2a, hNPAS4, hARNT2, and hBMAL1.
- 3) STRING-based external interactome of selected bHLH-PAS TFs with the "first shell" interactors. The confidence level of 0.7 was used in this analysis.
- 4) Plots of STRING analysis of individual proteins: hAHR, hAHRR, hSIM1, hSIM2, hHIF2a, hNPAS4, hARNT2, and hBMAL1.

1) Results of the analysis of hAHR, hAHRR, hSIM1, hSIM2, hHIF2a, hNPAS4, hARNT2, and hBMAL1 by HuVarBase, Human Variants Database:

<https://www.iitm.ac.in/bioinfo/huvarbase/mas18srch.php>

Mutations taking place in ordered (i.e., with the predicted intrinsic disorder scores evaluated by mean disorder predictor, ordered ($PIDS_{mean} \leq 0.15$), flexible (i.e., with $0.15 < PIDS_{mean} \leq 0.5$), and disordered regions ($PIDS_{mean} \geq 0.5$) are indicated by blue, pink, and red characters, respectively. Numeric values of the corresponding disorder scores are shown in the brackets.

hAHR (UniProt P35869)

No.	Gene Name	Protein Mutation	Disease / Tissue (COSMIC)	Database
1	AHR 	P18L (0.81±0.17)	liver, cancer	COSMIC 
2	AHR 	D132N (0.034±0.029)	lung, cancer	COSMIC
3	AHR 	T141N (0.079±0.055)	central_nervous_system, cancer	COSMIC 
4	AHR 	Q150K (0.135±0.096)	liver, cancer	COSMIC 
5	AHR 	E169K (0.20±0.09)	breast, cancer	COSMIC 
6	AHR 	T199P (0.43±0.19)	large_intestine, cancer	COSMIC 
7	AHR 	P260L (0.24±0.11)	large_intestine, cancer	COSMIC 
8	AHR 	N284H (0.149±0.077)	large_intestine, cancer	COSMIC 
9	AHR 	R305K (0.121±0.061)	large_intestine, cancer	COSMIC 
10	AHR 	T311I (0.176±0.096)	skin, cancer	COSMIC 
11	AHR 	R368C (0.22±0.15)	stomach, cancer	COSMIC 
12	AHR 	Q383H (0.39±0.18)	oesophagus, cancer	COSMIC 
13	AHR 	R398Q (0.45±0.10)	large_intestine, cancer	COSMIC 
14	AHR 	E488K (0.48±0.17)	kidney, cancer	COSMIC 
15	AHR 	N505S (0.508±0.098)	large_intestine, cancer	COSMIC 
16	AHR 	T507I (0.55±0.14)	large_intestine, cancer	COSMIC 
17	AHR 	R554K (0.243±0.078)	soft_tissue, cancer	COSMIC  Humsavar 
18	AHR 	V570I (0.244±0.093)	thyroid, cancer	COSMIC  Humsavar 
19	AHR 	S733F (0.58±0.15)	liver, cancer	COSMIC 
20	AHR 	P838S (0.688±0.070)	large_intestine, cancer	COSMIC 

hAHRR (UniProt A9YTQ3)

No.	Gene Name	Protein Mutation	Disease / Tissue (COSMIC)	Database
1	AHRR 	V29M (0.898±0.066)	large_intestine, cancer	COSMIC 
2	AHRR 	S53G (0.37±0.19)	stomach, cancer	COSMIC 
3	AHRR 	S63F (0.22±0.19)	large_intestine, cancer	COSMIC 
4	AHRR 	Q88R (0.44±0.22)	large_intestine, cancer	COSMIC 
5	AHRR 	A96V (0.72±0.10)	large_intestine, cancer	COSMIC 
6	AHRR 	P102S (0.76±0.14)	large_intestine, cancer	COSMIC 
7	AHRR 	A112V (0.45±0.15)	liver, cancer	COSMIC 
8	AHRR 	T152M (0.083±0.075)	large_intestine, cancer	COSMIC 
9	AHRR 	P189A (0.43±0.16)	central_nervous_system, cancer	COSMIC  Humsavar 
10	AHRR 	I226V (0.042±0.046)	large_intestine, cancer	COSMIC 
11	AHRR 	R230C (0.053±0.055)	large_intestine, cancer	COSMIC 
12	AHRR 	P283S (0.45±0.22)	skin, cancer	COSMIC 
13	AHRR 	R285W (0.52±0.20)	large_intestine, cancer	COSMIC 
14	AHRR 	A300T (0.63±0.21)	large_intestine, cancer	COSMIC 
15	AHRR 	A301V (0.53±0.18)	skin, cancer	COSMIC 
16	AHRR 	A371T (0.773±0.070)	endometrium, cancer	COSMIC 
17	AHRR 	T419I (0.919±0.028)	large_intestine, cancer	COSMIC 
18	AHRR 	G427E (0.924±0.063)	skin, cancer	COSMIC 
19	AHRR 	R485W (0.65±0.26)	large_intestine, cancer	COSMIC 
20	AHRR 	R491W (0.66±0.28)	large_intestine, cancer	COSMIC 
21	AHRR 	R491Q (0.66±0.28)	prostate, cancer	ClinVar  COSMIC 
22	AHRR 	G494S (0.63±0.27)	large_intestine, cancer	COSMIC 
23	AHRR 	T524M (0.565±0.098)	large_intestine, cancer	COSMIC 
24	AHRR 	C545F (0.433±0.099)	liver, cancer	COSMIC 
25	AHRR 	V553M (0.30±0.12)	large_intestine, cancer	COSMIC 
26	AHRR 	G612S (0.49±0.22)	oesophagus, cancer	COSMIC 
27	AHRR 	D645H (0.54±0.24)	prostate, cancer	COSMIC 
28	AHRR 	A674S (0.68±0.13)	liver, cancer	COSMIC 

hSIM1 (UniProt P81133)

No.	Gene Name	Protein Mutation	Disease / Tissue (COSMIC)	Database
1	SIM1 	E3D (0.88±0.13)	large_intestine, cancer	COSMIC 
2	SIM1 	R10W (0.81±0.13)	large_intestine, cancer	COSMIC 
3	SIM1 	S31L (0.28±0.10)	urinary_tract, cancer	COSMIC 
4	SIM1 	Q36P (0.27±0.12)	lung, cancer	COSMIC 
5	SIM1 	G65D (0.36±0.13)	upper_aerodigestive_tract, cancer	COSMIC 
6	SIM1 	D74Y (0.40±0.17)	urinary_tract, cancer	COSMIC 
7	SIM1 	E155K (0.13±0.10)	skin, cancer	COSMIC 
8	SIM1 	R192H (0.081±0.083)	lung, cancer	COSMIC 
9	SIM1 	R192C (0.081±0.083)	large_intestine, cancer	COSMIC 
10	SIM1 	V213M (0.17±0.12)	cervix, cancer	COSMIC 
11	SIM1 	L217P (0.23±0.17)	large_intestine, cancer	COSMIC 
12	SIM1 	V222I (0.22±0.14)	stomach, cancer	COSMIC 
13	SIM1 	E224K (0.19±0.13)	skin, cancer	COSMIC 
14	SIM1 	A236T (0.064±0.060)	large_intestine, cancer	COSMIC
15	SIM1 	H268Q (0.084±0.055)	Schaaf-yang syndrome	ClinVar 
16	SIM1 	H268Y (0.084±0.055)	skin, cancer	COSMIC 
17	SIM1 	G271S (0.084±0.071)	oesophagus, cancer	COSMIC 
18	SIM1 	T292N (0.071±0.051)	liver, cancer	COSMIC 
19	SIM1 	G303S (0.027±0.023)	stomach, cancer	COSMIC 
20	SIM1 	S309G (0.095±0.059)	upper_aerodigestive_tract, cancer	COSMIC 
21	SIM1 	A311V (0.119±0.067)	large_intestine, cancer	COSMIC 
22	SIM1 	V326I (0.17±0.10)	stomach, cancer	COSMIC 
23	SIM1 	P352T (0.47±0.12)	breast, cancer	1000 Genomes  (data @ Ensembl ) ClinVar  COSMIC  Humsavar 
24	SIM1 	A371V (0.84±0.14)	large_intestine, cancer	1000 Genomes  (data @ Ensembl ) ClinVar  COSMIC  Humsavar 
25	SIM1 	G392R (0.73±0.14)	lung, cancer	COSMIC 
26	SIM1 	H394Y (0.71±0.16)	skin, cancer	COSMIC 
27	SIM1 	E396D (0.67±0.19)	large_intestine, cancer	COSMIC 
28	SIM1 	E399K (0.68±0.21)	skin, cancer	COSMIC 
29	SIM1 	H402Y (0.73±0.16)	skin, cancer	COSMIC 
30	SIM1 	G408R (0.809±0.089)	haematopoietic_and_lymphoid_tissue, cancer	COSMIC 

31	SIM1	D424N (0.746±0.095)	skin, cancer	COSMIC
32	SIM1	S428F (0.63±0.16)	skin, cancer	COSMIC
33	SIM1	A432T (0.56±0.20)	large_intestine, cancer	COSMIC
34	SIM1	A435T (0.49±0.19)	stomach, cancer	COSMIC
35	SIM1	G448C (0.28±0.14)	liver, cancer	COSMIC
36	SIM1	S454L (0.28±0.14)	skin, cancer	COSMIC
37	SIM1	R471Q (0.28±0.10)	skin, cancer	COSMIC
38	SIM1	C472W (0.28±0.11)	large_intestine, cancer	COSMIC
39	SIM1	T481M (0.32±0.12)	haematopoietic_and_lymphoid_tissue, cancer	COSMIC
40	SIM1	R493C (0.43±0.10)	skin, cancer	COSMIC
41	SIM1	A494T (0.433±0.091)	breast, cancer	COSMIC
42	SIM1	E530K (0.66±0.18)	lung, cancer	COSMIC
43	SIM1	P539R (0.834±0.069)	central_nervous_system, cancer	COSMIC
44	SIM1	S541L (0.833±0.079)	stomach, cancer	COSMIC
45	SIM1	R548Q (0.846±0.059)	large_intestine, cancer	COSMIC
46	SIM1	R550C (0.835±0.063)	skin, cancer	COSMIC
47	SIM1	H559Q (0.78±0.12)	liver, cancer	COSMIC
48	SIM1	A570G (0.765±0.092)	lung, cancer	COSMIC
49	SIM1	P588L (0.688±0.092)	skin, cancer	COSMIC
50	SIM1	S603F (0.36±0.18)	skin, cancer	COSMIC
51	SIM1	N650Y (0.75±0.12)	lung, cancer	COSMIC
52	SIM1	R657W (0.76±0.13)	large_intestine, cancer	COSMIC
53	SIM1	P661L (0.75±0.13)	skin, cancer	COSMIC
54	SIM1	S663L (0.70±0.19)	large_intestine, cancer	COSMIC
55	SIM1	R665C (0.67±0.17)	skin, cancer	COSMIC
56	SIM1	S680L (0.43±0.16)	prostate, cancer	COSMIC
57	SIM1	S701C (0.22±0.13)	lung, cancer	COSMIC
58	SIM1	Q704H (0.16±0.11)	liver, cancer	COSMIC
59	SIM1	Q704L (0.16±0.11)	Schaaf-yang syndrome	ClinVar
60	SIM1	E725K (0.17±0.11)	oesophagus, cancer	ClinVar COSMIC

hSIM2 (UniProt Q14190)

