Supplementary Information for: *Module Networks*: Discovering Regulatory Modules and their Condition Specific Regulators from Gene Expression Data

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Candidate Regulators

We compiled a set of 466 candidate regulators whose SGD or YPD annotation suggests a potential regulatory role in the broad sense: both transcription factors and signaling proteins that may have transcriptional impact. We also included genes described to be similar to such regulators. We excluded global regulators, whose regulation is not specific to a small set of genes or processes. The full candidate regulators list is given below, in Table 1.

Table 1. Candidate regulators

#	ORF	Name	#	ORF	Name	#	ORF	Name	#	ORF	Name	#	ORF	Name
1	Yer045c	Aca1	48	Yfr028c	Cdc14	95	Yir023w	Dal81	142	Yjl110c	Gzf3	189	Yjl030w	Mad2
2	Ylr131c	Ace2	49	Yar019c	Cdc15	96	Ynl314w	Dal82	143	Ypr008w	Haa1	190	Yjl013c	Mad3
3	Ydr216w	Adr1	50	Ykl022c	Cdc16	97	Ygr092w	Dbf2	144	Yfl031w	Hac1	191	Ygr288w	Mal13
4	Ydr085c	Afr1	51	Ygl116w	Cdc20	98	Ypr111w	Dbf20	145	Yol089c	Hal9	192	Ybr297w	Mal33
5	Ypl202c	Aft2	52	Yal041w	Cdc24	99	Ydr052c	Dbf4	146	Ylr256w	Hap1	193	Ycr040w	Matalpha1
6	Ydr264c	Akr1	53	Ylr310c	Cdc25	100	Yal013w	Dep1	147	Ygl237c	Hap2	194	Ycr039c	Matalpha2
7	Ycl066w	Alpha1	54	Yfr036w	Cdc26	101	Ypl049c	Dig1	148	Ybl021c	Hap3	195	Yor298c-a	Mbf1
8	Ycl067c	Alpha2	55	Ybl084c	Cdc27	102	Ydr480w	Dig2	149	Ykl109w	Hap4	196	Ydl056w	Mbp1
9	Ynl172w	Apc1	56	Ybr160w	Cdc28	103	Ygl240w	Doc1	150	Yor358w	Hap5	197	Ynl307c	Mck1
10	Ydl008w	Apc11	57	Ydl165w	Cdc36	104	Ydl101c	Dun1	151	Ycr065w	Hcm1	198	Ymr043w	Mcm1
11	Ylr127c	Apc2	58	Ydr168w	Cdc37	105	Ylr228c	Ecm22	152	Ybl008w	Hir1	199	Ynl173c	Mdg1
12	Ydr118w	Apc4	59	Ycr093w	Cdc39	106	Ybr033w	Eds1	153	Yor038c	Hir2	200	Ybr136w	Mec1
13	Yor249c	Apc5	60	Ylr229c	Cdc42	107	Ykl048c	Elm1	154	Yjr140c	Hir3	201	Yor351c	Mek1
14	Ylr102c	Apc9	61	Ymr001c	Cdc5	108	Yjl157c	Far1	155	Ycr097w	Hmra1	202	Yil128w	Met18
15	Ygl180w	Apg1	62	Ycr094w	Cdc50	109	Ypr104c	Fhl1	156	Yor032c	Hms1	203	Yir017c	Met28
16	Ymr042w	Arg80	63	Ygl190c	Cdc55	110	Yil131c	Fkh1	157	Yjr147w	Hms2	204	Ypl038w	Met31
17	Yml099c	Arg81	64	Ydl017w	Cdc7	111	Ynl068c	Fkh2	158	Ylr113w	Hog1	205	Ydr253c	Met32
18	Ydr173c	Arg82	65	Ylr098c	Cha4	112	Yer109c	Flo8	159	Ymr172w	Hot1	206	Ynl103w	Met4
19	Ydr421w	Aro80	66	Yer164w	Chd1	113	Ycl026c-a	Frm2	160	Ybr215w	Hpc2	207	Ypl187w	Mf(alpha 1)
20	Ypr034w	Arp7	67	Ybr274w	Chk1	114	Ybl016w	Fus3	161	Ypl204w	Hrr25	208	Ygl089c	Mf(alpha 2)
21	Ymr033w	Arp9	68	Yor028c	Cin5	115	Ygl254w	Fzf1	162	Yol133w	Hrt1	209	Ygr249w	Mga1
22	Ypr199c	Arr1	69	Yil035c	Cka1	116	Yor178c	Gac1	163	Ygl073w	Hsf1	210	Ylr332w	Mid2
23	Yjl115w	Asf1	70	Yor061w	Cka2	117	Ydr009w	Gal3	164	Ykl101w	Hsl1	211	Ygl035c	Mig1
24	Ydl197c	Asf2	71	Ygl019w	Ckb1	118	Ypl248c	Gal4	165	Ybr133c	Hsl7	212	Ygl209w	Mig2
25	Ykl185w	Ash1	72	Yor039w	Ckb2	119	Yml051w	Gal80	166	Yjr094c	Ime1	213	Ymr036c	Mih1
26	Ygr097w	Ask10	73	Ybr135w	Cks1	120	Yer027c	Gal83	167	Yjl106w	Ime2	214	Yor231w	Mkk1
27	Yor113w	Azf1	74	Ygr108w	Clb1	121	Yfl021w	Gat1	168	Ygl192w	Ime4	215	Ypl140c	Mkk2
28	Ykr099w	Bas1	75	Ypr119w	Clb2	122	Ymr136w	Gat2	169	Yil154c	Imp2	216	Ynl076w	Mks1
29	Yjl095w	Bck1	76	Ydl155w	Clb3	123	Ylr013w	Gat3	170	Ydr123c	Ino2	217	Yer068w	Mot2
30	Yer167w	Bck2	77	Ylr210w	Clb4	124	Yir013c	Gat4	171	Yol108c	Ino4	218	Ymr070w	Mot3
31	Yil033c	Bcy1	78	Ypr120c	Clb5	125	Ygl195w	Gcn1	172	Ybr140c	Ira1	219	Ybr026c	Mrf1
32	Yer155c	Bem2	79	Ygr109c	Clb6	126	Ydr283c	Gcn2	173	Yol081w	Ira2	220	Ynl053w	Msg5
33	Ypl115c	Bem3	80	Ymr199w	Cln1	127	Yfr009w	Gcn20	174	Yhr079c	Ire1	221	Yol116w	Msn1
34	Ypl161c	Bem4	81	Ypl256c	Cln2	128	Yel009c	Gcn4	175	Yor304w	Isw2	222	Ymr037c	Msn2
35	Yjr053w	Bfa1	82	Yal040c	Cln3	129	Ypl075w	Gcr1	176	Ykl032c	Ixr1	223	Ykl062w	Msn4
36	Yer177w	Bmh1	83	Yfr014c	Cmk1	130	Ynl199c	Gcr2	177	Ycl055w	Kar4	224	Ymr164c	Mss11
37	Ydr099w	Bmh2	84	Yol016c	Cmk2	131	Yil130w	Gin1	178	Ycl024w	Kcc4	225	Ymr228w	Mtf1
38	Ygr188c	Bub1	85	Yml057w	Cmp2	132	Ybr045c	Gip1	179	Ycr091w	Kin82	226	Ydr277c	Mth1
39	Ymr055c	Bub2	86	Ylr433c	Cna1	133	Yer054c	Gip2	180	Yll019c	Kns1	227	Ygr023w	Mtl1
40	Yor026w	Bub3	87	Ykl190w	Cnb1	134	Ydr096w	Gis1	181	Yhr082c	Ksp1	228	Yor372c	Ndd1
41	Ydr423c	Cad1	88	Ynl027w	Crz1	135	Yer133w	Glc7	182	Ygr040w	Kss1	229	Yhr124w	Ndt80
42	Yjr122w	Caf17	89	Yil036w	Cst6	136	Ymr311c	Glc8	183	Ylr451w	Leu3	230	Ypr052c	Nhp6a
43	Yfl029c	Cak1	90	Ygl166w	Cup2	137	Yer040w	Gln3	184	Ydl240w	Lrg1	231	Ybr089c-a	Nhp6b
44	Ymr280c	Cat8	91	Ypl177c	Cup9	138	Yhr005c	Gpa1	185	Ygl099w	Lsg1	232	Yil038c	Not3
45	Yjr060w	Cbf1	92	Ybr112c	Cyc8	139	Yer020w	Gpa2	186	Ydr034c	Lys14	233	Ypr072w	Not5
46	Ynl161w	Cbk1	93	Yjl005w	Cyr1	140	Ydl035c	Gpr1	187	Ymr021c	Mac1	234	Ydr043c	Nrg1
47	Yal021c	Ccr4	94	Ykr034w	Dal80	141	Ygl181w	Gts1	188	Ygl086w	Mad1	235	Ybr066c	Nrg2

#	ORF	Name	#	ORF	Name	#	ORF	Name	#	ORF	Name	#	ORF	Name
236	Yal051w	Oaf1	283	Ybl056w	Ptc3	330	Yfr040w	Sap155	377	Ynr031c	Ssk2	424	Ydr207c	Ume6
237	Ynl099c	Oca1	284	Ybr125c	Ptc4	331	Yjl098w	Sap185	378	Ycr073c	Ssk22	425	Ydr213w	Upc2
238	Yhl020c	Opi1	285	Yor090c	Ptc5	332	Ykr028w	Sap190	379	Ylr452c	Sst2	426	Ynl229c	Ure2
239	Ybr279w	Paf1	286	Ydl230w	Ptp1	333	Ygl229c	Sap4	380	Ynl309w	Stb1	427	Ypl230w	Usv1
240	Ydr251w	Pam1	287	Yor208w	Ptp2	334	Yhr205w	Sch9	381	Ymr019w	Stb4	428	Ygl227w	Vid30
241	Yjl128c	Pbs2	288	Yer075c	Ptp3	335	Ykl193c	Sds22	382	Yhr178w	Stb5	429	Yml076c	War1
242	Ynl289w	Pcl1	289	Ykl015w	Put3	336	Ybl066c	Sef1	383	Yor047c	Std1	430	Ynl283c	Wsc2
243	Ygl134w	Pcl10	290	Ypl153c	Rad53	337	Yhr119w	Set1	384	Ylr362w	Ste11	431	Yol105c	Wsc3
244	Yil050w	Pcl7	291	Ydr217c	Rad9	338	Yor140w	Sfl1	385	Yhr084w	Ste12	432	Yhl028w	Wsc4
245	Ypl219w	Pcl8	292	Yor101w	Ras1	339	Ylr336c	Sgd1	386	Yjr086w	Ste18	433	Yor230w	Wtm1
246	Ygl248w	Pde1	293	Ynl098c	Ras2	340	Ypr161c	Sgv1	387	Yfl026w	Ste2	434	Yor229w	Wtm2
247	Yor360c	Pde2	294	Ygl158w	Rck1	341	Yer118c	Sho1	388	Yhl007c	Ste20	435	Yil101c	Xbp1
248	Ygl013c	Pdr1	295	Ylr248w	Rck2	342	Ybl058w	Shp1	389	Ykl178c	Ste3	436	Yjl141c	Yak1
249	Ybl005w	Pdr3	296	Ygl071w	Rcs1	343	Ylr079w	Sic1	390	Yor212w	Ste4	437	Yml007w	Yap1
250	Ylr266c	Pdr8	297	Ydl135c	Rdi1	344	Ydr422c	Sip1	391	Ydr103w	Ste5	438	Yhl009c	Yap3
251	Ykl043w	Phd1	298	Yor380w	Rdr1	345	Ygl208w	Sip2	392	Ycl032w	Ste50	439	Yir018w	Yap5
252	Ydl106c	Pho2	299	Ycr106w	Rds1	346	Ynl257c	Sip3	393	Ydl159w	Ste7	440	Ydr259c	Yap6
253	Yfr034c	Pho4	300	Ypl133c	Rds2	347	Yjl089w	Sip4	394	Ydr310c	Sum1	441	Yol028c	Yap7
254	Yol001w	Pho80	301	Ybr049c	Reb1	348	Ydl047w	Sit4	395	Ygl162w	Sut1	442	Yol128c	Ygk3
255	Ygr233c	Pho81	302	Ydr028c	Reg1	349	Ynl032w	Siw14	396	Yjl187c	Swe1	443	Ydr451c	Yhp1
256	Ypl031c	Pho85	303	Ybr050c	Reg2	350	Yol113w	Skm1	397	Ypl016w	Swi1	444	Ydl235c	Ypd1
257	Ylr273c	Pig1	304	Ylr176c	Rfx1	351	Yhr206w	Skn7	398	Yjl176c	Swi3	445	Ykl126w	Ypk1
258	Yor363c	Pip2	305	Yor127w	Rga1	352	Ynl167c	Sko1	399	Yer111c	Swi4	446	Ymr104c	Ypk2
259	Ybl105c	Pkc1	306	Ymr182c	Rgm1	353	Yor008c	Slg1	400	Ydr146c	Swi5	447	Yor162c	Yrr1
260	Ydr490c	Pkh1	307	Yor107w	Rgs2	354	Yil147c	Sln1	401	Ylr182w	Swi6	448	Yir026c	Yvh1
261	Yol100w	Pkh2	308	Ykl038w	Rgt1	355	Yhr030c	Slt2	402	Yil047c	Syg1	449	Yjl056c	Zap1
262	Ypl268w	Plc1	309	Ydl138w	Rgt2	356	Ypr054w	Smk1	403	Ymr028w	Tap42	450	Ymr273c	Zds1
263	Ydr183w	Plp1	310	Ypr165w	Rho1	357	Ybr182c	Smp1	404	Ybr150c	Tbs1	451	Yml109w	Zds2
264	Yor281c	Plp2	311	Ynl090w	Rho2	358	Ydr477w	Snf1	405	Yor337w	Tea1	452	Ybr0318	
265	Yil122w	Pog1	312	Yhl027w	Rim101	359	Ydr073w	Snf11	406	Ybr083w	Tec1	453	Ybr1622	
266	Ynr052c	Pop2	313	Ymr139w	Rim11	360	Ynr023w	Snf12	407	Yml064c	Tem1	454	Ybr239c	
267	Ydl134c	Pph21	314	Yfl033c	Rim15	361	Yor290c	Snf2	408	Ybr240c	Thi2	455	Yer184c	
268	Ydl188c	Pph22	315	Ypl089c	Rlm1	362	Ydl194w	Snf3	409	Ydl080c	Thi3	456	Yfl052w	
269	Ydr075w	Pph3	316	Ygr044c	Rme1	363	Ygl115w	Snf4	410	Ylr136c	Tis11	457	Yjl103c	
270	Ydr435c	Ppm1	317	Ylr371w	Rom2	364	Ybr289w	Snf5	411	Yjr066w	Tor1	458	Yjl206c	
271	Ylr014c	Ppr1	318	Ypr065w	Rox1	365	Yhl025w	Snf6	412	Ykl203c	Tor2	459	Ykl222c	
272	Ybr276c	Pps1	319	Yer169w	Rph1	366	Ypl002c	Snf8	413	Ygl096w	Tos8	460	Ykr064w	
273	Ygr123c	Ppt1	320	Yil119c	Rpi1	367	Ygl131c	Snt2	414	Yal016w	Tpd3	461	Yll016w	
274	Yml016c	Ppz1	321	Ydl020c	Rpn4	368	Ydr006c	Sok1	415	Yjl164c	Tpk1	462	Yll054c	
275	Ydr436w	Ppz2	322	Yil153w	Rrd1	369	Ymr016c	Sok2	416	Ypl203w	Tpk2	463	Ylr278c	
276	Ykl116c	Prr1	323	Ypl152w	Rrd2	370	Yhr136c	Spl2	417	Ykl166c	Tpk3	464	Ynr063w	
277	Ydl214c	Prr2	324	Ydr303c	Rsc3	371	Ydr523c	Sps1	418	Ycr084c	Tup1	465	Yor172w	
278	Yal017w	Psk1	325	Yhr056c	Rsc30	372	Yer161c	Spt2	419	Yor344c	Tye7	466	Ypr013c	
279	Yll010c	Psr1	326	Yol067c	Rtg1	373	Ykl020c	Spt23	420	Ydl064w	Ubc9			
280	Ylr019w	Psr2	327	Ybl103c	Rtg3	374	Ygr063c	Spt4	421	Ydl170w	Uga3			
281	Ydl006w	Ptc1	328	Yor014w	Rts1	375	Ynl138w	Srv2	422	Yil031w	Ulp2			
282	Yer089c	Ptc2	329	Ydr389w	Sac7	376	Ylr006c	Ssk1	423	Ypl139c	Ume1			

Sample Missing Annotations in SGD/GO (Version 1.311)

While automatic annotation using the Saccharomyces Genome Database is highly useful to evaluate module coherence, we note that the actual coherence levels may be considerably higher, as many genes are not annotated in current databases. Indeed, an in-depth inspection revealed many cases where genes known to be associated with the main process of the module were simply not annotated as such. Below, we provide some examples of such cases. We believe this problem will gradually diminish as the database annotation improves.

- Module 41 (Oxidative stress II, 15 genes) contains as most 8 genes labeled as associated with an oxidative stress response and/or oxidoreductase category (Gpx1, Ydr453c, Ttr1, Trx2, Ccp1, Ahp1, Tsa1, Gre2). However, 4 additional genes should have been included according to the current literature (Ynl134c, Yml131w, Atr1, Gsh1), resulting in an increase in coherence from ~50% to 80%.
- Module 34 (mitochondrial and protein fate, 37 genes) is not annotated with "mitochondrion". However, it includes 11 mitochondrial genes (~30%). Only 3 of these genes were labeled as "mitochondrion" in SGD. Thus, the automatic annotation scheme both reduces the actual coherence level of the module and misses an important annotation, which is likely to be significant (there are 91 genes annotated "mitochondrion" in our input set).
- Module 28 (cell wall and transport, 63 genes) receives only general automatic annotations (e.g., "cell growth and/or maintenance"). However inspection of individual genes indicates the presence of genes in categories such as cell wall function or biogenesis proteins (7/63, Ssd1, Ecm10, Rom1, Ecm12, Pkh2, Dfg16, Ymr085w). Only three of those (Rom1, Ecm12, Pkh2) were annotated as such in SGD, and hence the annotation was not significant (p=0.13).

Literature References for Table 1 (Summary of Module Analysis and Validation)

Regulation programs were evaluated by comparing the known function of their associated regulator with the method's predictions where known function is based on a compiled list of literature references in which direct experimental evidence exists for the role of the predicted regulators. Each regulator was assigned three scores: **M**, enrichment for a motif known to participate in regulation by the respective regulator, in promoters of genes in the module; **C**, experimental evidence for contribution of the respective regulator to the transcriptional response under the predicted conditions; **G**, direct experimental evidence showing that at least one of the genes in the module, or a process significantly over-represented in the module genes, is regulated by the respective regulator. Filled boxes for these scores in Table 1 indicate biological experiments confirming the prediction, washed-out colored boxes indicate indirect or partial evidence. Below, in supplementary information Table 2, we provide the full list of references that were the basis for assigning the above scores.

Table 2. References for Table 1 from the paper

#	*Module*	*Regulator*	*M*	*C*	*G*
1	Respiration and carbon regulation	Hap4	1	2,3	2
		Alpha2			
		Cmk1			
		Gac1		4,5	6
		Xbp1		7,8	
		Msn4	9	10-12	
2	Energy, osmolarity and cAMP signaling	Tpk1	13-15	12,16,17	12,13,18,19
		Kin82			
		Yer184c			
		Cmk1			
		Ppt1		20	
		Kns1			
3	Energy and Osmotic stress I	Xbp1		7,8	
		Kin82			
		Tpk1	13	12,13	13,21-23
4	Energy and Osmotic stress II	Ypl230w			
		Yap6			
		Gac1	24,25	5	6
		Wsc4		26	26,27
5	Glycolysis and Folding	Gcn20			
		Ecm22			
		Bmh1			
		Bas1			
6	Galactose metabolism	Gal4	28	25	25
		Gac1		5	
		Hir1			
		Ime4			
7	Snf kinase regulated processes	Ypl230w			
		Yap6			
		Tos8			
		Sip2	29,30	25	31-34
8	Nitrogen catabolite repression	Gat1	35	35	35,36
		Plp2			
9	AA metabolism I	Gat1	35	35	35,37
		Ime4		38	
		Cdc20			
		Slt2		39	
10	AA metabolism II	Xbp1		7,8	7,40
		Hap4			
		Afr1			
		Ppt1			
		Uga3		41	

# Module	Regulator	M	C	G
11 AA and purine metabolism	Gat1		35	37,42
	Ppz1			
	Rim11			
12 Nuclear	Alpha2			43
	Ino2			
13 Mixed I	Pph3			
	Ras2		10,44	
	Tpk1		13,45	
14 Ribosomal and phosphate metabolism	Ppt1			
	Sip2		25	
	Cad1		46	
15 mRNA,rRNA and tRNA processing	Lsg1			
	Tpk2		20,47	
	Ppt1		20	
16 RNA Processing and Cell Cycle	Ypl230w			
	Ime4	48	38	49
	Ppt1			
	Tpk2		13	
	Rho2			
	Mcm1			50
17 DNA and RNA processing	Tpk1		12,16,17	
	Gis1		51	
	Ppt1		20	
18 TFs and RNA processing	Gis1			
	Pph3		52-54	
	Lsg1			
	Tpk2		13	
19 TFs and nuclear transport	Ypl230w			
	Met18			
	Ppt1		20	
20 TFs I	Cdc14			
	Mcm1			55,56
	Ksp1			
21 TFs II				
22 TFs, cell wall and mating	Ptc3			
	Sps1	57,58		59
23 TFs and sporulation	Rcs1			60
	Ypl133c			
24 Sporulation and TFs	Gcn20			
	Gat1			
	Ste5			

# Module	Regulator	M	C	G
25 Sporulation and cAMP pathway	Xbp1		7,8	61
	Ypl230w			
	Sip2	25,29	25	25,62
	Not3			
26 Sporulation and Cell wall	Ypl230w			
	Yap6			
	Msn4		63	
27 Cell wall and transport I	Shp1			
	Bcy1		64,65	
	Gal80		25	
	Yak1			
	Ime1		38	
28 Cell wall and Transport II	Ypl230w			
	Kin82			
	Msn4	9	12	
29 Cell differentiation	Ypl230w			
	Ypk1			66-68
	Cna1			69-72
30 Cell cycle (G2/M)	Cdc14			73,74
	Clb1		75	76,77
	Far1			78
31 Cell cycle, TFs and DNA metabolism	Gis1			
	Ste5			
	Clb5			79
32 Cell cycle and general TFs	Ime4		38	49
	Ume1		80	80
	Xbp1		7,8	7,40
	Prr1			
	Arp9			
	Cnb1		70	69,70
33 Mitochondrial and Signaling	Tpk1	13	16	19
	Cmk1			
	Yer184c			
	Gis1		51	
34 Mitochondrial and Protein fate	Yak1	81	45,64,65	
	Sds22			
	Rsc3			
35 Trafficking and Mitochondrial	Tpk1		16	17,19,82
	Sds22			
	Mrf1’			
36 ER and Nuclear	Gcn20		83,84	84
	Yjl103c			
	Not3			85,86
	Tup1		87	

# *Module*	*Regulator*	*M*	*C*	*G*
37 Proteasome and Endocytosis	Ime4		38	
	Cup9			88
	Bmh1			
	Hrt1			89
38 Protein modification and trafficking	Ypl230w			
	Ptc3		90	90
	Cdc42			
39 Protein folding	Bmh1			
	Bcy1		64,65	65,91
	Ypl230w			
40 Oxidative stress I	Yap1	92	93	92
	Far1			
	Sko1			94
41 Oxidative stress II	Tos8			
	Flo8			
42 Unkown (sub-telomeric)	Gcn20			
43 Unknown genes I				
44 Unknown genes II	Apg1		31,95	96
	Pcl10			
45 Unknown genes III	Xbp1		7,8	
	Kar4			
46 Mixed II	Gcn20			
	Tos8			
	Sip2		25	
47 Mixed III	Gcn20		83,84	84
	Ume1		80	
	Cnb1			69
48 Mixed IV	Fkh1			
	Cbf1			
	Sho1			
49 Ty ORFs				
50 Missing values				

References for Table 2

1. Forsburg, S.L. & Guarente, L. Identification and characterization of HAP4: a third component of the CCAAT-bound HAP2/HAP3 heteromer. *Genes Dev* **3**, 1166-78 (1989).
2. Bourgarel, D., Nguyen, C.C. & Bolotin-Fukuhara, M. HAP4, the glucose-repressed regulated subunit of the HAP transcriptional complex involved in the fermentation-respiration shift, has a functional homologue in the respiratory yeast Kluyveromyces lactis. *Mol Microbiol* **31**, 1205-15 (1999).

3. Flattery-O'Brien, J.A., Grant, C.M. & Dawes, I.W. Stationary-phase regulation of the *Saccharomyces cerevisiae* SOD2 gene is dependent on additive effects of HAP2/3/4/5- and STRE-binding elements. *Mol Microbiol* **23**, 303-12 (1997).
4. Lin, J.T. & Lis, J.T. Glycogen synthase phosphatase interacts with heat shock factor to activate CUP1 gene transcription in *Saccharomyces cerevisiae*. *Mol Cell Biol* **19**, 3237-45 (1999).
5. Parrou, J.L. et al. Dynamic responses of reserve carbohydrate metabolism under carbon and nitrogen limitations in *Saccharomyces cerevisiae*. *Yeast* **15**, 191-203 (1999).
6. Wu, X., Hart, H., Cheng, C., Roach, P.J. & Tatchell, K. Characterization of Gac1p, a regulatory subunit of protein phosphatase type I involved in glycogen accumulation in *Saccharomyces cerevisiae*. *Mol Genet Genomics* **265**, 622-35 (2001).
7. Mai, B. & Breeden, L. Xbp1, a stress-induced transcriptional repressor of the *Saccharomyces cerevisiae* Swi4/Mbp1 family. *Mol Cell Biol* **17**, 6491-501 (1997).
8. Miled, C., Mann, C. & Faye, G. Xbp1-mediated repression of CLB gene expression contributes to the modifications of yeast cell morphology and cell cycle seen during nitrogen-limited growth. *Mol Cell Biol* **21**, 3714-24 (2001).
9. Moskvina, E., Schuller, C., Maurer, C.T., Mager, W.H. & Ruis, H. A search in the genome of *Saccharomyces cerevisiae* for genes regulated via stress response elements. *Yeast* **14**, 1041-50 (1998).
10. Hong, S.K., Cha, M.K., Choi, Y.S., Kim, W.C. & Kim, I.H. Msn2p/Msn4p act as a key transcriptional activator of yeast cytoplasmic thiol peroxidase II. *J Biol Chem* **277**, 12109-17 (2002).
11. Rep, M., Krantz, M., Thevelein, J.M. & Hohmann, S. The transcriptional response of *Saccharomyces cerevisiae* to osmotic shock. Hot1p and Msn2p/Msn4p are required for the induction of subsets of high osmolarity glycerol pathway-dependent genes. *J Biol Chem* **275**, 8290-300 (2000).
12. Garreau, H. et al. Hyperphosphorylation of Msn2p and Msn4p in response to heat shock and the diauxic shift is inhibited by cAMP in *Saccharomyces cerevisiae*. *Microbiology* **146 (Pt 9)**, 2113-20 (2000).
13. Norbeck, J. & Blomberg, A. The level of cAMP-dependent protein kinase A activity strongly affects osmotolerance and osmo-instigated gene expression changes in *Saccharomyces cerevisiae*. *Yeast* **16**, 121-37 (2000).
14. Denis, C.L., Kemp, B.E. & Zoller, M.J. Substrate specificities for yeast and mammalian cAMP-dependent protein kinases are similar but not identical. *J Biol Chem* **266**, 17932-5 (1991).
15. Zaragoza, O. & Gancedo, J.M. Elements from the cAMP signaling pathway are involved in the control of expression of the yeast gluconeogenic gene FBP1. *FEBS Lett* **506**, 262-6 (2001).
16. Reinders, A., Burckert, N., Boller, T., Wiemken, A. & De Virgilio, C. *Saccharomyces cerevisiae* cAMP-dependent protein kinase controls entry into stationary phase through the Rim15p protein kinase. *Genes Dev* **12**, 2943-55 (1998).

17. Pan, X. & Heitman, J. Cyclic AMP-dependent protein kinase regulates pseudohyphal differentiation in *Saccharomyces cerevisiae*. *Mol Cell Biol* **19**, 4874-87 (1999).
18. Thevelein, J.M. & de Winde, J.H. Novel sensing mechanisms and targets for the cAMP-protein kinase A pathway in the yeast *Saccharomyces cerevisiae*. *Mol Microbiol* **33**, 904-18 (1999).
19. Dejean, L. et al. cAMP-induced modulation of the growth yield of *Saccharomyces cerevisiae* during respiratory and respiro-fermentative metabolism. *Biochim Biophys Acta* **1554**, 159-69 (2002).
20. Morita, K. et al. Negative feedback regulation of ASK1 by protein phosphatase 5 (PP5) in response to oxidative stress. *Embo J* **20**, 6028-36 (2001).
21. Boy-Marcotte, E., Perrot, M., Bussereau, F., Boucherie, H. & Jacquet, M. Msn2p and Msn4p control a large number of genes induced at the diauxic transition which are repressed by cyclic AMP in *Saccharomyces cerevisiae*. *J Bacteriol* **180**, 1044-52 (1998).
22. Parrou, J.L., Enjalbert, B. & Francois, J. STRE- and cAMP-independent transcriptional induction of *Saccharomyces cerevisiae* GSY2 encoding glycogen synthase during diauxic growth on glucose. *Yeast* **15**, 1471-84 (1999).
23. Geymonat, M., Wang, L., Garreau, H. & Jacquet, M. Ssa1p chaperone interacts with the guanine nucleotide exchange factor of ras Cdc25p and controls the cAMP pathway in *Saccharomyces cerevisiae*. *Mol Microbiol* **30**, 855-64 (1998).
24. De Vit, M.J., Waddle, J.A. & Johnston, M. Regulated nuclear translocation of the Mig1 glucose repressor. *Mol Biol Cell* **8**, 1603-18 (1997).
25. Gancedo, J.M. Yeast carbon catabolite repression. *Microbiol Mol Biol Rev* **62**, 334-61 (1998).
26. Zu, T., Verna, J. & Ballester, R. Mutations in WSC genes for putative stress receptors result in sensitivity to multiple stress conditions and impairment of Rlm1-dependent gene expression in *Saccharomyces cerevisiae*. *Mol Genet Genomics* **266**, 142-55 (2001).
27. Alonso-Monge, R. et al. Hyperosmotic stress response and regulation of cell wall integrity in *Saccharomyces cerevisiae* share common functional aspects. *Mol Microbiol* **41**, 717-30 (2001).
28. Ren, B. et al. Genome-wide location and function of DNA binding proteins. *Science* **290**, 2306-9 (2000).
29. Young, E.T., Kacherovsky, N. & Van Riper, K. Snf1 protein kinase regulates Adr1 binding to chromatin but not transcription activation. *J Biol Chem* **277**, 38095-103 (2002).
30. Mayordomo, I., Estruch, F. & Sanz, P. Convergence of the target of rapamycin and the Snf1 protein kinase pathways in the regulation of the subcellular localization of Msn2, a transcriptional activator of STRE (Stress Response Element)-regulated genes. *J Biol Chem* **277**, 35650-6 (2002).
31. Wang, Z., Wilson, W.A., Fujino, M.A. & Roach, P.J. Antagonistic controls of autophagy and glycogen accumulation by Snf1p, the yeast homolog of AMP-activated protein kinase, and the cyclin-dependent kinase Pho85p. *Mol Cell Biol* **21**, 5742-52 (2001).