No.	Gene Name	Protein Mutation	Disease / Tissue (COSMIC)	Database
1	SIM2 	A40V (0.215±0.080)	lung, cancer	COSMIC 
2	SIM2 	R44G (0.154±0.046)	kidney, cancer	COSMIC 
3	SIM2 	F56L (0.152±0.066)	liver, cancer	COSMIC 
4	SIM2 	P57S (0.163±0.079)	skin, cancer	COSMIC 
5	SIM2 	A63V (0.29±0.10)	large_intestine, cancer	COSMIC 
6	SIM2 	A70T (0.33±0.13)	liver, cancer	COSMIC 
7	SIM2 	V76I (0.36±0.14)	thyroid, cancer	COSMIC 
8	SIM2 	V92F (0.045±0.020)	skin, cancer	COSMIC 
9	SIM2 	E106K (0.167±0.064)	large_intestine, cancer	COSMIC 
10	SIM2 	A108T (0.181±0.075)	liver, cancer	COSMIC 
11	SIM2 	T120M (0.178±0.091)	central_nervous_system, cancer	COSMIC 
12	SIM2 	I124M (0.229±0.055)	stomach, cancer	COSMIC 
13	SIM2 	Y125H (0.273±0.074)	liver, cancer	COSMIC 
14	SIM2 	D134N (0.28±0.12)	lung, cancer	COSMIC 
15	SIM2 	P145L (0.240±0.090)	prostate, cancer	COSMIC 
16	SIM2 	H147Y (0.24±0.10)	thyroid, cancer	COSMIC 
17	SIM2 	M164I (0.083±0.059)	skin, cancer	COSMIC 
18	SIM2 	L168F (0.079±0.057)	large_intestine, cancer	COSMIC 
19	SIM2 	A169V (0.089±0.062)	large_intestine, cancer	COSMIC 
20	SIM2 	G174S (0.094±0.066)	liver, cancer	COSMIC 
21	SIM2 	K190N (0.046±0.049)	endometrium, cancer	COSMIC 
22	SIM2 	Y194H (0.053±0.054)	skin, cancer	COSMIC 
23	SIM2 	S199Y (0.052±0.057)	bone, cancer	COSMIC 
24	SIM2 	D202N (0.043±0.042)	large_intestine, cancer	COSMIC 
25	SIM2 	V211G (0.14±0.15)	breast, cancer	COSMIC 
26	SIM2 	A212V (0.15±0.17)	large_intestine, cancer	COSMIC 
27	SIM2 	A221T (0.19±0.13)	stomach, cancer	COSMIC 
28	SIM2 	T223I (0.16±0.10)	skin, cancer	COSMIC 
29	SIM2 	M231I (0.050±0.040)	liver, cancer	COSMIC 
30	SIM2 	D239Y (0.050±0.039)	liver, cancer	COSMIC 
31	SIM2 	L240P (0.053±0.039)	thyroid, cancer	COSMIC 
32	SIM2 	D246N (0.101±0.065)	skin, cancer	COSMIC 
33	SIM2 	T253M (0.22±0.15)	breast, cancer	COSMIC 
34	SIM2 	G254R (0.24±0.13)	skin, cancer	COSMIC 
35	SIM2 	E262K (0.15±0.13)	skin, cancer	COSMIC 
36	SIM2 	H267Y (0.070±0.045)	skin, cancer	COSMIC 

37	SIM2	G271D (0.063±0.053)	large_intestine, cancer	COSMIC
38	SIM2	D273N (0.065±0.062)	skin, cancer	COSMIC
39	SIM2	R278C (0.043±0.035)	liver, cancer	COSMIC
40	SIM2	A280T (0.040±0.031)	large_intestine, cancer	COSMIC
41	SIM2	L283V (0.056±0.036)	prostate, cancer	COSMIC
42	SIM2	G303S (0.061±0.043)	pancreas, cancer	COSMIC
43	SIM2	A311V (0.17±0.14)	bone, cancer	COSMIC
44	SIM2	V313A (0.23±0.13)	lung, cancer	COSMIC
45	SIM2	R318L (0.31±0.20)	oesophagus, cancer	COSMIC
46	SIM2	R318H (0.31±0.20)	prostate, cancer	COSMIC
47	SIM2	C324Y (0.214±0.065)	thyroid, cancer	COSMIC
48	SIM2	C324F (0.214±0.065)	liver, cancer	COSMIC
49	SIM2	V326M (0.174±0.057)	large_intestine, cancer	COSMIC
50	SIM2	V326G (0.174±0.057)	thyroid, cancer	COSMIC
51	SIM2	E339K (0.23±0.12)	skin, cancer	COSMIC
52	SIM2	S343Y (0.33±0.12)	lung, cancer	COSMIC
53	SIM2	E345K (0.37±0.12)	skin, cancer	COSMIC
54	SIM2	A350S (0.41±0.18)	haematopoietic_and_lymphoid_tissue, cancer	COSMIC
55	SIM2	S355F (0.54±0.11)	lung, cancer	COSMIC
56	SIM2	K368N (0.79±0.15)	cervix, cancer	COSMIC
57	SIM2	M377I (0.78±0.14)	skin, cancer	COSMIC
58	SIM2	P385H (0.61±0.16)	lung, cancer	COSMIC
59	SIM2	F394S (0.51±0.24)	liver, cancer	COSMIC
60	SIM2	T433M (0.44±0.20)	large_intestine, cancer	COSMIC
61	SIM2	P448S (0.33±0.23)	skin, cancer	COSMIC
62	SIM2	D450N (0.35±0.22)	skin, cancer	COSMIC
63	SIM2	F454S (0.38±0.21)	skin, cancer	COSMIC
64	SIM2	Q469P (0.32±0.17)	lung, cancer	COSMIC
65	SIM2	L483M (0.28±0.22)	thyroid, cancer	COSMIC
				Humsavar
66	SIM2	C489G (0.30±0.22)	fallopian_tube, cancer	COSMIC
67	SIM2	S502W (0.78±0.12)	upper_aerodigestive_tract, cancer	COSMIC
68	SIM2	S503Y (0.79±0.13)	cervix, cancer	COSMIC
69	SIM2	T646P (0.78±0.13)	lung, cancer	COSMIC

hHIF-2 α (EPAS1, UniProt Q99814)

No.	Gene Name	Protein Mutation	Disease / Tissue (COSMIC)	Database
1	EPAS1	T31M (0.60 $\pm$ 0.33)	large_intestine, cancer	COSMIC
2	EPAS1	S49Y (0.39 $\pm$ 0.13)	Familial erythrocytosis	ClinVar
3	EPAS1	S55F (0.25 $\pm$ 0.17)	breast, cancer	COSMIC
4	EPAS1	S72L (0.44 $\pm$ 0.11)	lung, cancer	COSMIC
5	EPAS1	E82K (0.54 $\pm$ 0.18)	haematopoietic_and_lymphoid_tissue, cancer	COSMIC
6	EPAS1	A94T (0.155 $\pm$ 0.062)	liver, cancer	COSMIC
7	EPAS1	R144C (0.47 $\pm$ 0.13)	upper_aerodigestive_tract, cancer	COSMIC
8	EPAS1	H248N (0.23 $\pm$ 0.15)	large_intestine, cancer	COSMIC
9	EPAS1	S276L (0.174 $\pm$ 0.065)	large_intestine, cancer	COSMIC
10	EPAS1	E279V (0.190 $\pm$ 0.060)	liver, cancer	COSMIC
11	EPAS1	Q294H (0.29 $\pm$ 0.16)	Familial erythrocytosis	ClinVar
12	EPAS1	G314E (0.108 $\pm$ 0.075)	haematopoietic_and_lymphoid_tissue, cancer	COSMIC
13	EPAS1	V317M (0.057 $\pm$ 0.038)	large_intestine, cancer	COSMIC
14	EPAS1	S355F (0.290 $\pm$ 0.072)	skin, cancer	COSMIC
15	EPAS1	S372N (0.28 $\pm$ 0.16)	large_intestine, cancer	COSMIC
16	EPAS1	A410T (0.45 $\pm$ 0.10)	Familial erythrocytosis	1000 Genomes (data @ Ensembl) ClinVar
17	EPAS1	S474T (0.84 $\pm$ 0.13)	stomach, cancer	COSMIC
18	EPAS1	Y489H (0.56 $\pm$ 0.18)	large_intestine, cancer	COSMIC
19	EPAS1	M507T (0.40 $\pm$ 0.12)	prostate, cancer	COSMIC
20	EPAS1	L529P (0.55 $\pm$ 0.12)	autonomic_ganglia, cancer	COSMIC
21	EPAS1	A530V (0.52 $\pm$ 0.14)	autonomic_ganglia, cancer	COSMIC
22	EPAS1	A530T (0.52 $\pm$ 0.14)	pancreas, cancer	COSMIC
23	EPAS1	A530E (0.52 $\pm$ 0.14)	autonomic_ganglia, cancer	COSMIC
24	EPAS1	P531L (0.53 $\pm$ 0.14)	adrenal_gland, cancer	COSMIC
25	EPAS1	P531S (0.53 $\pm$ 0.14)	adrenal_gland, cancer	COSMIC
26	EPAS1	Y532C (0.54 $\pm$ 0.13)	adrenal_gland, cancer	COSMIC
27	EPAS1	M535V (0.58 $\pm$ 0.12)	erythrocytosis, familial, 4	ClinVar Humsavar SwissVar (variant page)
28	EPAS1	M535T (0.58 $\pm$ 0.12)	erythrocytosis, familial, 4	Humsavar SwissVar (variant page)
29	EPAS1	G537R (0.56 $\pm$ 0.13)	Erythrocytosis, familial, 4	ClinVar Humsavar SwissVar (variant page)

30	EPAS1 	G537W (0.56±0.13)	Erythrocytosis, familial, 4	ClinVar  Humsavar  SwissVar  (variant page )
31	EPAS1 	D539Y (0.58±0.12)	autonomic_ganglia, cancer	COSMIC 
32	EPAS1 	F540L (0.604±0.099)	erythrocytosis, familial, 4	Humsavar  SwissVar  (variant page )
33	EPAS1 	L542R (0.56±0.18)	liver, cancer	COSMIC 
34	EPAS1 	F608L (0.60±0.19)	Familial erythrocytosis	ClinVar 
35	EPAS1 	S672Y (0.57±0.15)	large_intestine, cancer	COSMIC 
36	EPAS1 	S703A (0.43±0.15)	Familial erythrocytosis	ClinVar 
37	EPAS1 	R710Q (0.40±0.16)	lung, cancer	COSMIC 
38	EPAS1 	S723N (0.689±0.082)	ovary, cancer	COSMIC 
39	EPAS1 	P727L (0.635±0.095)	urinary_tract, cancer	COSMIC 
40	EPAS1 	D753E (0.68±0.12)	oesophagus, cancer	COSMIC 
41	EPAS1 	T766P (0.64±0.25)	pancreas, cancer	1000 Genomes  (data @ Ensembl ) ClinVar  COSMIC  Humsavar 
42	EPAS1 	N768T (0.65±0.28)	large_intestine, cancer	COSMIC 
43	EPAS1 	P785T (0.837±0.084)	Familial erythrocytosis	1000 Genomes  (data @ Ensembl ) ClinVar  Humsavar 
44	EPAS1 	I789V (0.80±0.10)	Familial erythrocytosis	ClinVar 
45	EPAS1 	R798G (0.58±0.13)	Familial erythrocytosis	1000 Genomes  (data @ Ensembl ) ClinVar 
46	EPAS1 	R825Q (0.328±0.096)	Familial erythrocytosis	ClinVar 
47	EPAS1 	E832D (0.27±0.11)	Familial erythrocytosis	1000 Genomes  (data @ Ensembl ) ClinVar 

hNPAS4 (UniProt Q8IUM7)

No.	Gene Name	Protein Mutation	Disease / Tissue (COSMIC)	Database
1	NPAS4 	A8T (0.70±0.17)	large_intestine, cancer	COSMIC 
2	NPAS4 	R51H (0.047±0.031)	large_intestine, cancer	COSMIC 
3	NPAS4 	A63V (0.24±0.13)	stomach, cancer	COSMIC 
4	NPAS4 	P82H (0.121±0.099)	skin, cancer	COSMIC 
5	NPAS4 	G83S (0.115±0.094)	large_intestine, cancer	COSMIC 
6	NPAS4 	D121N (0.133±0.061)	large_intestine, cancer	COSMIC 
7	NPAS4 	R132H (0.210±0.083)	breast, cancer	COSMIC 
8	NPAS4 	R145C (0.277±0.090)	skin, cancer	COSMIC 
9	NPAS4 	R150L (0.36±0.20)	liver, cancer	COSMIC 
10	NPAS4 	S156F (0.43±0.19)	NS, cancer	COSMIC 
11	NPAS4 	R159C (0.39±0.18)	large_intestine, cancer	COSMIC 
12	NPAS4 	V167M (0.244±0.068)	breast, cancer	COSMIC 
13	NPAS4 	R172Q (0.157±0.091)	large_intestine, cancer	COSMIC 
14	NPAS4 	A175T (0.16±0.11)	oesophagus, cancer	COSMIC 
15	NPAS4 	P194S (0.41±0.13)	skin, cancer	COSMIC 
16	NPAS4 	P194L (0.41±0.13)	liver, cancer	COSMIC 
17	NPAS4 	P199H (0.669±0.070)	large_intestine, cancer	COSMIC 
18	NPAS4 	R200H (0.678±0.081)	breast, cancer	COSMIC 
19	NPAS4 	G204D (0.65±0.16)	central_nervous_system, cancer	COSMIC 
20	NPAS4 	A210V (0.40±0.10)	liver, cancer	COSMIC 
21	NPAS4 	S219N (0.18±0.15)	large_intestine, cancer	COSMIC 
22	NPAS4 	R220H (0.16±0.15)	large_intestine, cancer	COSMIC 
23	NPAS4 	I236V (0.10±0.10)	NS, cancer	COSMIC 
24	NPAS4 	L322I (0.35±0.10)	large_intestine, cancer	COSMIC 
25	NPAS4 	Q332K (0.43±0.12)	liver, cancer	COSMIC 
26	NPAS4 	L351I (0.59±0.13)	large_intestine, cancer	COSMIC 
27	NPAS4 	R392Q (0.65±0.21)	NS, cancer	COSMIC 
28	NPAS4 	P405L (0.63±0.16)	liver, cancer	COSMIC 
29	NPAS4 	D419N (0.60±0.16)	skin, cancer	COSMIC 
30	NPAS4 	S453C (0.803±0.098)	upper_aerodigestive_tract, cancer	COSMIC 
31	NPAS4 	L455F (0.831±0.089)	skin, cancer	COSMIC 
32	NPAS4 	Q469H (0.71±0.19)	upper_aerodigestive_tract, cancer	COSMIC 
33	NPAS4 	S493L (0.80±0.10)	thyroid, cancer	COSMIC 
34	NPAS4 	P533S (0.79±0.11)	skin, cancer	COSMIC 
35	NPAS4 	P533L (0.79±0.11)	skin, cancer	COSMIC 
36	NPAS4 	S544N (0.71±0.15)	skin, cancer	COSMIC 
37	NPAS4 	Q547H (0.75±0.12)	liver, cancer	COSMIC 

38	NPAS4	T558I (0.60±0.22)	skin, cancer	COSMIC
39	NPAS4	T587M (0.56±0.13)	central_nervous_system, cancer	COSMIC Humsavar
40	NPAS4	G566E (0.48±0.24)	NS, cancer	COSMIC
41	NPAS4	A592V (0.36±0.15)	oesophagus, cancer	COSMIC
42	NPAS4	R595W (0.35±0.16)	kidney, cancer	COSMIC
43	NPAS4	P597S (0.41±0.13)	endometrium, cancer	COSMIC
44	NPAS4	E628G (0.43±0.11)	breast, cancer	COSMIC
45	NPAS4	Q629H (0.42±0.11)	cervix, cancer	COSMIC
46	NPAS4	R634H (0.47±0.13)	pancreas, cancer	COSMIC
47	NPAS4	I639V (0.49±0.11)	liver, cancer	COSMIC
48	NPAS4	D647N (0.585±0.068)	liver, cancer	COSMIC
49	NPAS4	P679L (0.54±0.14)	liver, cancer	COSMIC
50	NPAS4	S683I (0.41±0.16)	liver, cancer	COSMIC
51	NPAS4	T708M (0.71±0.13)	stomach, cancer	COSMIC
52	NPAS4	V710M (0.73±0.13)	oesophagus, cancer	COSMIC
53	NPAS4	D716N (0.846±0.088)	skin, cancer	COSMIC
54	NPAS4	E724K (0.915±0.073)	bone, cancer	COSMIC
55	NPAS4	E725K (0.937±0.059)	skin, cancer	COSMIC
56	NPAS4	D730N (0.951±0.052)	skin, cancer	COSMIC
57	NPAS4	S747F (0.759±0.079)	liver, cancer	COSMIC

hARNT2 (UniProt Q9HBZ2)

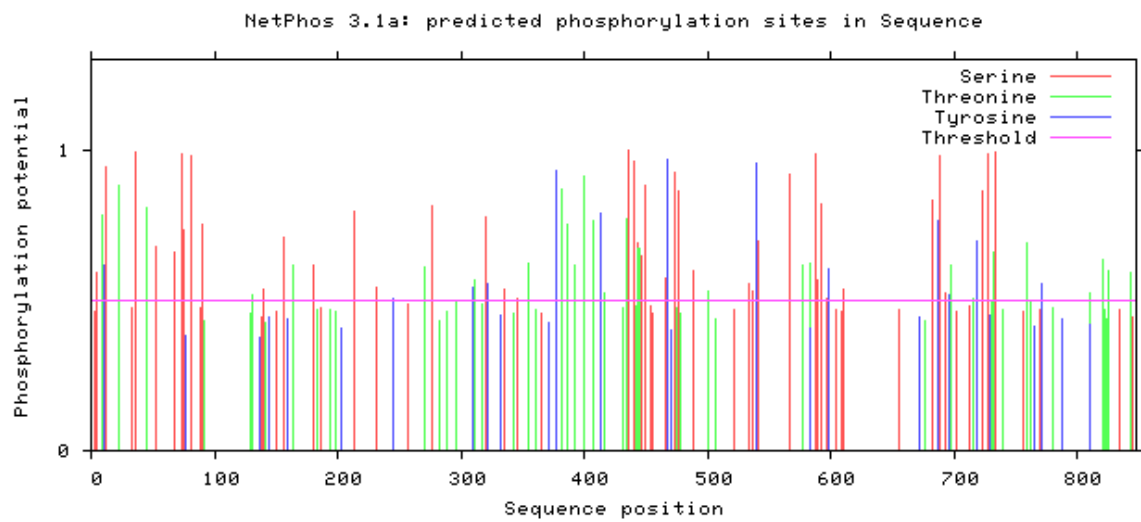
No.	Gene Name	Protein Mutation	Disease / Tissue (COSMIC)	Database
1	ARNT2 	A25T (0.76±0.18)	lung, cancer	COSMIC
2	ARNT2 	A28V (0.76±0.19)	large_intestine, cancer	COSMIC 
3	ARNT2 	G31R (0.78±0.18)	stomach, cancer	COSMIC 
4	ARNT2 	R47C (0.78±0.14)	large_intestine, cancer	COSMIC 
5	ARNT2 	E72K (0.78±0.14)	stomach, cancer	COSMIC 
6	ARNT2 	R76W (0.71±0.12)	endometrium, cancer	COSMIC 
7	ARNT2 	I105V (0.47±0.13)	central_nervous_system, cancer	COSMIC 
8	ARNT2 	V110I (0.51±0.16)	large_intestine, cancer	COSMIC 
9	ARNT2 	V167I (0.30±0.14)	liver, cancer	COSMIC 
10	ARNT2 	D191G (0.442±0.090)	liver, cancer	COSMIC 
11	ARNT2 	R209Q (0.48±0.15)	upper_aerodigestive_tract, cancer	COSMIC 
12	ARNT2 	R240K (0.37±0.20)	large_intestine, cancer	COSMIC 
13	ARNT2 	P269S (0.41±0.12)	pancreas, cancer	COSMIC 
14	ARNT2 	M328I (0.36±0.13)	lung, cancer	COSMIC 
15	ARNT2 	S332L (0.301±0.064)	pancreas, cancer	COSMIC 
16	ARNT2 	S343F (0.219±0.083)	upper_aerodigestive_tract, cancer	COSMIC 
17	ARNT2 	D344N (0.207±0.075)	large_intestine, cancer	COSMIC 
18	ARNT2 	D344G (0.207±0.075)	endometrium, cancer	COSMIC 
19	ARNT2 	R404C (0.18±0.13)	skin, cancer	COSMIC 
20	ARNT2 	P423S (0.15±0.11)	skin, cancer	COSMIC 
21	ARNT2 	Y430N (0.147±0.077)	central_nervous_system, cancer	COSMIC 
22	ARNT2 	S458L (0.52±0.15)	skin, cancer	COSMIC 
23	ARNT2 	P529S (0.62±0.21)	skin, cancer	COSMIC 
24	ARNT2 	H543R (0.58±0.21)	haematopoietic_and_lymphoid_tissue, cancer	COSMIC 
25	ARNT2 	P579S (0.80±0.11)	large_intestine, cancer	COSMIC 
26	ARNT2 	T602M (0.84±0.11)	large_intestine, cancer	COSMIC 
27	ARNT2 	R652Q (0.65±0.28)	large_intestine, cancer	COSMIC 
28	ARNT2 	V683L (0.868±0.040)	lung, cancer	COSMIC 
29	ARNT2 	G710A (0.63±0.16)	liver, cancer	COSMIC 