32. Schmidt, M.C. & McCartney, R.R. beta-subunits of Snf1 kinase are required for kinase function and substrate definition. *Embo J* **19**, 4936-43 (2000).
33. Ozcan, S. & Johnston, M. Function and regulation of yeast hexose transporters. *Microbiol Mol Biol Rev* **63**, 554-69 (1999).
34. Wright, R.M. & Poyton, R.O. Release of two *Saccharomyces cerevisiae* cytochrome genes, COX6 and CYC1, from glucose repression requires the SNF1 and SSN6 gene products. *Mol Cell Biol* **10**, 1297-300 (1990).
35. ter Schure, E.G., van Riel, N.A. & Verrips, C.T. The role of ammonia metabolism in nitrogen catabolite repression in *Saccharomyces cerevisiae*. *FEMS Microbiol Rev* **24**, 67-83 (2000).
36. Coffman, J.A., Rai, R., Cunningham, T., Svetlov, V. & Cooper, T.G. Gat1p, a GATA family protein whose production is sensitive to nitrogen catabolite repression, participates in transcriptional activation of nitrogen-catabolic genes in *Saccharomyces cerevisiae*. *Mol Cell Biol* **16**, 847-58 (1996).
37. Stanbrough, M., Rowen, D.W. & Magasanik, B. Role of the GATA factors Gln3p and Nil1p of *Saccharomyces cerevisiae* in the expression of nitrogen-regulated genes. *Proc Natl Acad Sci U S A* **92**, 9450-4 (1995).
38. Shah, J.C. & Clancy, M.J. IME4, a gene that mediates MAT and nutritional control of meiosis in *Saccharomyces cerevisiae*. *Mol Cell Biol* **12**, 1078-86 (1992).
39. Hahn, J.S. & Thiele, D.J. Regulation of the *Saccharomyces cerevisiae* Slt2 kinase pathway by the stress-inducible Sdp1 dual specificity phosphatase. *J Biol Chem* **277**, 21278-84 (2002).
40. Xu, H., Kim, U.J., Schuster, T. & Grunstein, M. Identification of a new set of cell cycle-regulatory genes that regulate S-phase transcription of histone genes in *Saccharomyces cerevisiae*. *Mol Cell Biol* **12**, 5249-59 (1992).
41. Vissers, S., Andre, B., Muyldermans, F. & Grenson, M. Induction of the 4-aminobutyrate and urea-catabolic pathways in *Saccharomyces cerevisiae*. Specific and common transcriptional regulators. *Eur J Biochem* **187**, 611-6 (1990).
42. Soussi-Boudekou, S., Vissers, S., Urrestarazu, A., Jauniaux, J.C. & Andre, B. Gzf3p, a fourth GATA factor involved in nitrogen-regulated transcription in *Saccharomyces cerevisiae*. *Mol Microbiol* **23**, 1157-68 (1997).
43. Zhong, H., McCord, R. & Vershon, A.K. Identification of target sites of the alpha2-Mcm1 repressor complex in the yeast genome. *Genome Res* **9**, 1040-7 (1999).
44. Verna, J., Lodder, A., Lee, K., Vagts, A. & Ballester, R. A family of genes required for maintenance of cell wall integrity and for the stress response in *Saccharomyces cerevisiae*. *Proc Natl Acad Sci U S A* **94**, 13804-9 (1997).
45. Charizanis, C., Juhnke, H., Krems, B. & Entian, K.D. The oxidative stress response mediated via Pos9/Skn7 is negatively regulated by the Ras/PKA pathway in *Saccharomyces cerevisiae*. *Mol Gen Genet* **261**, 740-52 (1999).
46. Stephen, D.W., Rivers, S.L. & Jamieson, D.J. The role of the YAP1 and YAP2 genes in the regulation of the adaptive oxidative stress responses of *Saccharomyces cerevisiae*. *Mol Microbiol* **16**, 415-23 (1995).

47. Cameron, S., Levin, L., Zoller, M. & Wigler, M. cAMP-independent control of sporulation, glycogen metabolism, and heat shock resistance in *S. cerevisiae*. *Cell* **53**, 555-66 (1988).
48. Bowdish, K.S. & Mitchell, A.P. Bipartite structure of an early meiotic upstream activation sequence from *Saccharomyces cerevisiae*. *Mol Cell Biol* **13**, 2172-81 (1993).
49. Colomina, N., Gari, E., Gallego, C., Herrero, E. & Aldea, M. G1 cyclins block the Ime1 pathway to make mitosis and meiosis incompatible in budding yeast. *Embo J* **18**, 320-9 (1999).
50. Kumar, R., Reynolds, D.M., Shevchenko, A., Goldstone, S.D. & Dalton, S. Forkhead transcription factors, Fkh1p and Fkh2p, collaborate with Mcm1p to control transcription required for M-phase. *Curr Biol* **10**, 896-906 (2000).
51. Pedruzzi, I., Burckert, N., Egger, P. & De Virgilio, C. *Saccharomyces cerevisiae* Ras/cAMP pathway controls post-diauxic shift element-dependent transcription through the zinc finger protein Gis1. *Embo J* **19**, 2569-79 (2000).
52. Hu, G.Z. & Ronne, H. Overexpression of yeast PAM1 gene permits survival without protein phosphatase 2A and induces a filamentous phenotype. *J Biol Chem* **269**, 3429-35 (1994).
53. Cooper, T.G. Transmitting the signal of excess nitrogen in *Saccharomyces cerevisiae* from the Tor proteins to the GATA factors: connecting the dots. *FEMS Microbiol Rev* **26**, 223-38 (2002).
54. Bertram, P.G. et al. Tripartite regulation of Gln3p by TOR, Ure2p, and phosphatases. *J Biol Chem* **275**, 35727-33 (2000).
55. Perlman, R., Yablonski, D., Simchen, G. & Levitzki, A. Cloning of the STE5 gene of *Saccharomyces cerevisiae* as a suppressor of the mating defect of cdc25 temperature-sensitive mutants. *Proc Natl Acad Sci U S A* **90**, 5474-8 (1993).
56. Mead, J. et al. Interactions of the Mcm1 MADS box protein with cofactors that regulate mating in yeast. *Mol Cell Biol* **22**, 4607-21 (2002).
57. Chu, S. & Herskowitz, I. Gametogenesis in yeast is regulated by a transcriptional cascade dependent on Ndt80. *Mol Cell* **1**, 685-96 (1998).
58. Xie, J. et al. Sum1 and Hst1 repress middle sporulation-specific gene expression during mitosis in *Saccharomyces cerevisiae*. *Embo J* **18**, 6448-54 (1999).
59. Friesen, H., Lunz, R., Doyle, S. & Segall, J. Mutation of the SPS1-encoded protein kinase of *Saccharomyces cerevisiae* leads to defects in transcription and morphology during spore formation. *Genes Dev* **8**, 2162-75 (1994).
60. Yun, C.W. et al. Desferrioxamine-mediated iron uptake in *Saccharomyces cerevisiae*. Evidence for two pathways of iron uptake. *J Biol Chem* **275**, 10709-15 (2000).
61. Mai, B. & Breeden, L. CLN1 and its repression by Xbp1 are important for efficient sporulation in budding yeast. *Mol Cell Biol* **20**, 478-87 (2000).
62. Kuchin, S., Vyas, V.K. & Carlson, M. Snf1 protein kinase and the repressors Nrg1 and Nrg2 regulate FLO11, haploid invasive growth, and diploid pseudohyphal differentiation. *Mol Cell Biol* **22**, 3994-4000 (2002).
63. Causton, H.C. et al. Remodeling of yeast genome expression in response to environmental changes. *Mol Biol Cell* **12**, 323-37 (2001).

64. Sasaki, T., Toh-e, A. & Kikuchi, Y. Extragenic suppressors that rescue defects in the heat stress response of the budding yeast mutant tom1. *Mol Gen Genet* **262**, 940-8 (2000).
65. Silva, J.T., Vericimo, M.A., Floriano, W.B., Dutra, M.B. & Panek, A.D. On the hsp26 of *Saccharomyces cerevisiae*. *Biochem Mol Biol Int* **33**, 211-20 (1994).
66. Roelants, F.M., Torrance, P.D., Bezman, N. & Thorner, J. Pkh1 and pkh2 differentially phosphorylate and activate ypk1 and ykr2 and define protein kinase modules required for maintenance of cell wall integrity. *Mol Biol Cell* **13**, 3005-28 (2002).
67. Schmelzle, T., Helliwell, S.B. & Hall, M.N. Yeast protein kinases and the RHO1 exchange factor TUS1 are novel components of the cell integrity pathway in yeast. *Mol Cell Biol* **22**, 1329-39 (2002).
68. deHart, A.K., Schnell, J.D., Allen, D.A. & Hicke, L. The conserved Pkh-Ypk kinase cascade is required for endocytosis in yeast. *J Cell Biol* **156**, 241-8 (2002).
69. Yoshimoto, H. et al. Genome-wide analysis of gene expression regulated by the calcineurin/Crz1p signaling pathway in *Saccharomyces cerevisiae*. *J Biol Chem* **277**, 31079-88 (2002).
70. Mizunuma, M., Hirata, D., Miyahara, K., Tsuchiya, E. & Miyakawa, T. Role of calcineurin and Mpk1 in regulating the onset of mitosis in budding yeast. *Nature* **392**, 303-6 (1998).
71. Withee, J.L., Mulholland, J., Jeng, R. & Cyert, M.S. An essential role of the yeast pheromone-induced Ca2+ signal is to activate calcineurin. *Mol Biol Cell* **8**, 263-77 (1997).
72. Matheos, D.P., Kingsbury, T.J., Ahsan, U.S. & Cunningham, K.W. Tcn1p/Crz1p, a calcineurin-dependent transcription factor that differentially regulates gene expression in *Saccharomyces cerevisiae*. *Genes Dev* **11**, 3445-58 (1997).
73. Shou, W. et al. Exit from mitosis is triggered by Tem1-dependent release of the protein phosphatase Cdc14 from nucleolar RENT complex. *Cell* **97**, 233-44 (1999).
74. Visintin, R. et al. The phosphatase Cdc14 triggers mitotic exit by reversal of Cdk-dependent phosphorylation. *Mol Cell* **2**, 709-18 (1998).
75. Ahn, S.H., Acurio, A. & Kron, S.J. Regulation of G2/M progression by the STE mitogen-activated protein kinase pathway in budding yeast filamentous growth. *Mol Biol Cell* **10**, 3301-16 (1999).
76. Zhu, G. et al. Two yeast forkhead genes regulate the cell cycle and pseudohyphal growth. *Nature* **406**, 90-4 (2000).
77. Koch, C., Schleiffer, A., Ammerer, G. & Nasmyth, K. Switching transcription on and off during the yeast cell cycle: Cln/Cdc28 kinases activate bound transcription factor SBF (Swi4/Swi6) at start, whereas Clb/Cdc28 kinases displace it from the promoter in G2. *Genes Dev* **10**, 129-41 (1996).
78. Dorer, R., Pryciak, P.M. & Hartwell, L.H. *Saccharomyces cerevisiae* cells execute a default pathway to select a mate in the absence of pheromone gradients. *J Cell Biol* **131**, 845-61 (1995).
79. Li, X. & Cai, M. Recovery of the yeast cell cycle from heat shock-induced G(1) arrest involves a positive regulation of G(1) cyclin expression by the S phase cyclin Clb5. *J Biol Chem* **274**, 24220-31 (1999).

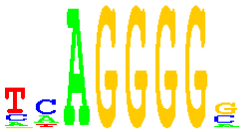
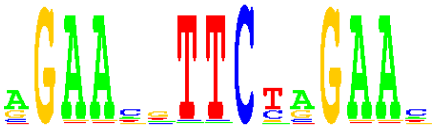
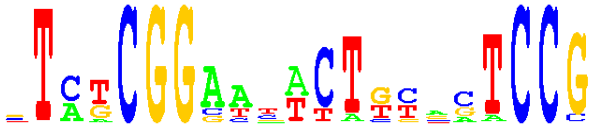
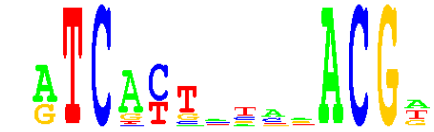
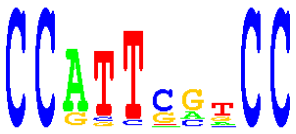
80. Strich, R., Slater, M.R. & Esposito, R.E. Identification of negative regulatory genes that govern the expression of early meiotic genes in yeast. *Proc Natl Acad Sci U S A* **86**, 10018-22 (1989).
81. Marchler, G., Schuller, C., Adam, G. & Ruis, H. A *Saccharomyces cerevisiae* UAS element controlled by protein kinase A activates transcription in response to a variety of stress conditions. *Embo J* **12**, 1997-2003 (1993).
82. Yaguchi, S., Mitsui, K., Iha, H. & Tsurugi, K. Phosphorylation of the GTS1 gene product of the yeast *Saccharomyces cerevisiae* and its effect on heat tolerance and flocculation. *FEMS Microbiol Lett* **187**, 179-84 (2000).
83. Grundmann, O., Mosch, H.U. & Braus, G.H. Repression of GCN4 mRNA translation by nitrogen starvation in *Saccharomyces cerevisiae*. *J Biol Chem* **276**, 25661-71 (2001).
84. Vazquez de Aldana, C.R., Marton, M.J. & Hinnebusch, A.G. GCN20, a novel ATP binding cassette protein, and GCN1 reside in a complex that mediates activation of the eIF-2 alpha kinase GCN2 in amino acid-starved cells. *Embo J* **14**, 3184-99 (1995).
85. de Barros Lopes, M., Ho, J.Y. & Reed, S.I. Mutations in cell division cycle genes CDC36 and CDC39 activate the *Saccharomyces cerevisiae* mating pheromone response pathway. *Mol Cell Biol* **10**, 2966-72 (1990).
86. Liu, H.Y. et al. DBF2, a cell cycle-regulated protein kinase, is physically and functionally associated with the CCR4 transcriptional regulatory complex. *Embo J* **16**, 5289-98 (1997).
87. Carrico, P.M. & Zitomer, R.S. Mutational analysis of the Tup1 general repressor of yeast. *Genetics* **148**, 637-44 (1998).
88. Turner, G.C., Du, F. & Varshavsky, A. Peptides accelerate their uptake by activating a ubiquitin-dependent proteolytic pathway. *Nature* **405**, 579-83 (2000).
89. Blondel, M., Galan, J.M. & Peter, M. Isolation and characterization of HRT1 using a genetic screen for mutants unable to degrade Gic2p in *saccharomyces cerevisiae*. *Genetics* **155**, 1033-44 (2000).
90. Welihinda, A.A., Tirasophon, W., Green, S.R. & Kaufman, R.J. Protein serine/threonine phosphatase Ptc2p negatively regulates the unfolded-protein response by dephosphorylating Ire1p kinase. *Mol Cell Biol* **18**, 1967-77 (1998).
91. Shin, D.Y., Matsumoto, K., Iida, H., Uno, I. & Ishikawa, T. Heat shock response of *Saccharomyces cerevisiae* mutants altered in cyclic AMP-dependent protein phosphorylation. *Mol Cell Biol* **7**, 244-50 (1987).
92. Delneri, D., Gardner, D.C. & Oliver, S.G. Analysis of the seven-member AAD gene set demonstrates that genetic redundancy in yeast may be more apparent than real. *Genetics* **153**, 1591-600 (1999).
93. Coleman, S.T., Epping, E.A., Steggerda, S.M. & Moye-Rowley, W.S. Yap1p activates gene transcription in an oxidant-specific fashion. *Mol Cell Biol* **19**, 8302-13 (1999).
94. Rep, M. et al. The *Saccharomyces cerevisiae* Sko1p transcription factor mediates HOG pathway-dependent osmotic regulation of a set of genes encoding enzymes implicated in protection from oxidative damage. *Mol Microbiol* **40**, 1067-83 (2001).

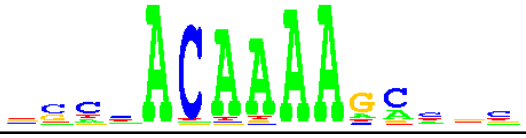
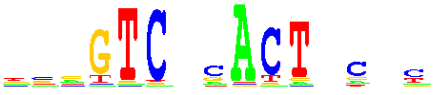
95. Tsukada, M. & Ohsumi, Y. Isolation and characterization of autophagy-defective mutants of *Saccharomyces cerevisiae*. *FEBS Lett* **333**, 169-74 (1993).
96. Kamada, Y. et al. Tor-mediated induction of autophagy via an Apg1 protein kinase complex. *J Cell Biol* **150**, 1507-13 (2000).

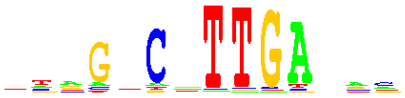
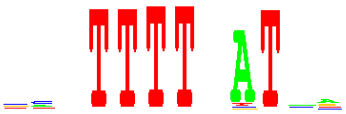
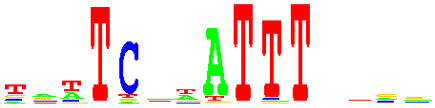
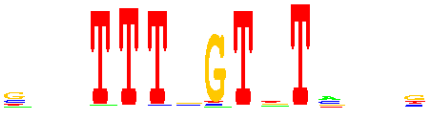
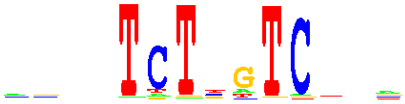
Cis-regulatory Motifs Used

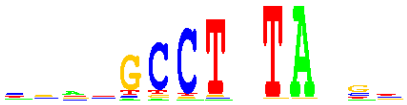
The *cis*-regulatory binding site motifs used in the paper in order to evaluate the results came from two sources: known motifs from the TRANSFAC database and *de novo* motifs (discovered by a motif-finding program applied to the 500bp upstream regions of the genes in each module; *de novo* motifs are named with the character 'N' followed by the module number from which the motif was discovered). The table below lists all motifs used along with their sequence logo.