hBMAL1 (UniProt O00327)

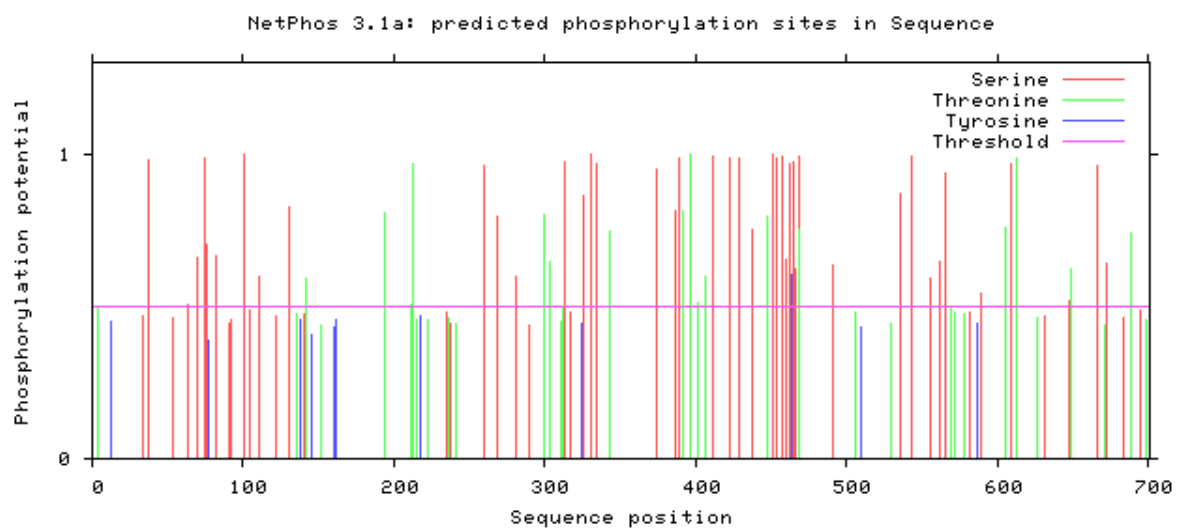
No.	Gene Name	Protein Mutation	Disease / Tissue (COSMIC)	Database
1	ARNTL 	Q4L (0.88±0.12)	liver, cancer	COSMIC 
2	ARNTL 	D22N (0.74±0.15)	large_intestine, cancer	COSMIC 
3	ARNTL 	S27Y (0.74±0.14)	large_intestine, cancer	COSMIC 
4	ARNTL 	R37C (0.76±0.14)	large_intestine, cancer	COSMIC 
5	ARNTL 	R37H (0.76±0.14)	large_intestine, cancer	COSMIC 
6	ARNTL 	E62Q (0.778±0.079)	oesophagus, cancer	COSMIC 
7	ARNTL 	E65K (0.770±0.070)	genital_tract, cancer	COSMIC 
8	ARNTL 	H66P (0.760±0.065)	thyroid, cancer	COSMIC 
9	ARNTL 	I80F (0.76±0.11)	thyroid, cancer	COSMIC 
10	ARNTL 	R83Q (0.69±0.13)	liver, cancer	COSMIC 
11	ARNTL 	R84H (0.68±0.11)	stomach, cancer	COSMIC 
12	ARNTL 	R85Q (0.65±0.14)	ovary, cancer	COSMIC 
13	ARNTL 	M88I (0.58±0.15)	NS, cancer	COSMIC 
14	ARNTL 	S90I (0.50±0.12)	haematopoietic_and_lymphoid_tissue, cancer	COSMIC 
15	ARNTL 	A104T (0.29±0.10)	central_nervous_system, cancer	COSMIC
16	ARNTL 	D110Y (0.301±0.072)	large_intestine, cancer	COSMIC 
17	ARNTL 	T140S (0.23±0.13)	breast, cancer	COSMIC 
18	ARNTL 	D145N (0.17±0.12)	large_intestine, cancer	COSMIC 
19	ARNTL 	D145E (0.17±0.12)	pancreas, cancer	COSMIC 
20	ARNTL 	V162I (0.033±0.022)	biliary_tract, cancer	COSMIC 
21	ARNTL 	R166G (0.045±0.032)	breast, cancer	COSMIC 
22	ARNTL 	Q190E (0.127±0.076)	upper_aerodigestive_tract, cancer	COSMIC 
23	ARNTL 	P198L (0.187±0.097)	skin, cancer	COSMIC 
24	ARNTL 	T224S (0.58±0.18)	stomach, cancer	COSMIC 
25	ARNTL 	P234H (0.54±0.17)	skin, cancer	COSMIC 
26	ARNTL 	R238Q (0.49±0.21)	large_intestine, cancer	COSMIC 
27	ARNTL 	R244Q (0.47±0.24)	large_intestine, cancer	COSMIC 
28	ARNTL 	S246C (0.48±0.24)	cervix, cancer	COSMIC 
29	ARNTL 	C249R (0.50±0.29)	thyroid, cancer	COSMIC 
30	ARNTL 	V260A (0.60±0.22)	large_intestine, cancer	COSMIC 
31	ARNTL 	P292T (0.41±0.16)	pancreas, cancer	COSMIC 
32	ARNTL 	D299Y (0.580±0.056)	liver, cancer	COSMIC 
33	ARNTL 	A345T (0.120±0.045)	liver, cancer	COSMIC 
34	ARNTL 	S372L (0.084±0.056)	breast, cancer	COSMIC 
35	ARNTL 	E375G (0.084±0.056)	large_intestine, cancer	COSMIC 

2) Graphical presentation of the NetPhos 3.1 server phosphorylation sites prediction for hAHR, hAHRR, hSIM1, hSIM2, hHIF2a, hNPAS4, hARNT2, and hBMAL1.

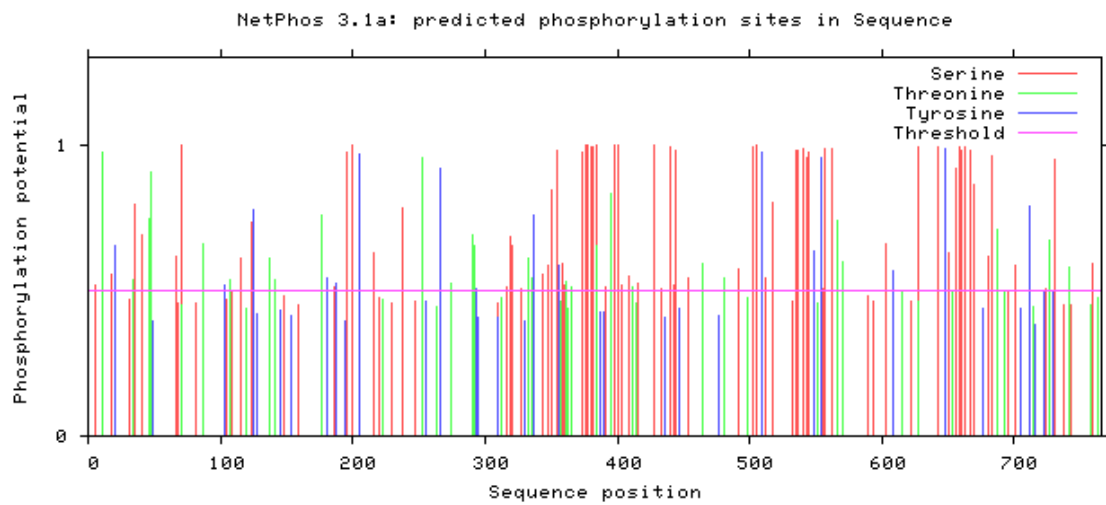
hAHR



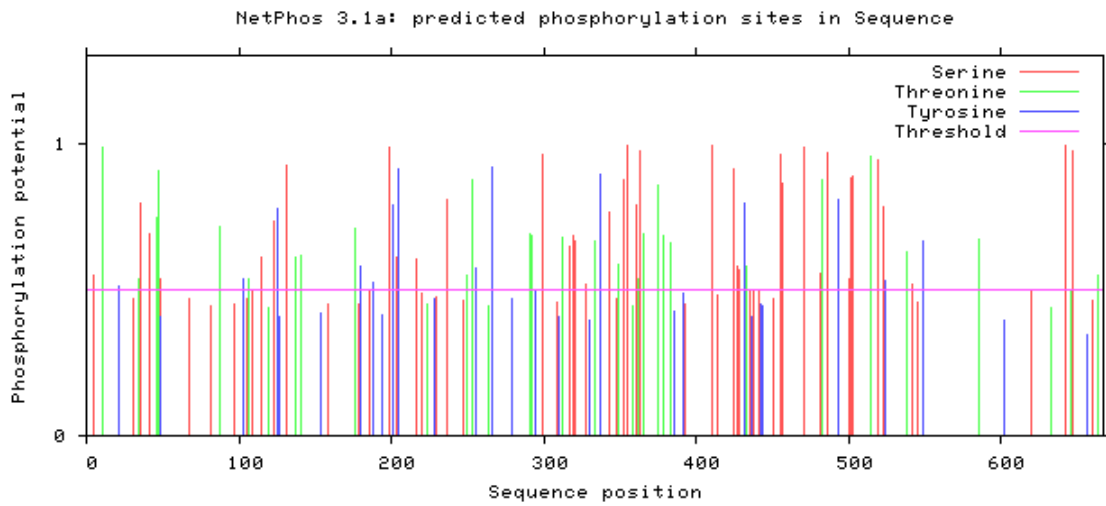
hAHRR



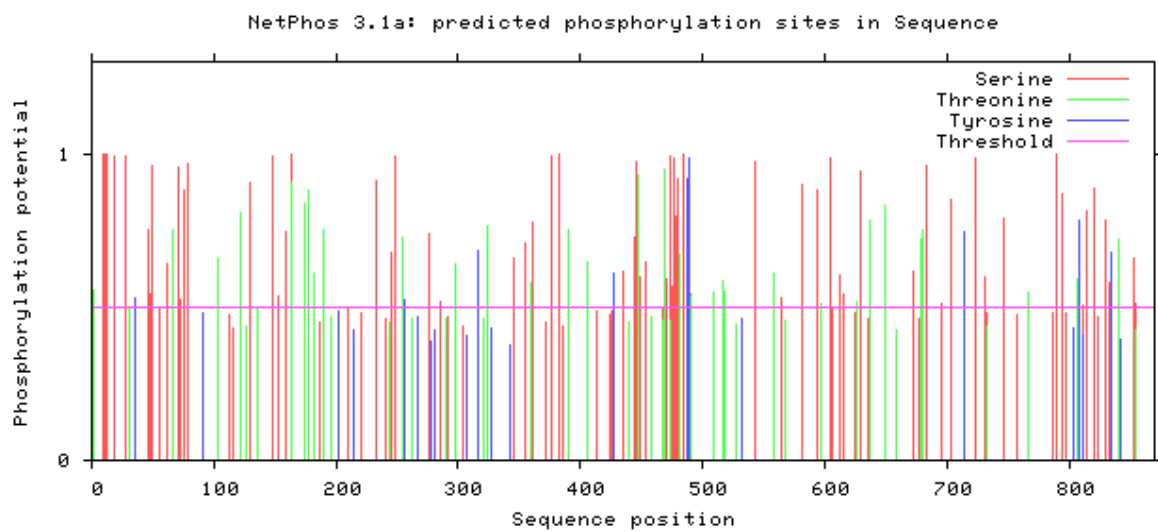
hSIM1



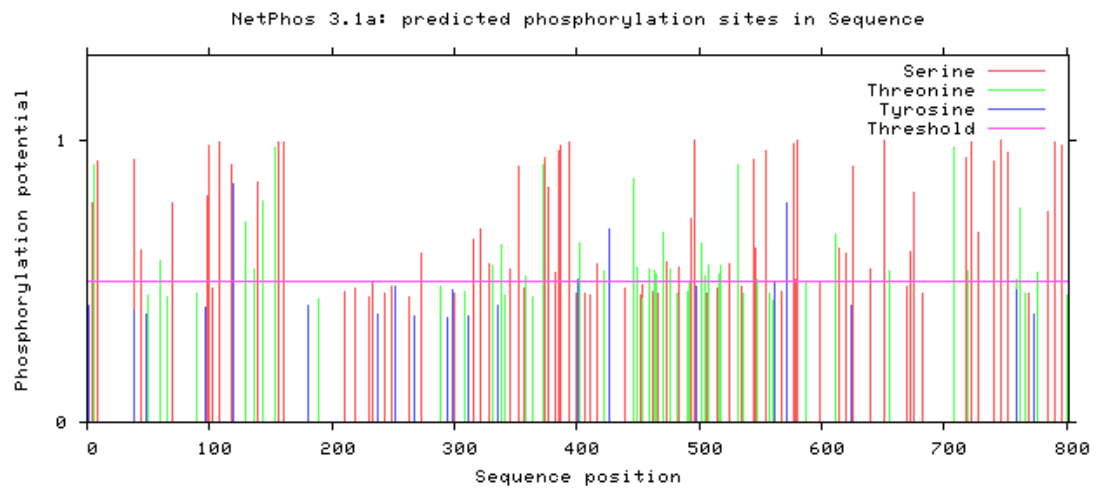
hSIM2



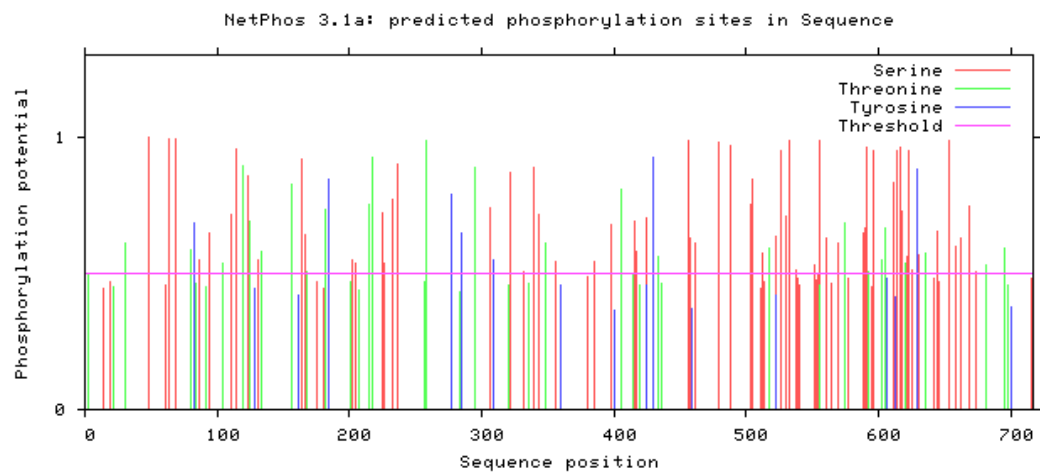
hHIF2a



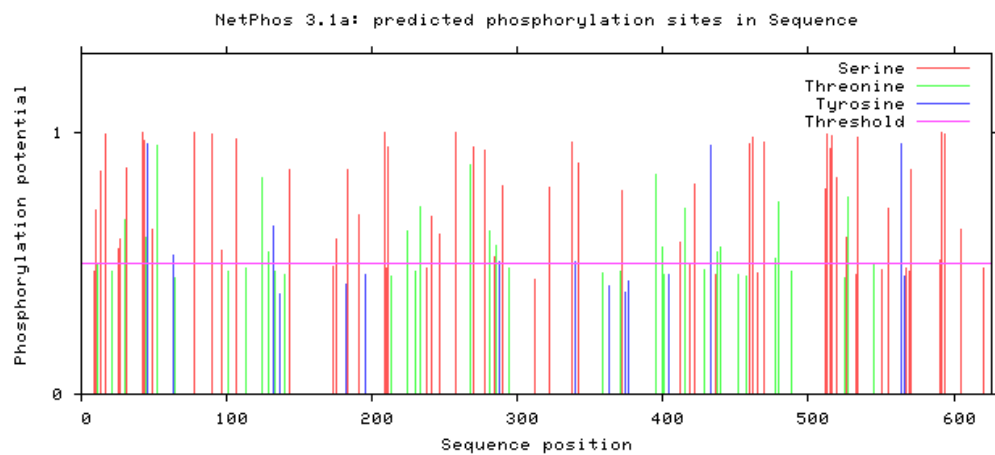
hNPAS4



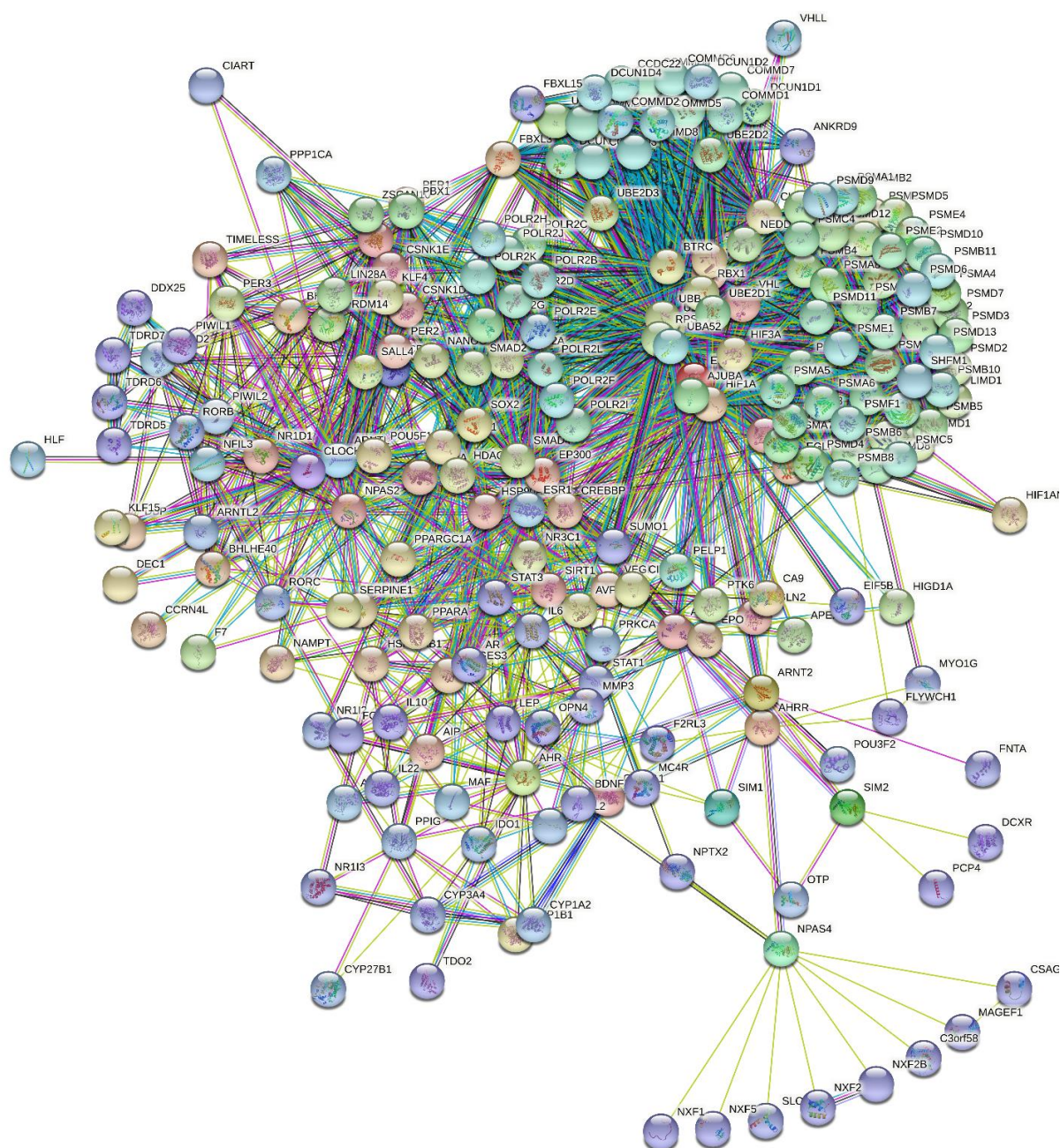
hARNT2



hBMAL1

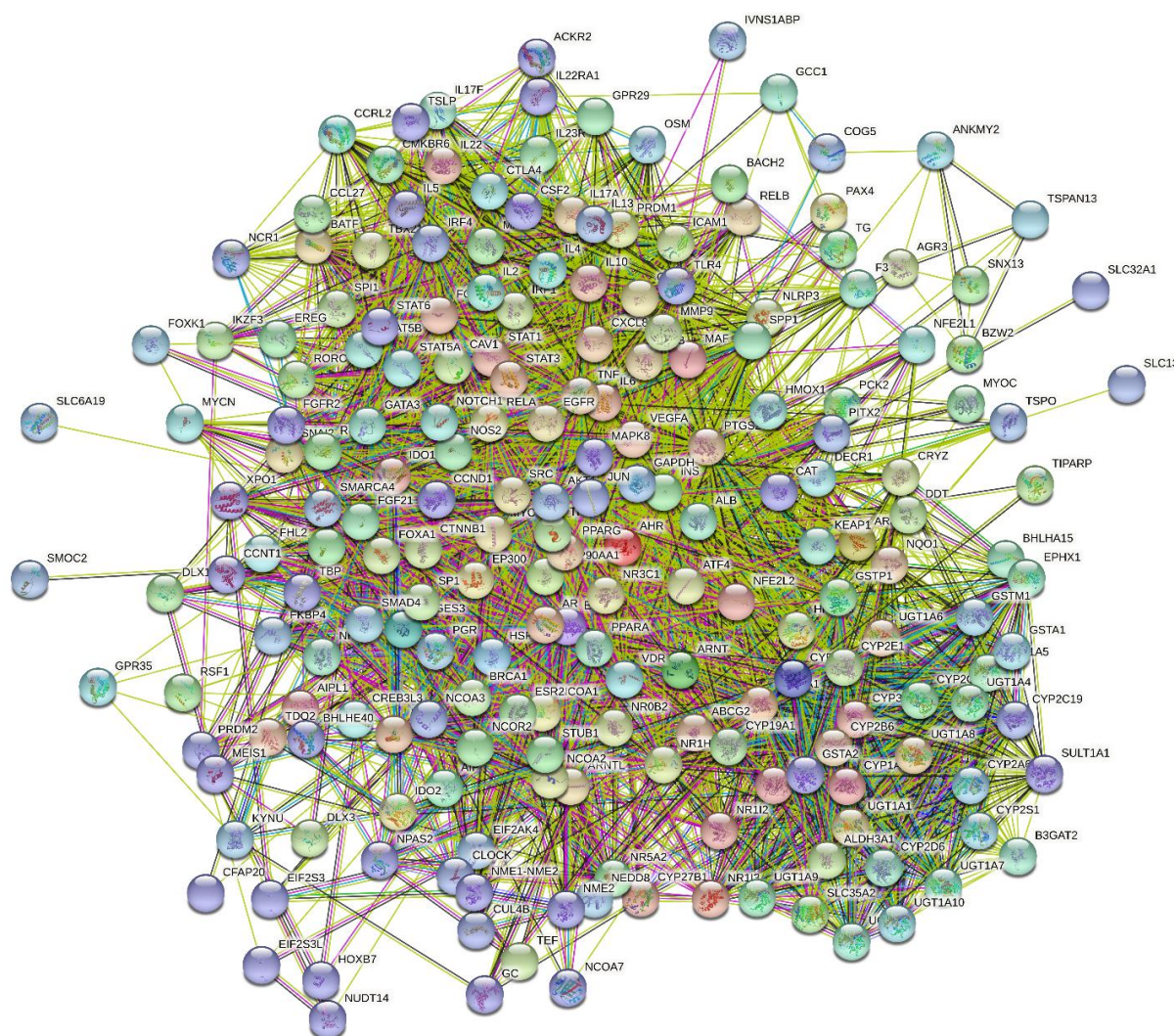


2) STRING-based external interactome of selected bHLH-PAS TFs with the "first shell" interactors.