Table 3. *Cis*-regulatory motifs used

DNA motif binding site	Motif logo
MCM1_01	
GCN4_01	
STRE_01	
HSF_04	
LAC9_C	
STE12_Q4	
XBP1_Q2	
ABF_C	
HAP234_01	
ADR1_01	
CAT8_Q6	
HAC1_Q2	

DNA motif binding site	Motif logo
CBF1_B	
REPCAR1_01	
MIG1_01	
GCR1	
GATA	
YAP1	
MSE	
N7	
N11	
N12	
N13	
N14	

DNA motif binding site	Motif logo
N16	
N18	
N19	
N20	
N21	
N23	
N24	
N26	
N27	
N30	
N32	
N33	

DNA motif binding site	Motif logo
N34	
N35	
N36	
N37	
N38	
N41	
N43	
N44	
N45	
N46	
N48	
N50	

Significant Combinations of *cis*-Regulatory Motifs

To further evaluate the partition of closely related modules, we rigorously searched for significant pairs of *cis*-regulatory motifs enriched in the upstream regions of module genes. Motifs include both known motifs (TRANSFAC, named motifs) and *de novo* motifs. The results are summarized in Table 4. Shown for each module are pairs of motifs that *together* are significantly enriched in upstream regions of its member genes (see Methods). Note that in some cases, one or both of the motifs in the pair are not significant as an individual motif. Motifs that are also individually enriched are shown in bold (these also appear in Fig. 4a, top left matrices). Functionally related modules are characterized by overlapping but distinct motif combinations (e.g., amino acid metabolism related modules (8-11)), supporting the module partitions, and possibly pointing to combinatorial regulation. General stress motifs (e.g., STRE, ADR1) appear in many modules as might be expected in a stress dataset, but in combination with different motifs in distinct modules.

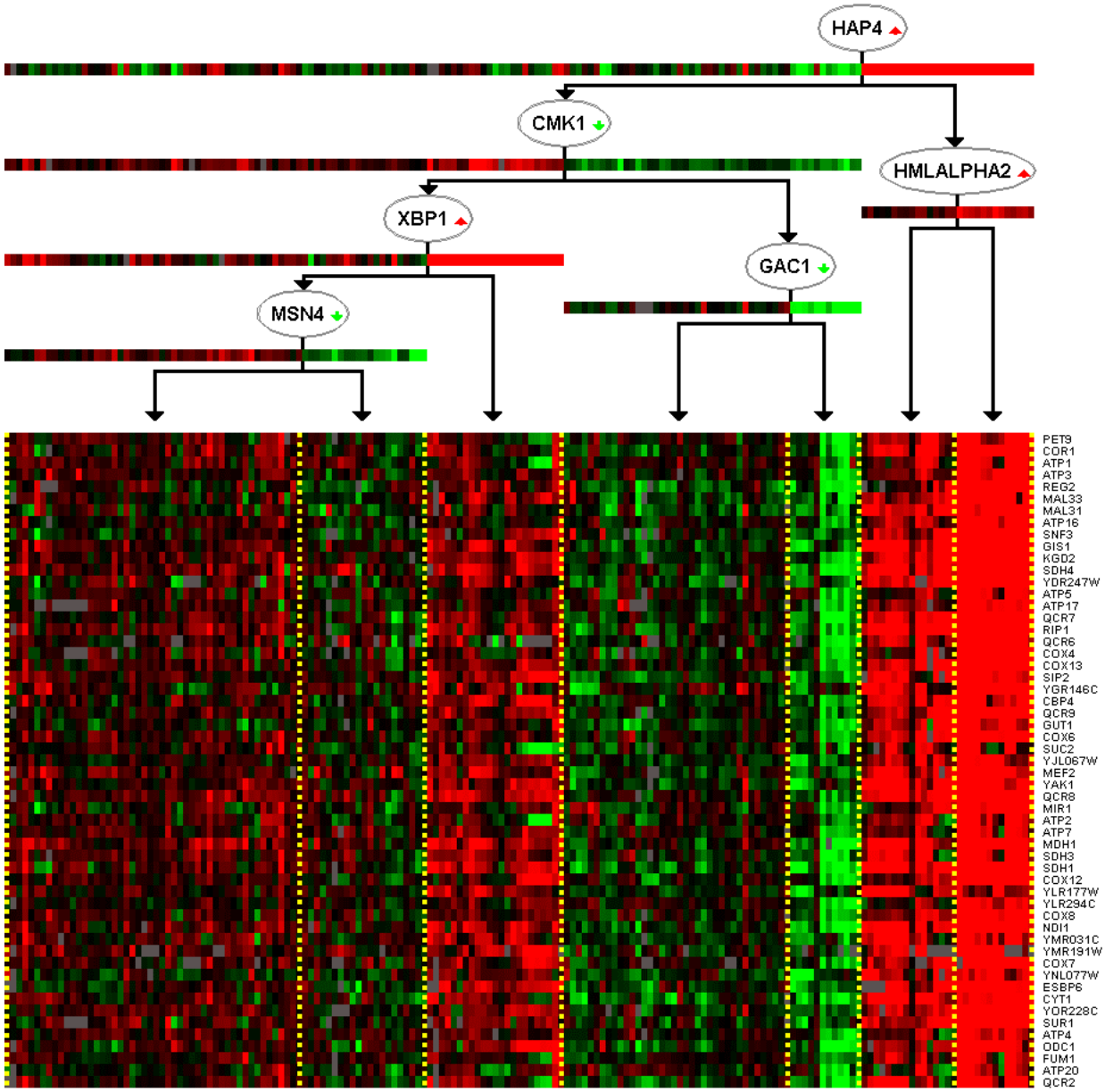
Table 4. Characterization of modules by combinations of *cis*-regulatory motifs

#	Module	Motif Signature
1	Respiration and carbon regulation	[**HAP234**, ADR1] [**HAP234, STRE**]
2	Energy, osmolarity and cAMP signaling	[**STRE**, ADR1] [**STRE**, CAT8]
3	Energy and Osmotic stress I	[**STRE**, MIG1] [**STRE**, ADR1]
4	Energy and Osmotic stress II	[**REPCAR**,**ADR1**] [**REPCAR**, STRE] [**ADR1**, **CAT8**]
5	Glycolysis and Folding	[**GCR1**, CBF1] [**GCR1**, STRE]
6	Galactose metabolism	[**GAL4**, REPCAR] [**GAL4**, ADR1]
7	Snf kinase regulated processes	[**N7**, ADR1] [**N7**, STRE] [**N7**, GCR1]
8	Nitrogen catabolite repression	[**GATA**, STRE] [**GATA**,CBF1] [**GATA**,**GCN4**]
9	AA metabolism I	[**GCN4**,**CBF1**] [**GCN4**,GATA]
10	AA metabolism II	[**GCN4**,STE12] [**GCN4**,STRE]
11	AA and purine metabolism	[**N11**,**GCN4**] [**N11**,STRE]
12	Nuclear	[**N12**,STRE]
13	Mixed I	[**N13**,ADR1]
14	Ribosomal and phosphate metabolism	[**N13**, LEU3]
15	mRNA,rRNA and tRNA processing	[**N13**,REB1] [**N13**,ABF1]
16	RNA Processing and Cell Cycle	[**N16**, **GCR1**]
17	DNA and RNA processing	[**N13**, GCN4]
18	TFs and RNA processing	[**N18**, **N13**]
19	TFs and nuclear transport	[**N19**, N38] [**N19**, ABF1]
20	TFs I	[**N20**,N48]
21	TFs II	[**N21**, ADR1]
22	TFs, cell wall and mating	[**MSE**, CBF1] [**MSE**, MATA]
23	TFs and sporulation	[**N23**, REB1]
24	Sporulation and TFs	[**N24**,N46]
25	Sporulation and cAMP pathway	[ADR1, **STRE**]
26	Sporulation and Cell wall	[**N26, ADR1**] [**N26**, STRE]
27	Cell wall and transport I	[**N27**,ADR1] [**N27**,STRE]
28	Cell wall and Transport II	[STRE, MCM1]
29	Cell differentiation	[**STE12**, XBP1]
30	Cell cycle (G2/M)	[**N30**,**MCM1**]
31	Cell cycle, TFs and DNA metabolism	
32	Cell cycle and general TFs	[**N32**,ABF1]
33	Mitochondrial and Signaling	[**N33**,**STRE**] [**N33**, ADR1] [**STRE**, ADR1]
34	Mitochondrial and Protein fate	[**N34**, STRE] [**N34**, XBP1]
35	Trafficking and Mitochondrial	[**N35**, N30]
36	ER and Nuclear	[**N36**, **ABF1**] [**N36**, XBP1]
37	Proteasome and Endocytosis	[**N37**, REB1] [**N37**, ABF1] [**N37**, ADR1] [**N37**, HSF]
38	Protein modification and trafficking	[**N38**, N7]
39	Protein folding	[**HSF**, **XBP1**] [**HSF**, ADR1] [**HSF**, GCN4] [**HSF**, CAT8]
40	Oxidative stress I	[**YAP1**, STRE] [**YAP1**, HSF] [**YAP1**, XBP1]
41	Oxidative stress II	[**N41**, **STRE**]
42	Unkown (sub-telomeric)	
43	Unknown genes I	[STRE, PHO4] [STRE, STE12]
44	Unknown genes II	[**N44**, STRE]
45	Unknown genes III	[**N45**, STRE]
46	Mixed II	[**N46**, STRE]
47	Mixed III	[**XBP1**, **HAC1**] [**XBP1**, REB1]
48	Mixed IV	[**N48**, N34]
49	Ty ORFs	
50	Missing values	[**N50**, STRE]

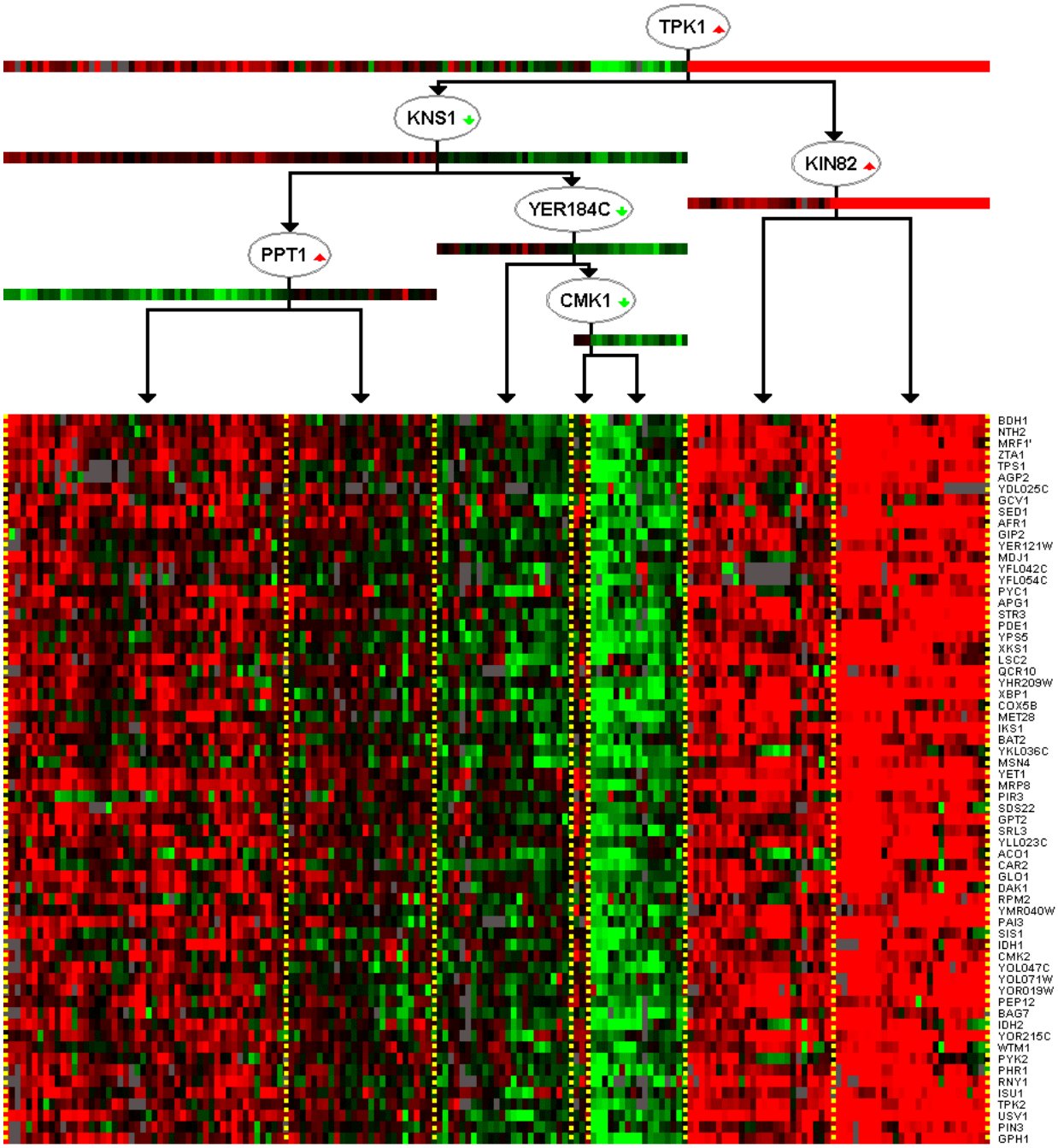
Regulation Programs for All Modules

Below are regulation programs for all 50 modules, in the same format as in Figure 3 from the paper. Each node in the tree consists of a regulatory gene (e.g., 'Hap4') and a query on its qualitative value, in which an upward arrow (red) denotes the query “is gene up-regulated?” and a downward arrow (green) denotes the query “is gene down-regulated?”. Right branches represent instances for which the answer to the query in the node is TRUE; left branches represent instances for which the answer is FALSE. The expression of the regulatory genes themselves is shown below their respective node.

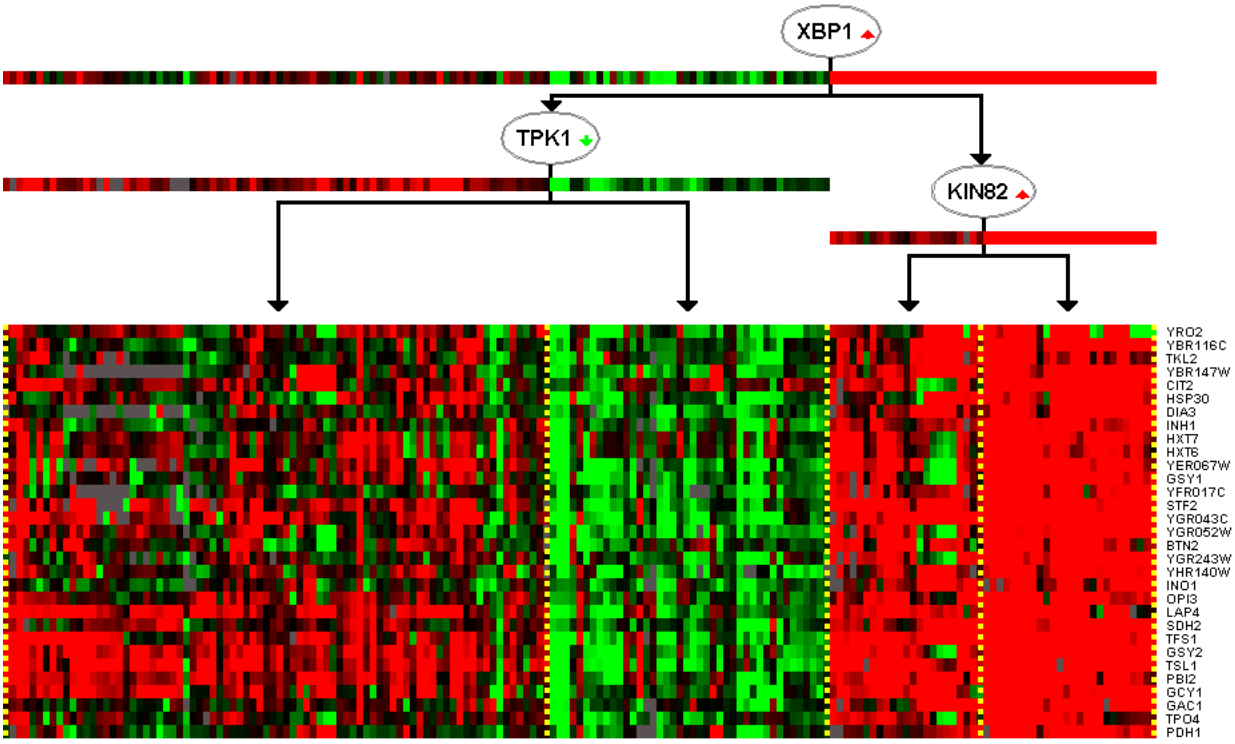
Module 1: Respiration and carbon regulation