The confidence level of 0.7 was used in this analysis



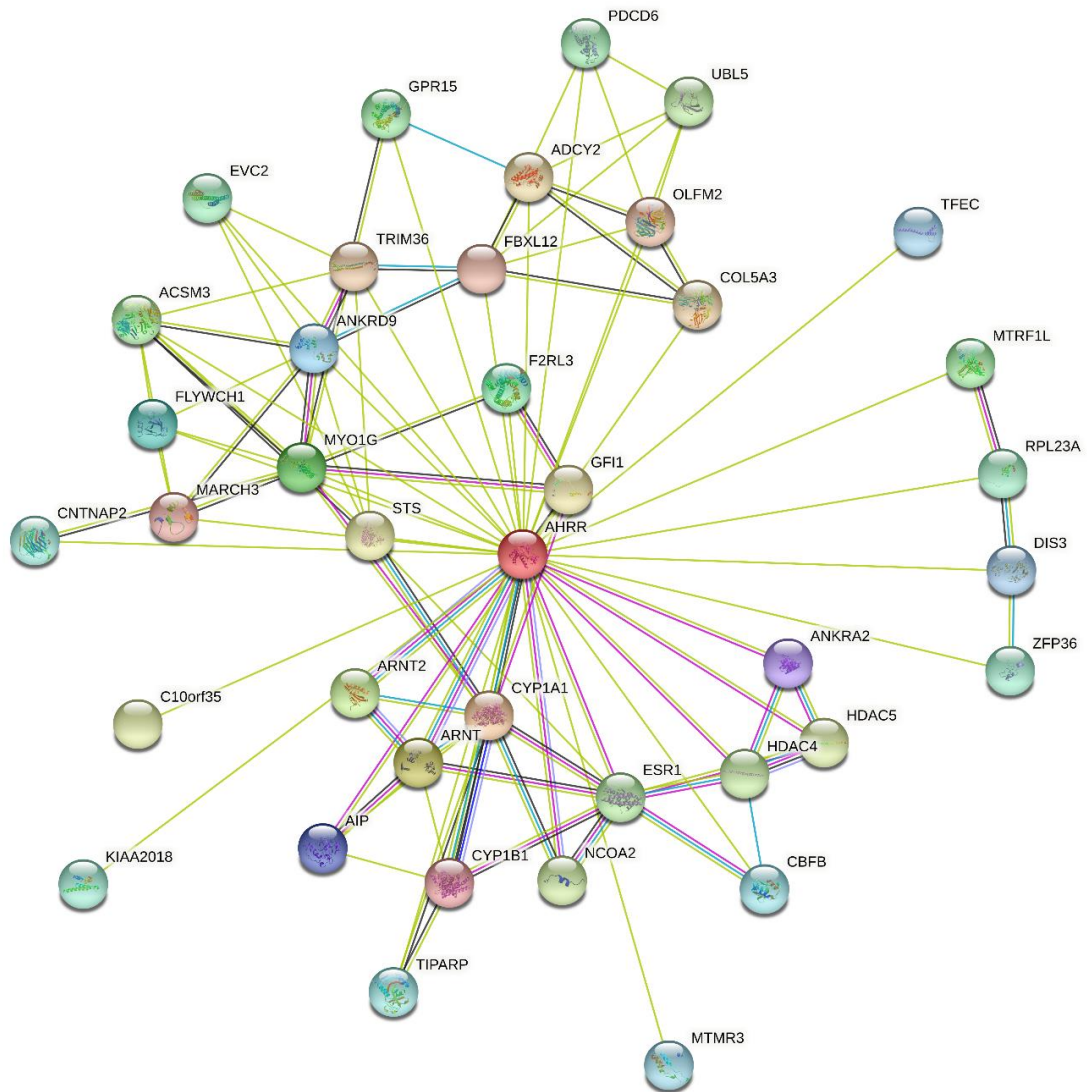
```
Confidence: 0.7
number of nodes: 223
number of edges: 3721
average node degree: 33.4
avg. local clustering coefficient: 0.736
expected number of edges: 1216
PPI enrichment p-value: < 1.0e-16
```

3) Plots of STRING analysis of individual proteins: hAHR, hAHRR, hSIM1, hSIM2, hHIF2a, hNPAS4, hARNT2, and hBMAL1