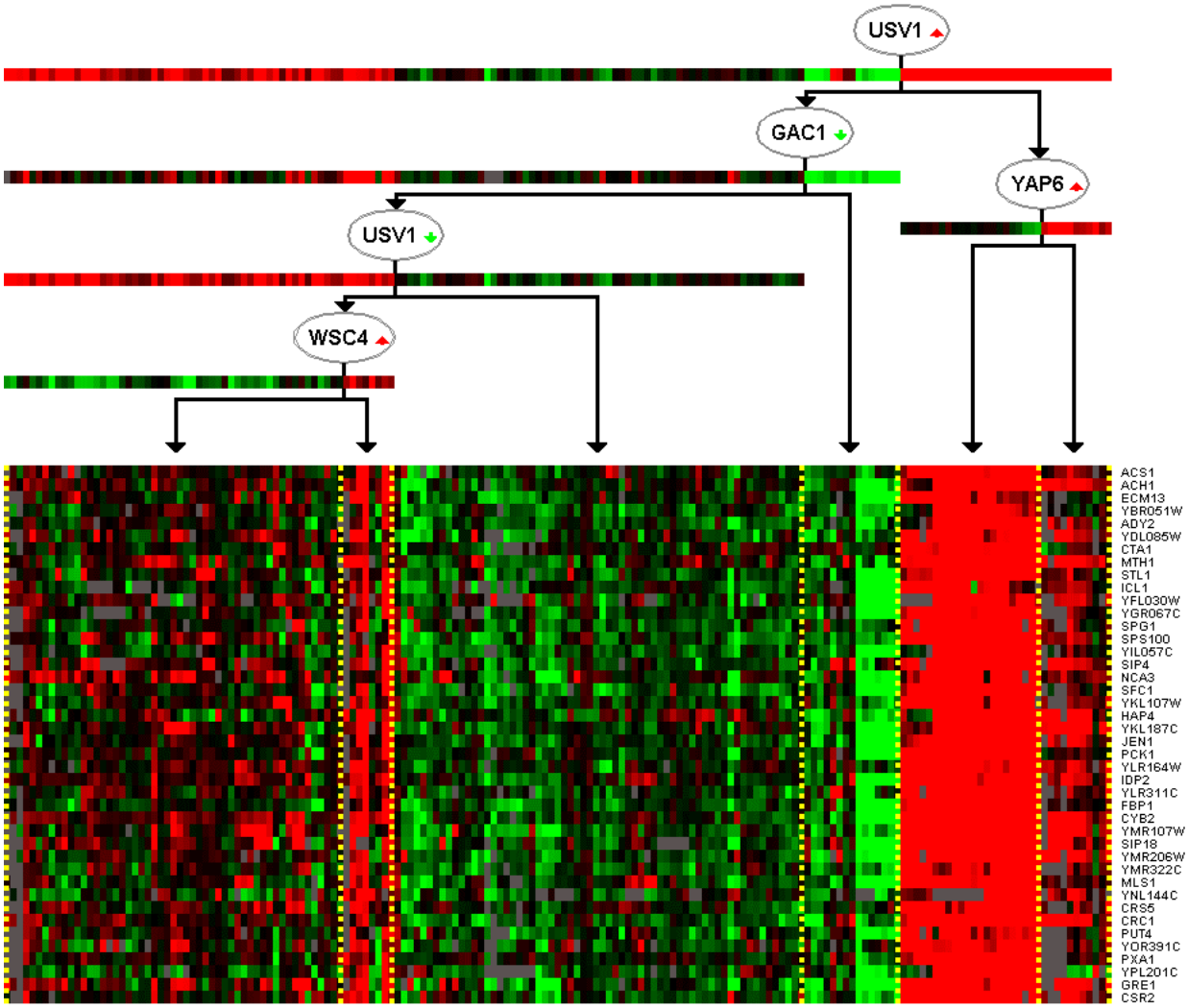
Module 2: Energy, osmolarity and cAMP signaling



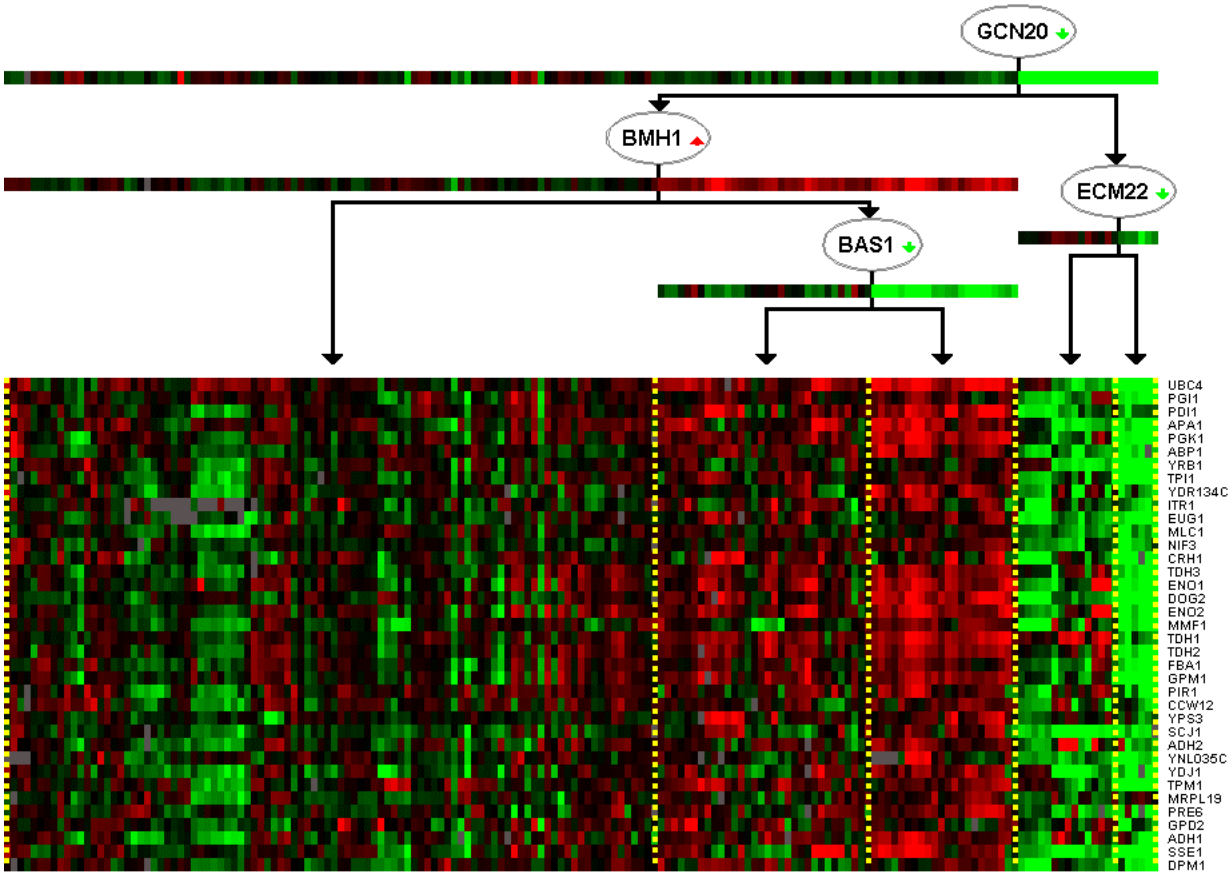
Module 3: Energy and Osmotic stress I



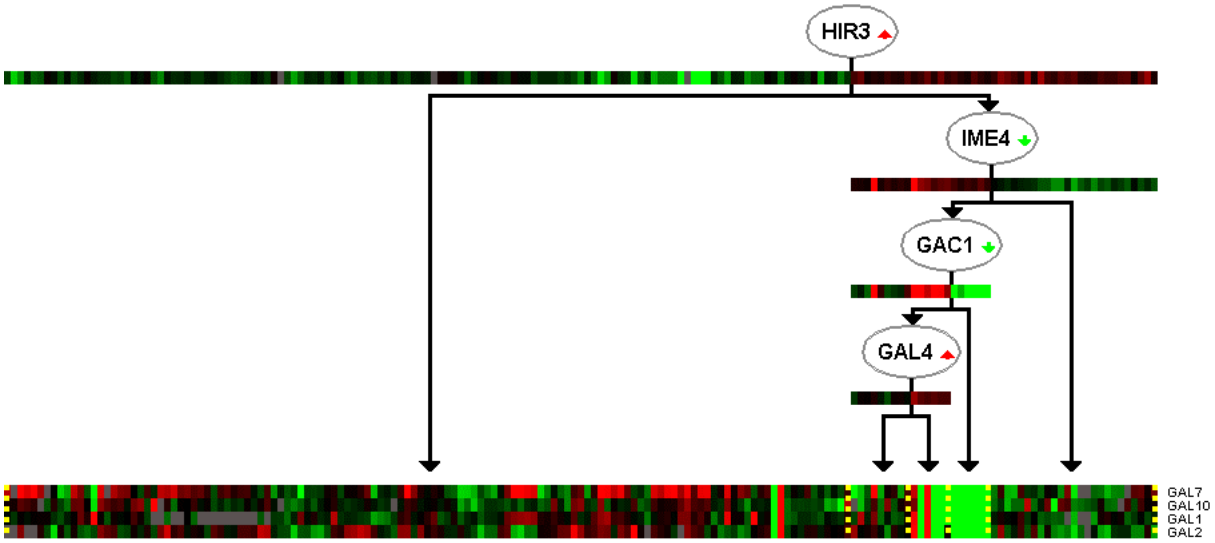
Module 4: Energy and Osmotic stress II



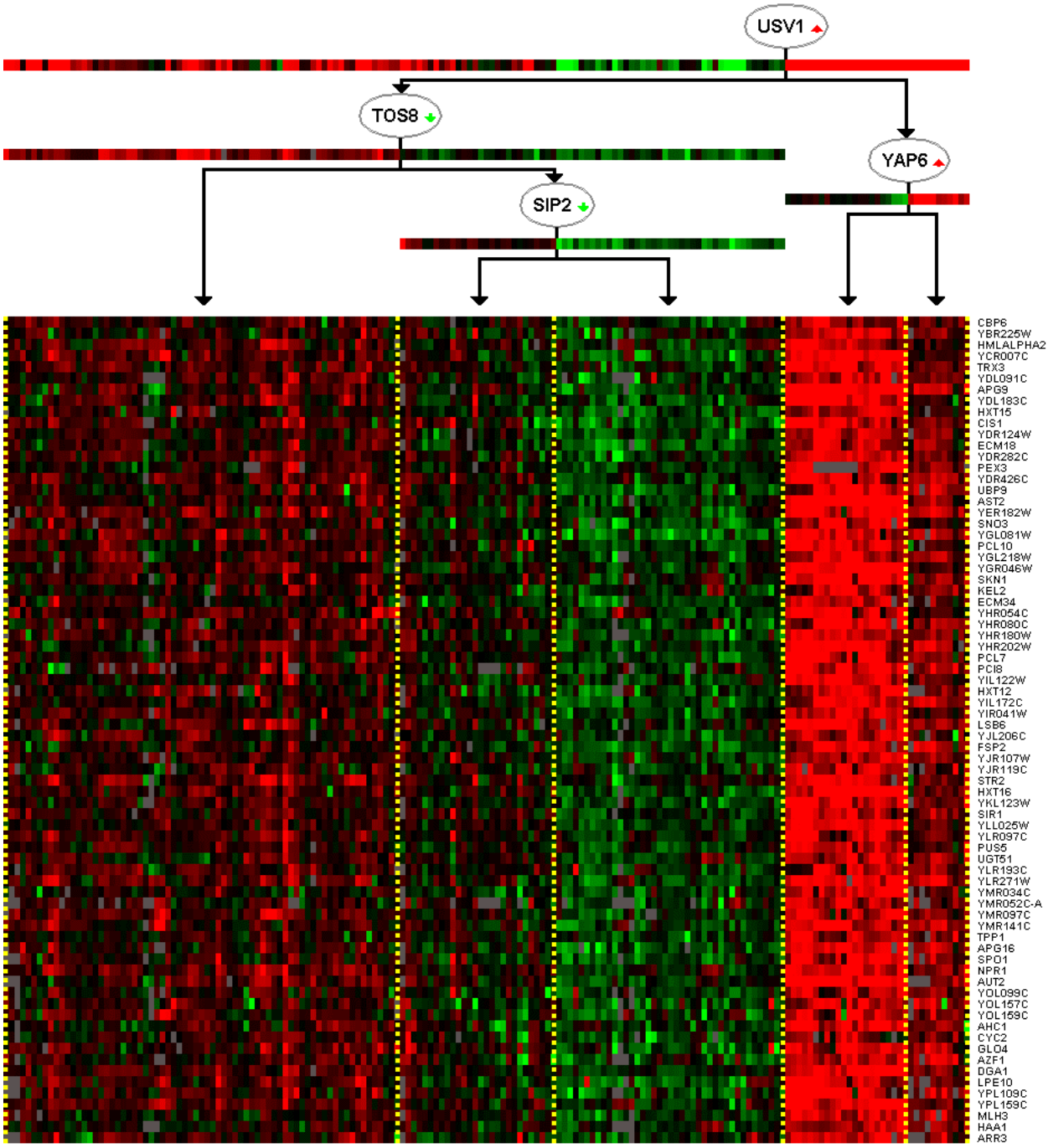
Module 5: Glycolysis and Folding



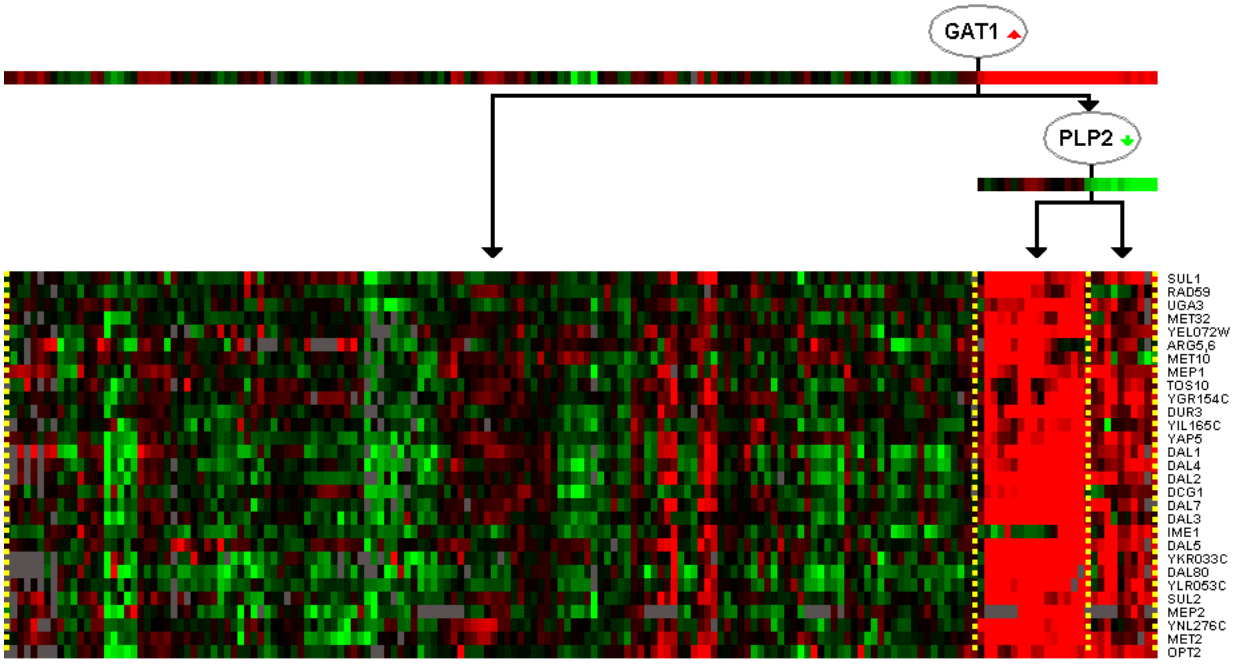
Module 6: Galactose metabolism



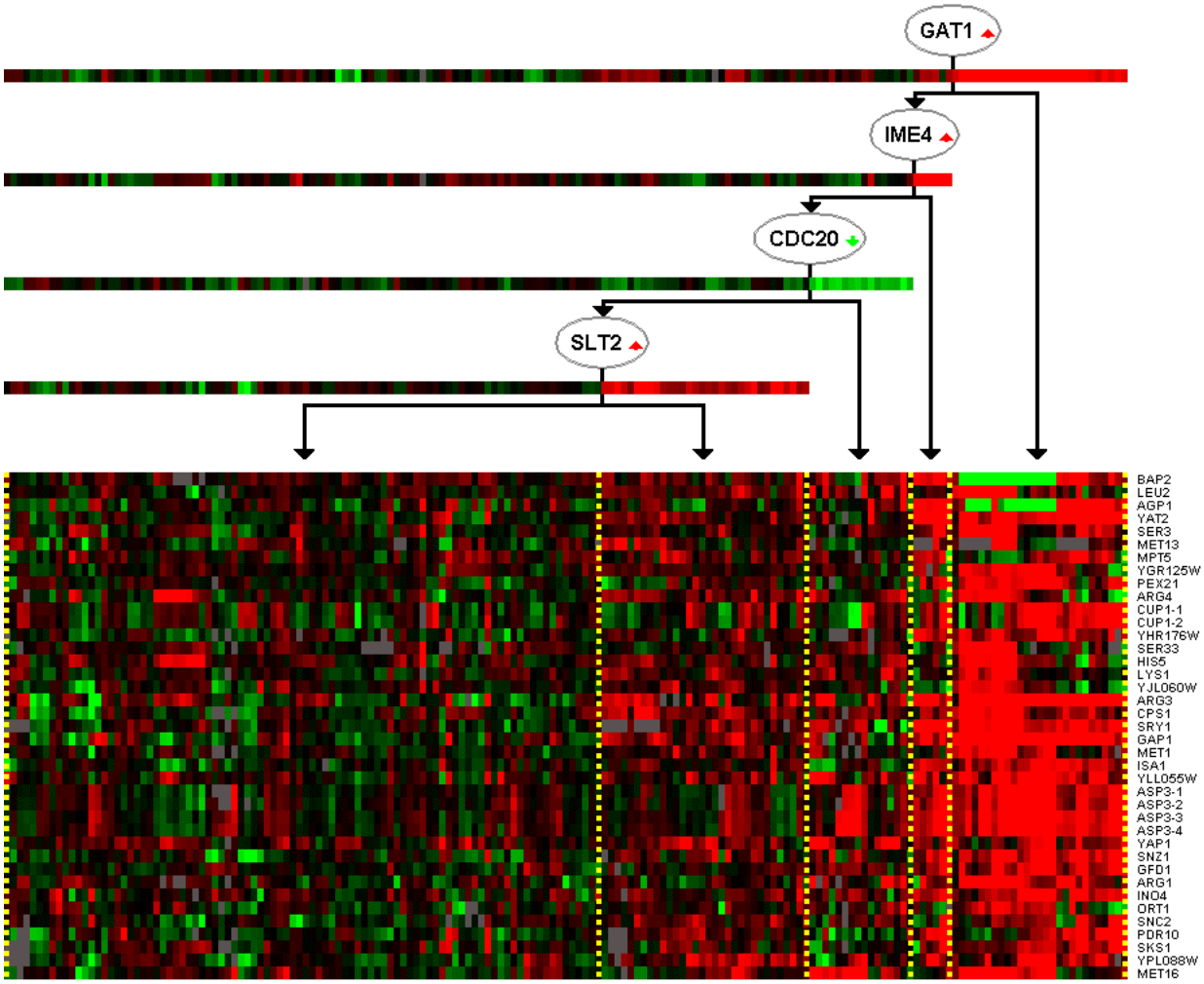
Module 7: Snf kinase regulated processes



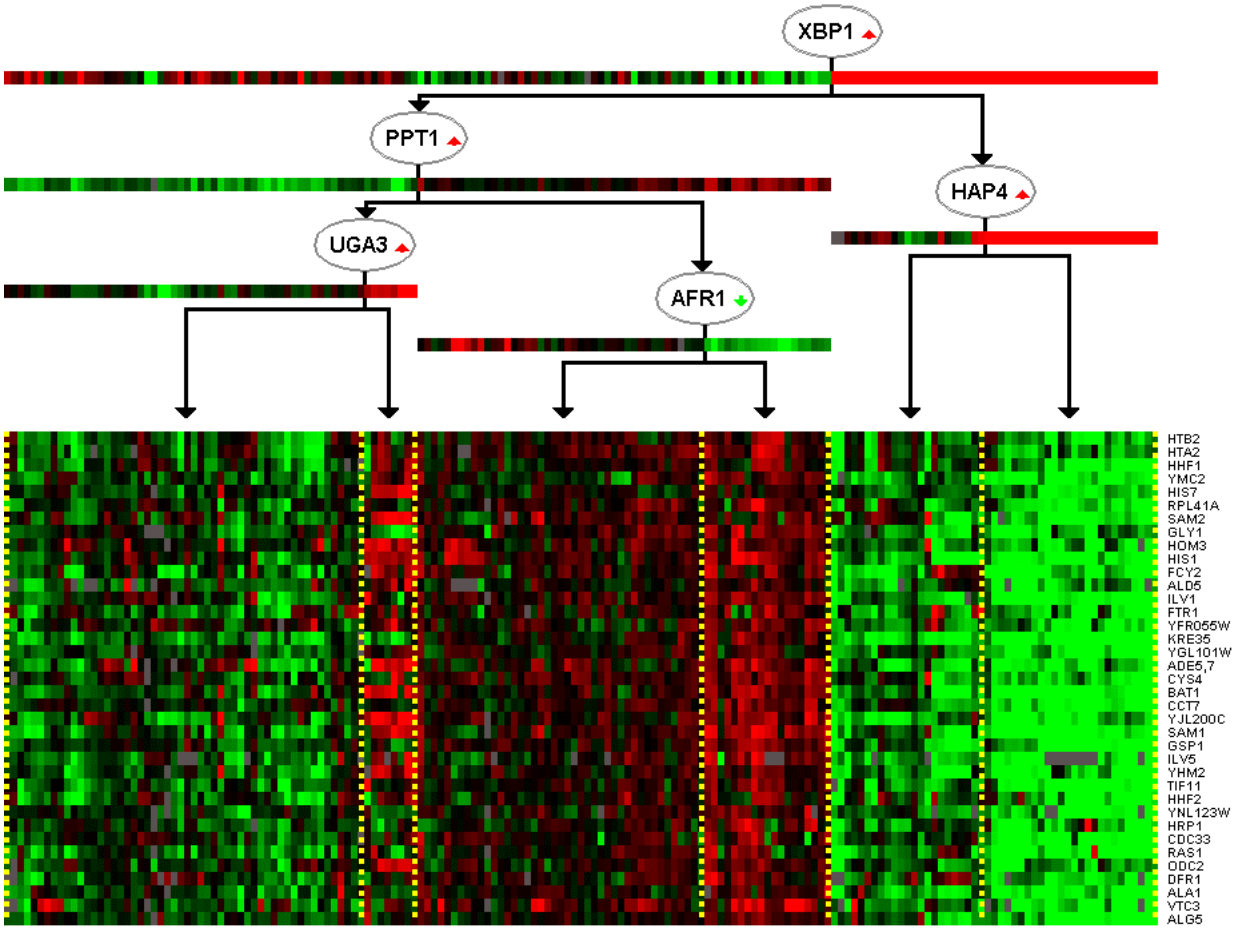
Module 8: Nitrogen catabolite repression