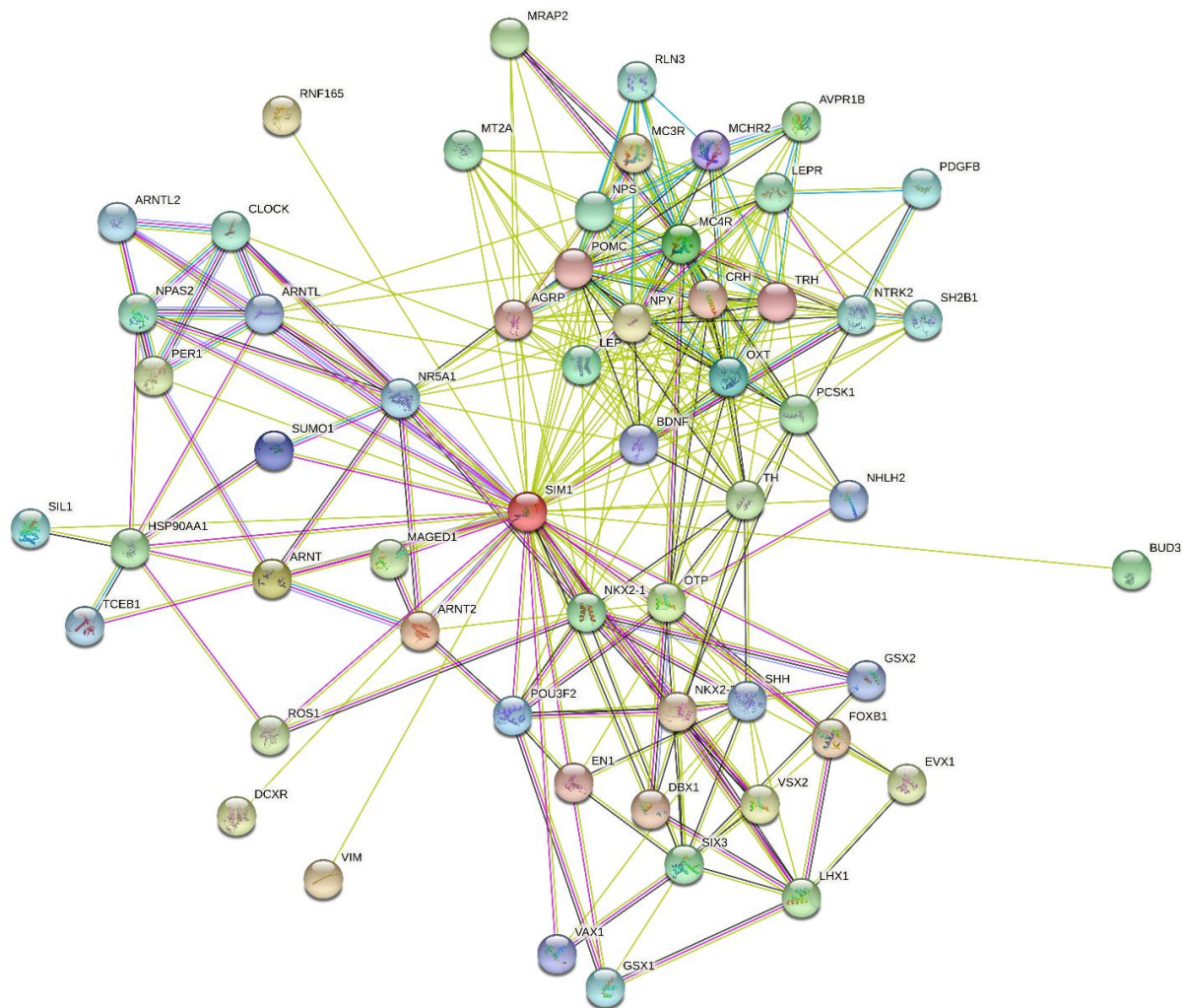
number of nodes: 207
number of edges: 4071
average node degree: 39.3
avg. local clustering coefficient: 0.66
expected number of edges: 1367
PPI enrichment p-value: $< 1.0\text{e-}16$

STRING-based external interactome of AhR with "first shell" interactors with moderate confidence level of 0.4 and corresponding description of this PPI.



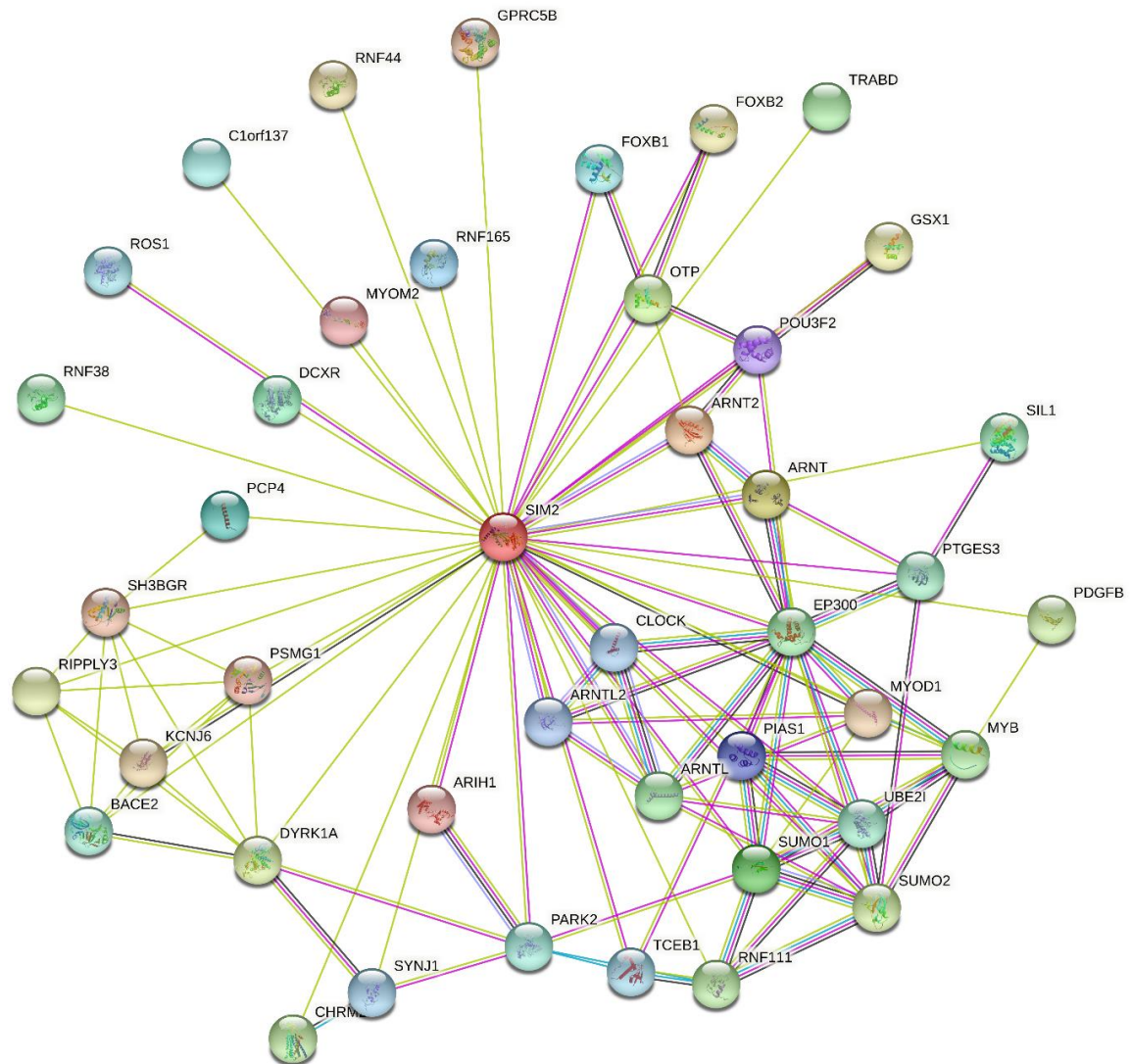
Confidence: 0.4
 number of nodes: 39
 number of edges: 105
 average node degree: 5.38
 avg. local clustering coefficient: 0.809
 expected number of edges: 48
 PPI enrichment p-value: 1.01e-12

STRING-based external interactome of AhRR with "first shell" interactors with moderate confidence level of 0.4 and corresponding description of this PPI.



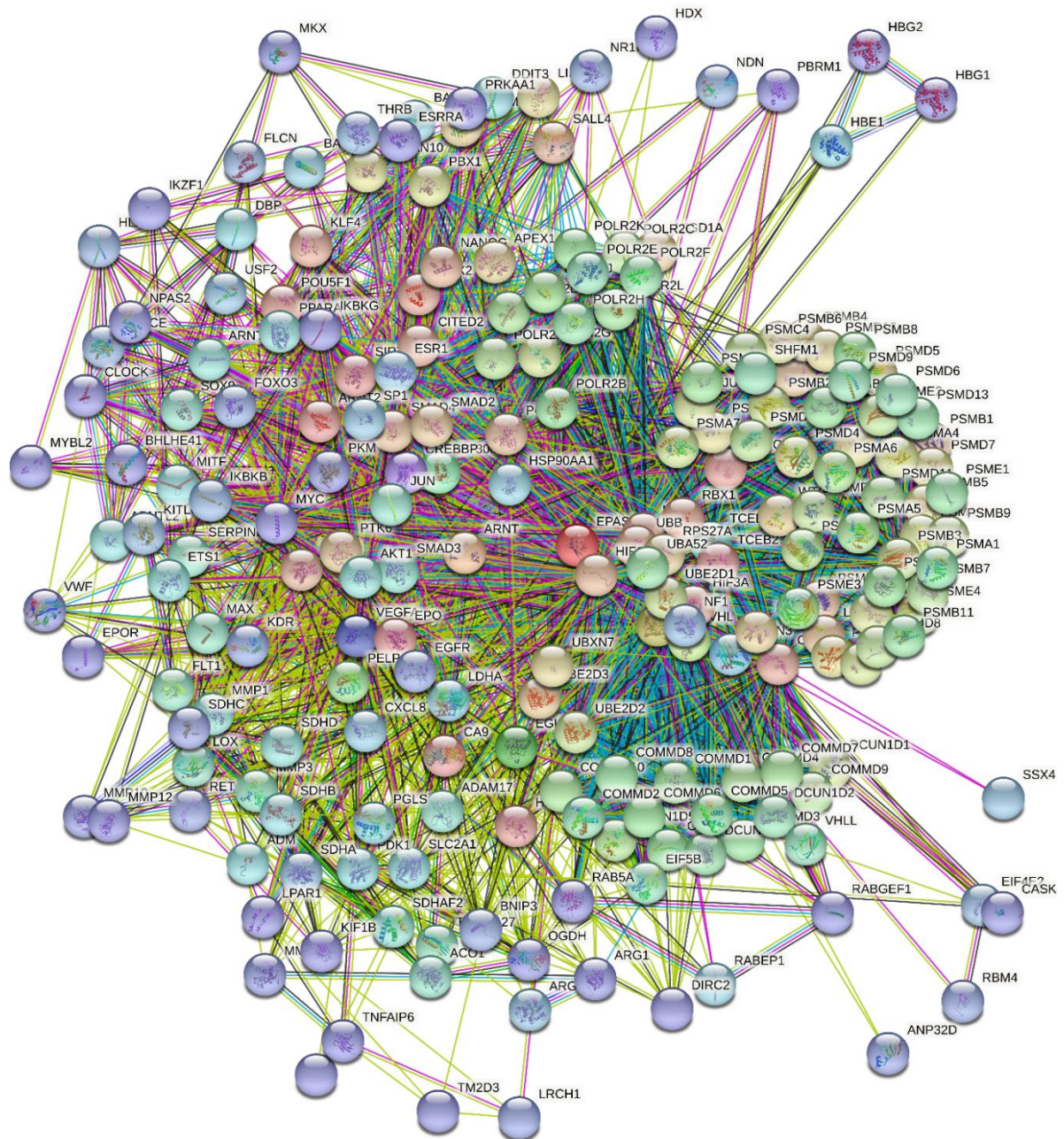
Confidence: 0.4
 Number of nodes: 57
 number of edges: 288
 average node degree: 10.1
 avg. local clustering coefficient: 0.713
 expected number of edges: 92
 PPI enrichment p-value: $< 1.0e-16$