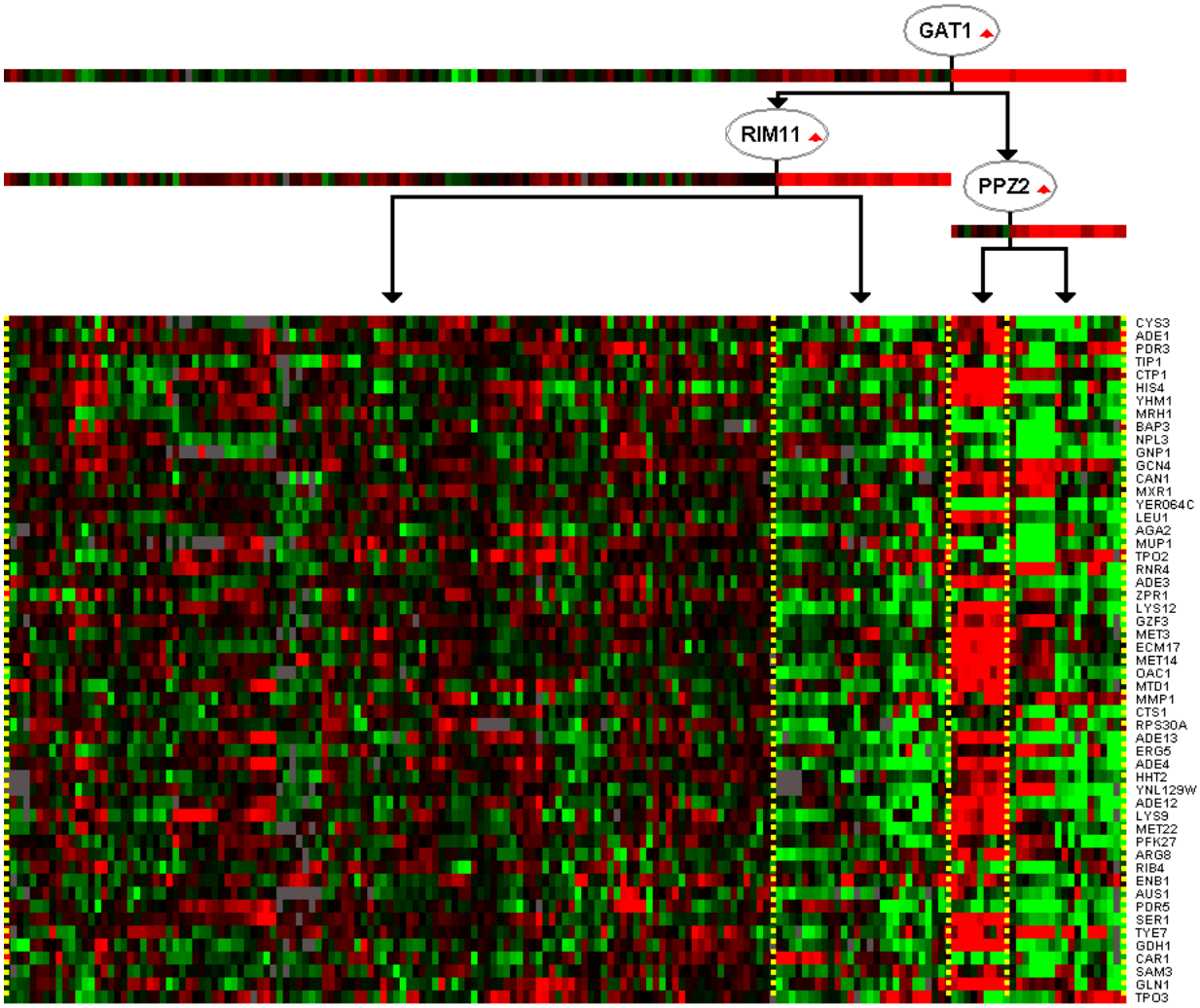
Module 9: AA metabolism I



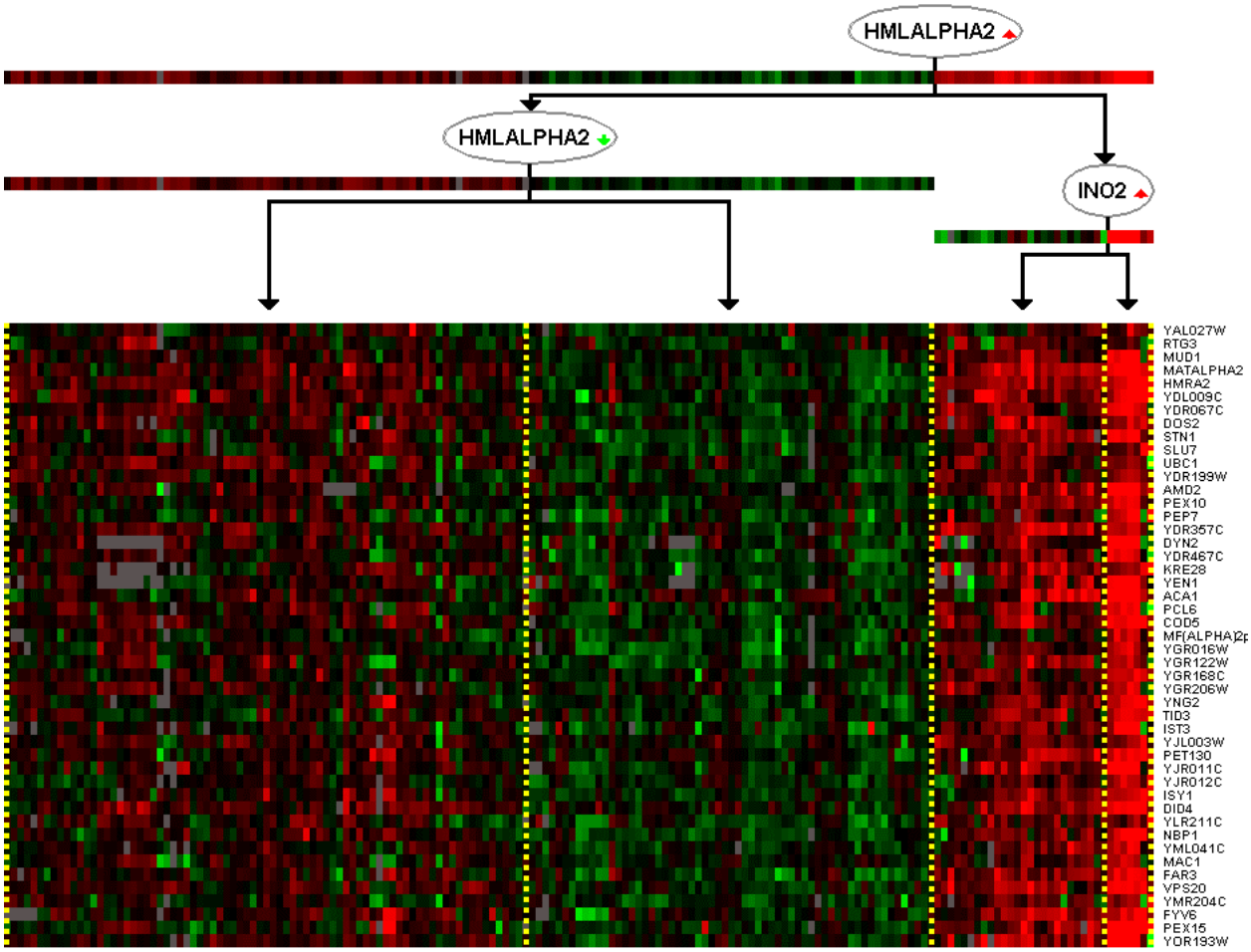
Module 10: AA metabolism II



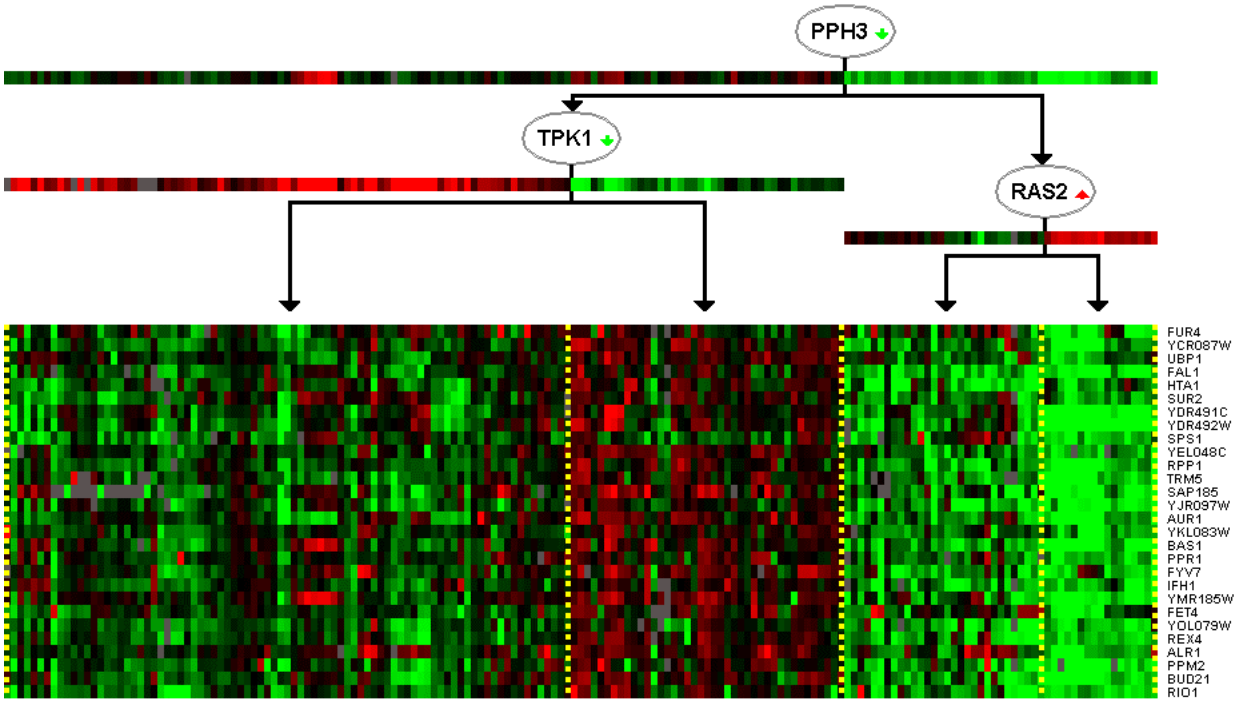
Module 11: AA and purine metabolism



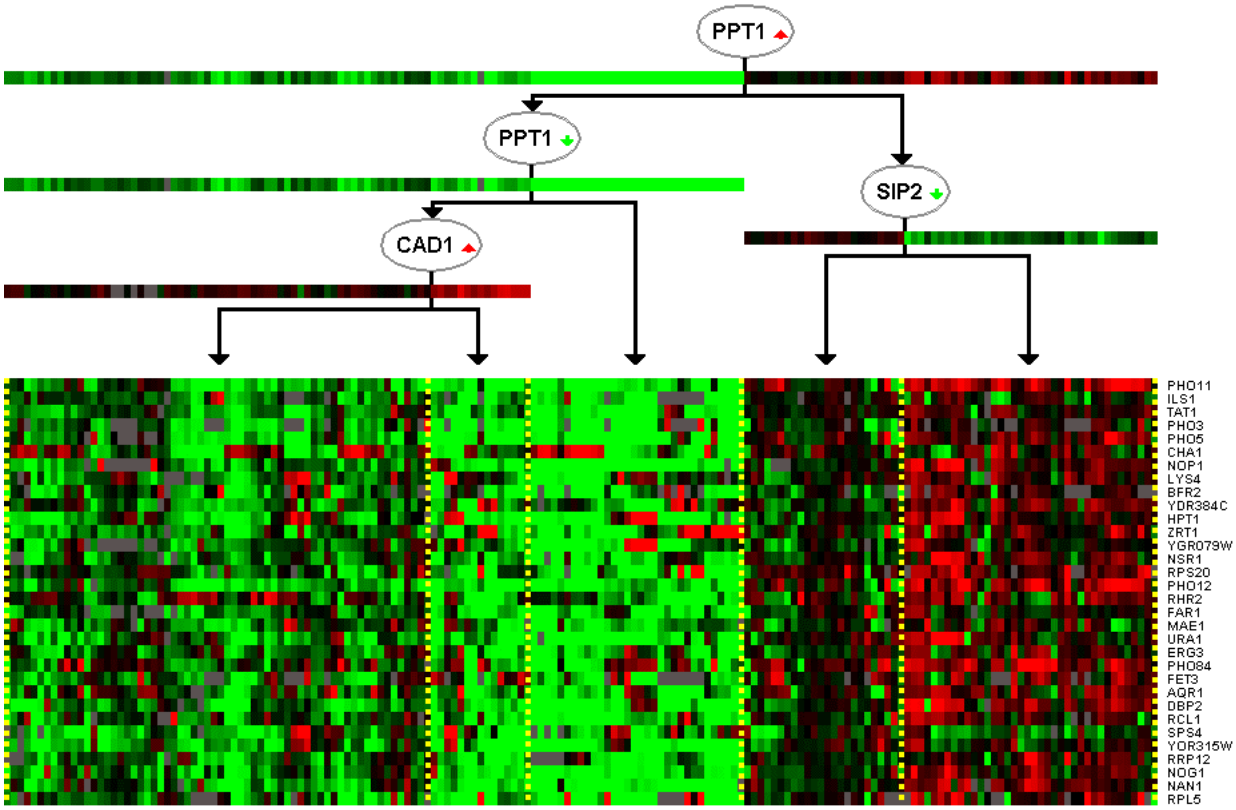
Module 12: Nuclear



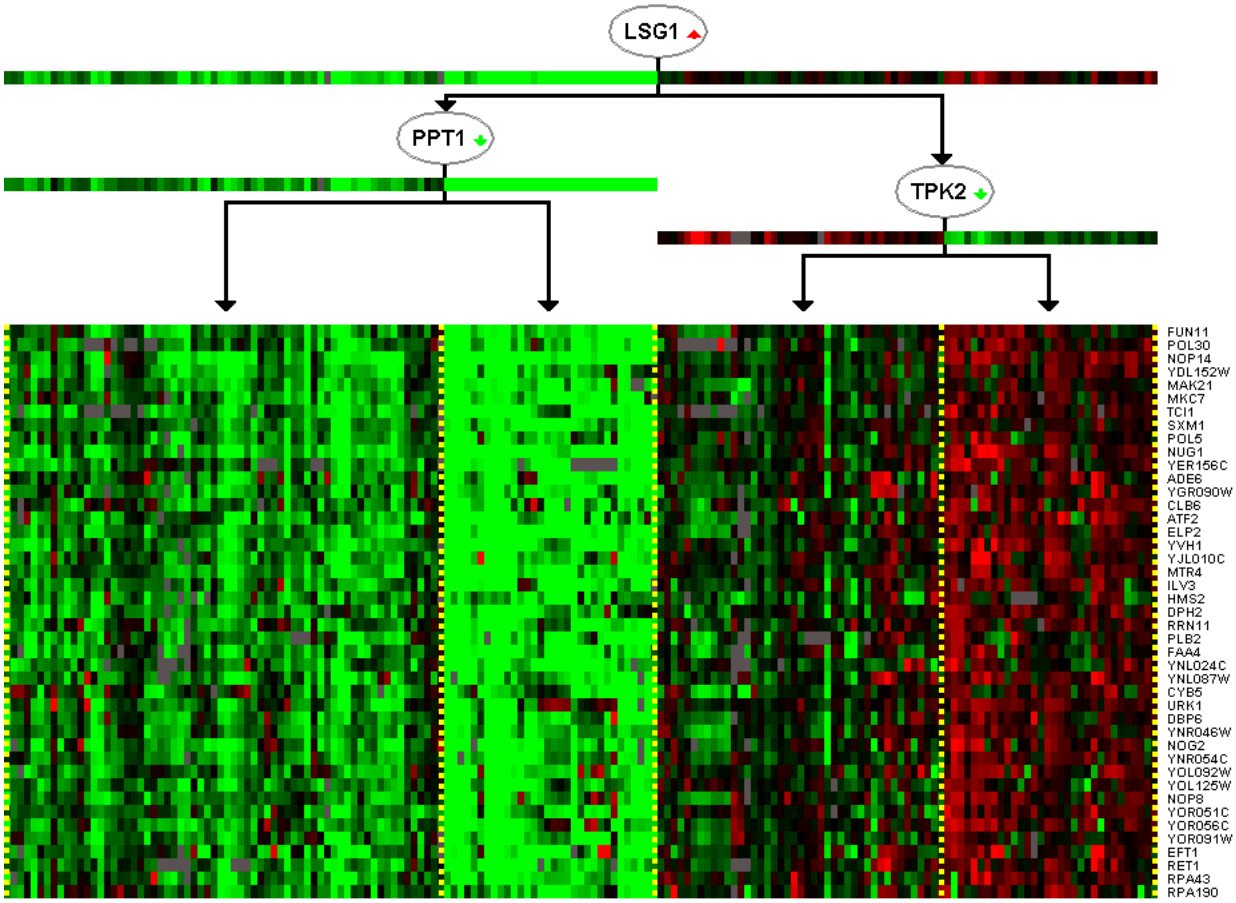
Module 13: Mixed I



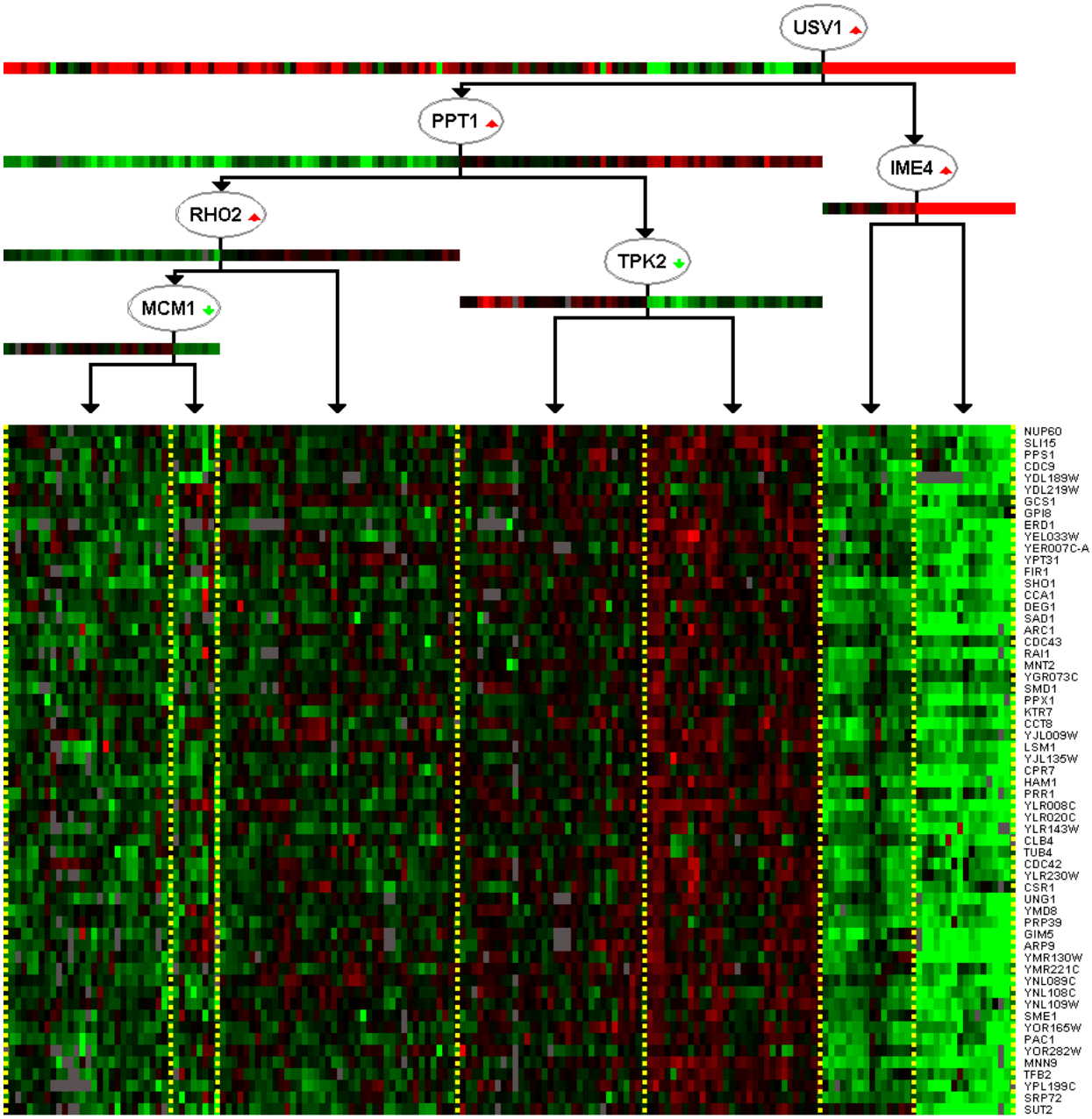
Module 14: Ribosomal and phosphate metabolism



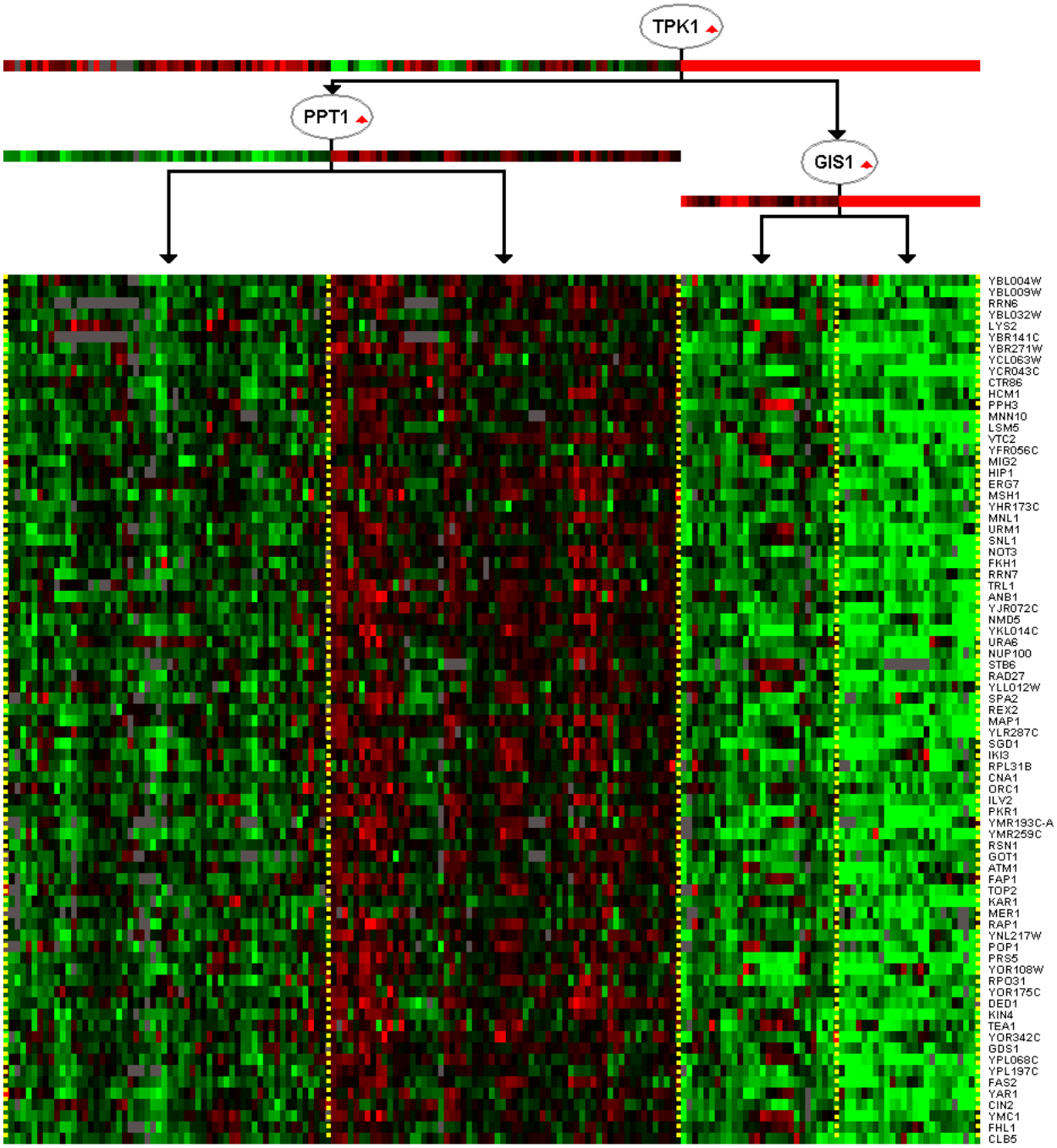
Module 15: mRNA,rRNA and tRNA processing