STRING-based external interactome of SIM1 with "first shell" interactors with moderate confidence level of 0.4 and corresponding description of this PPI.



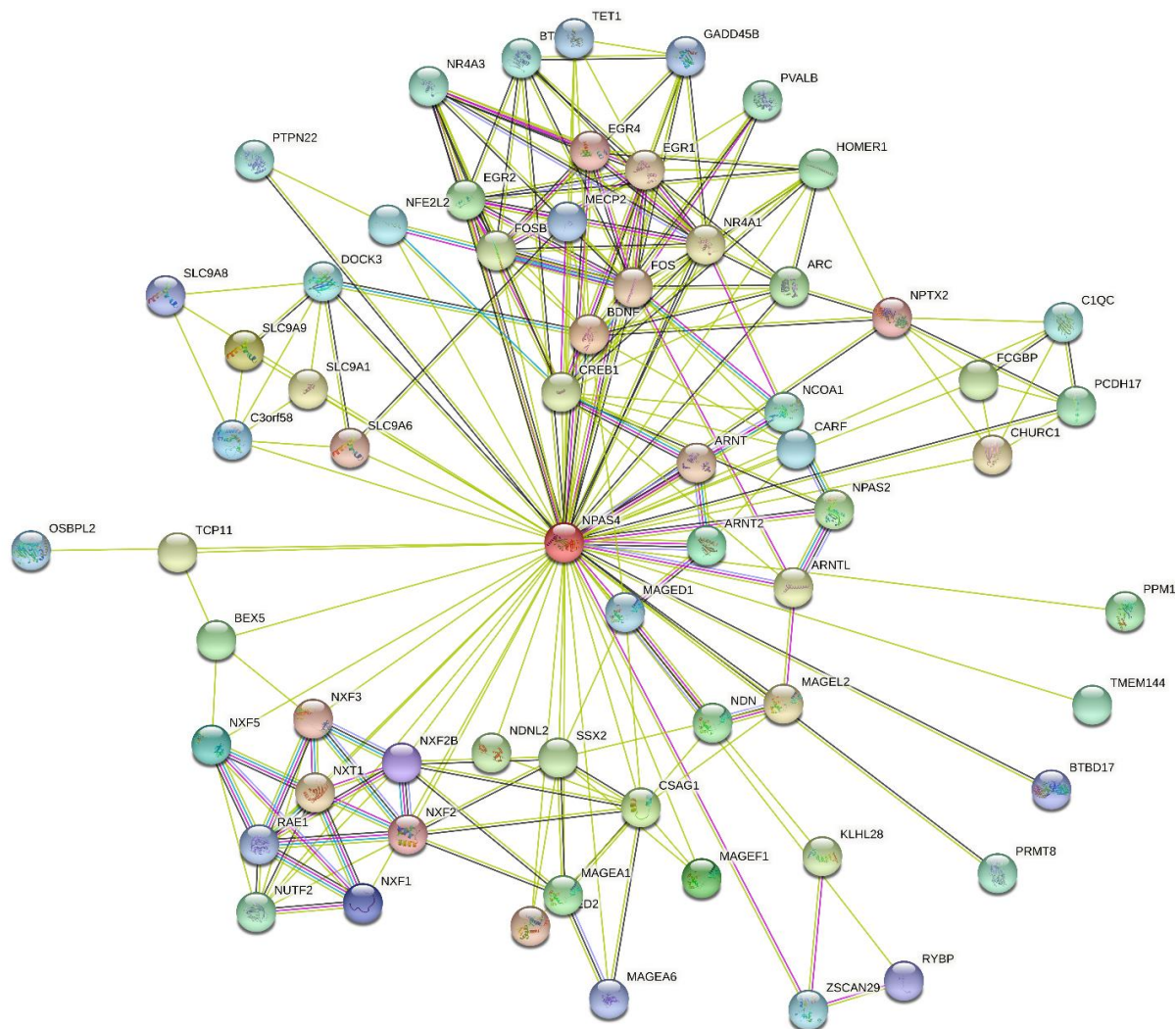
Confidence: 0.4
 number of nodes: 43
 number of edges: 114
 average node degree: 5.3
 avg. local clustering coefficient: 0.826
 expected number of edges: 58
 PPI enrichment p-value: $3.75e-11$

STRING-based external interactome of SIM2 with "first shell" interactors with moderate confidence level of 0.4 and corresponding description of this PPI.



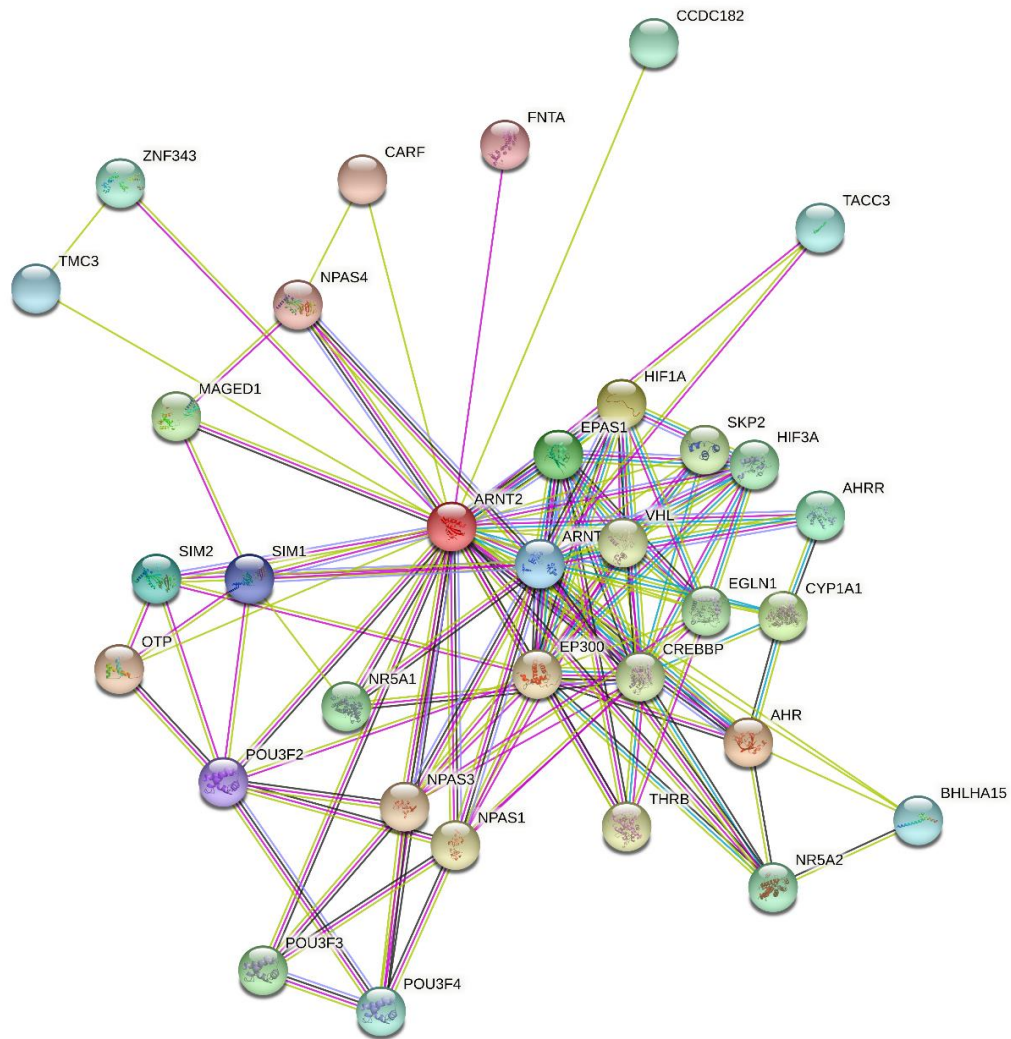
Confidence: 0.4
 number of nodes: 213
 number of edges: 4257
 average node degree: 40
 avg. local clustering coefficient: 0.74
 expected number of edges: 1514
 PPI enrichment p-value: $< 1.0e-16$

STRING-based external interactome of Hif-2 α (EPAS1) with "first shell" interactors with moderate confidence level of 0.4 and corresponding description of this PPI.



Confidence: 0.4
 number of nodes: 64
 number of edges: 223
 average node degree: 6.97
 avg. local clustering coefficient: 0.771
 expected number of edges: 79
 PPI enrichment p-value: $< 1.0e-16$

STRING-based external interactome of NPAS4 with "first shell" interactors with moderate confidence level of 0.4 and corresponding description of this PPI.



Confidence: 0.4
 number of nodes: 33
 number of edges: 117
 average node degree: 7.09
 avg. local clustering coefficient: 0.759
 expected number of edges: 40
 PPI enrichment p-value: $< 1.0e-16$

STRING-based external interactome of ARNT2 with "first shell" interactors with moderate confidence level of 0.4 and corresponding description of this PPI.