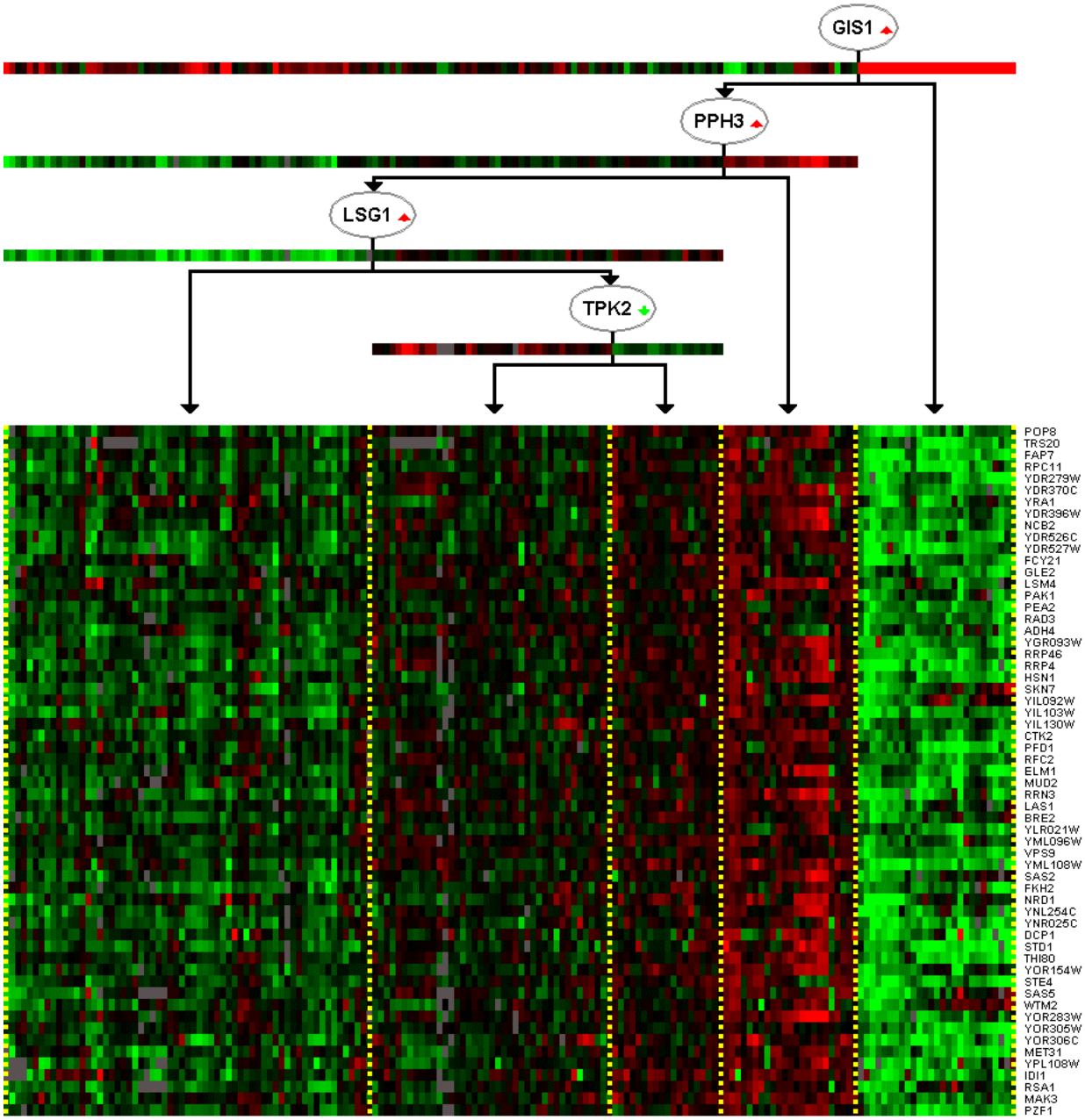
Module 16: RNA Processing and Cell Cycle



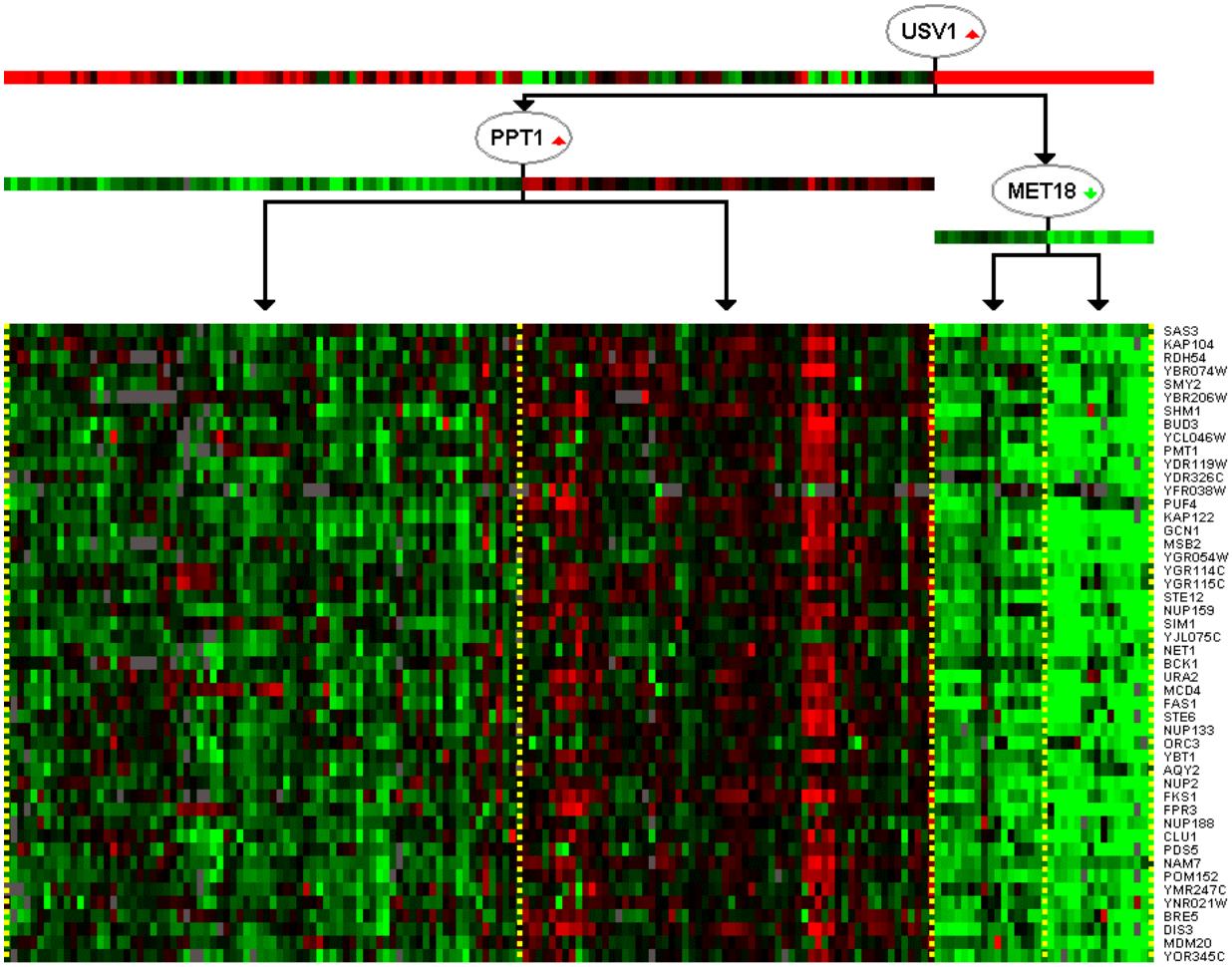
Module 17: DNA and RNA processing



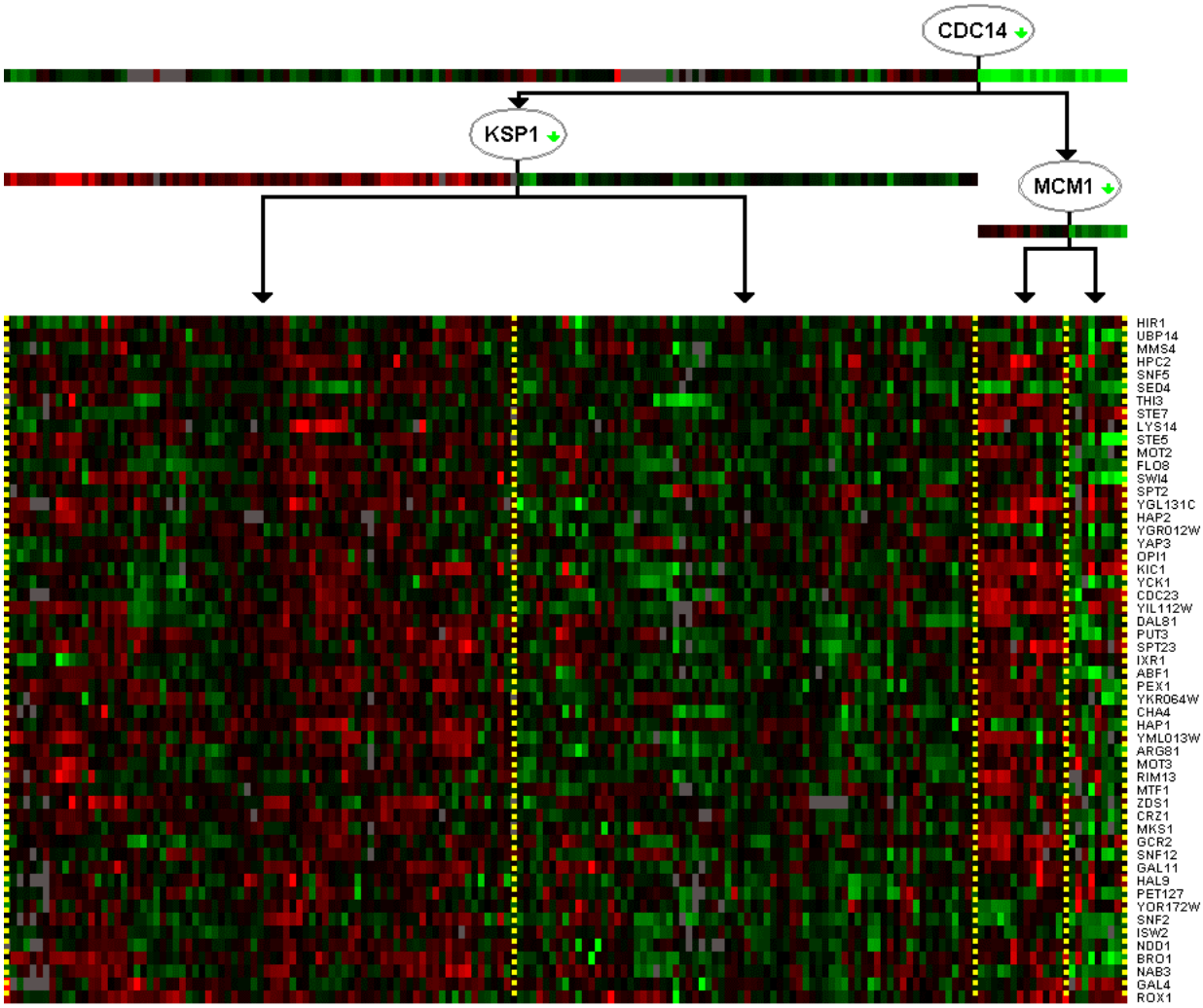
Module 18: TFs and RNA processing



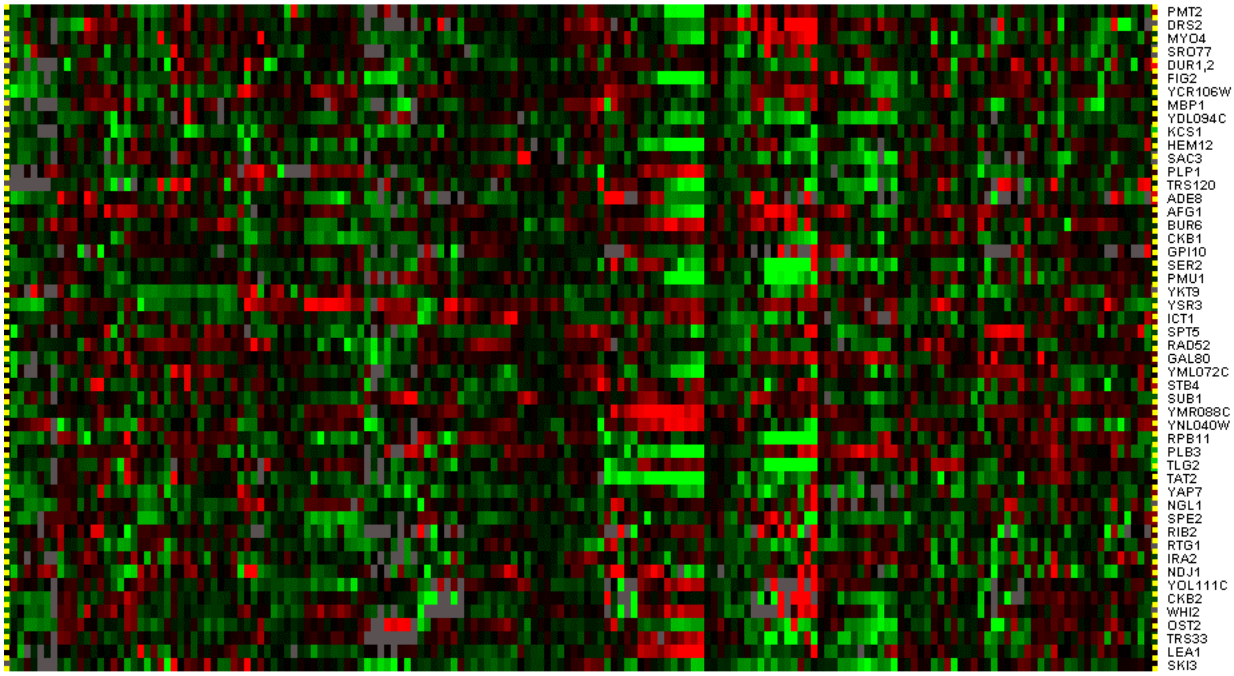
Module 19: TFs and nuclear transport



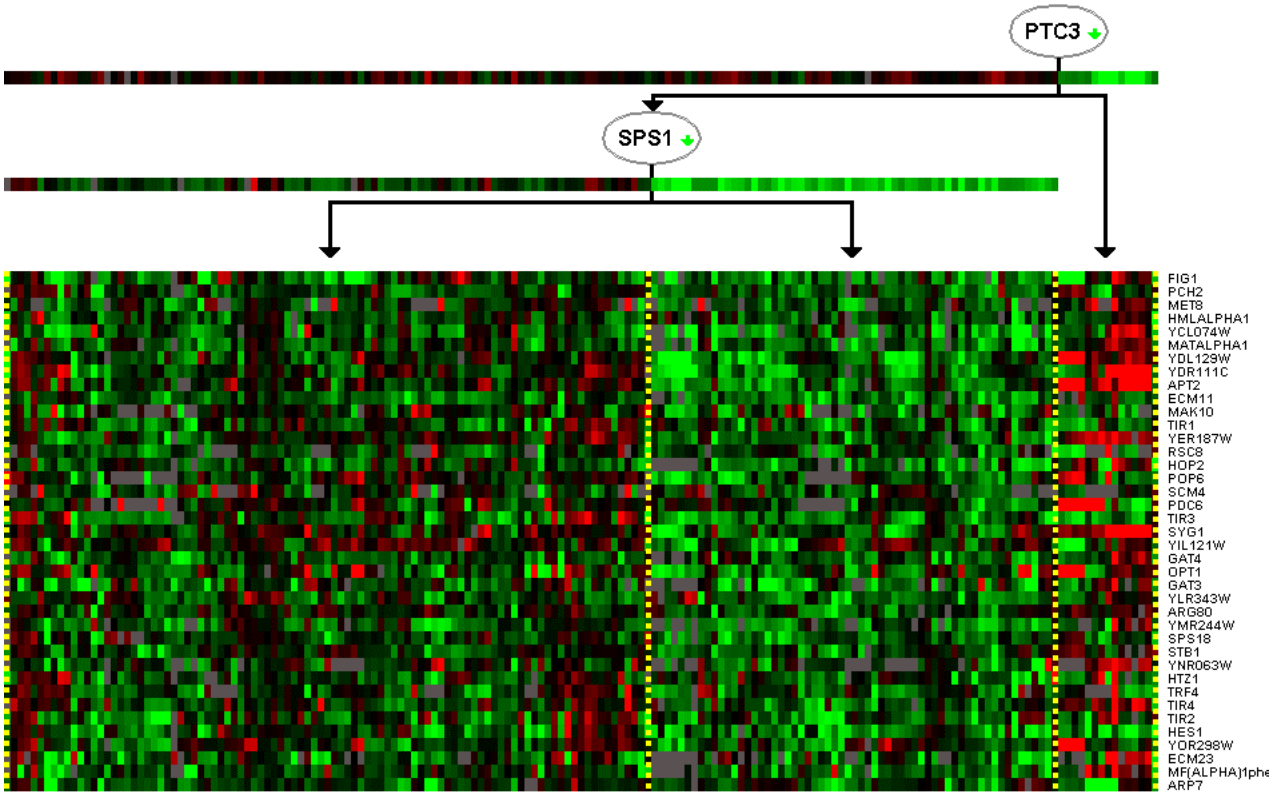
Module 20: TFs I



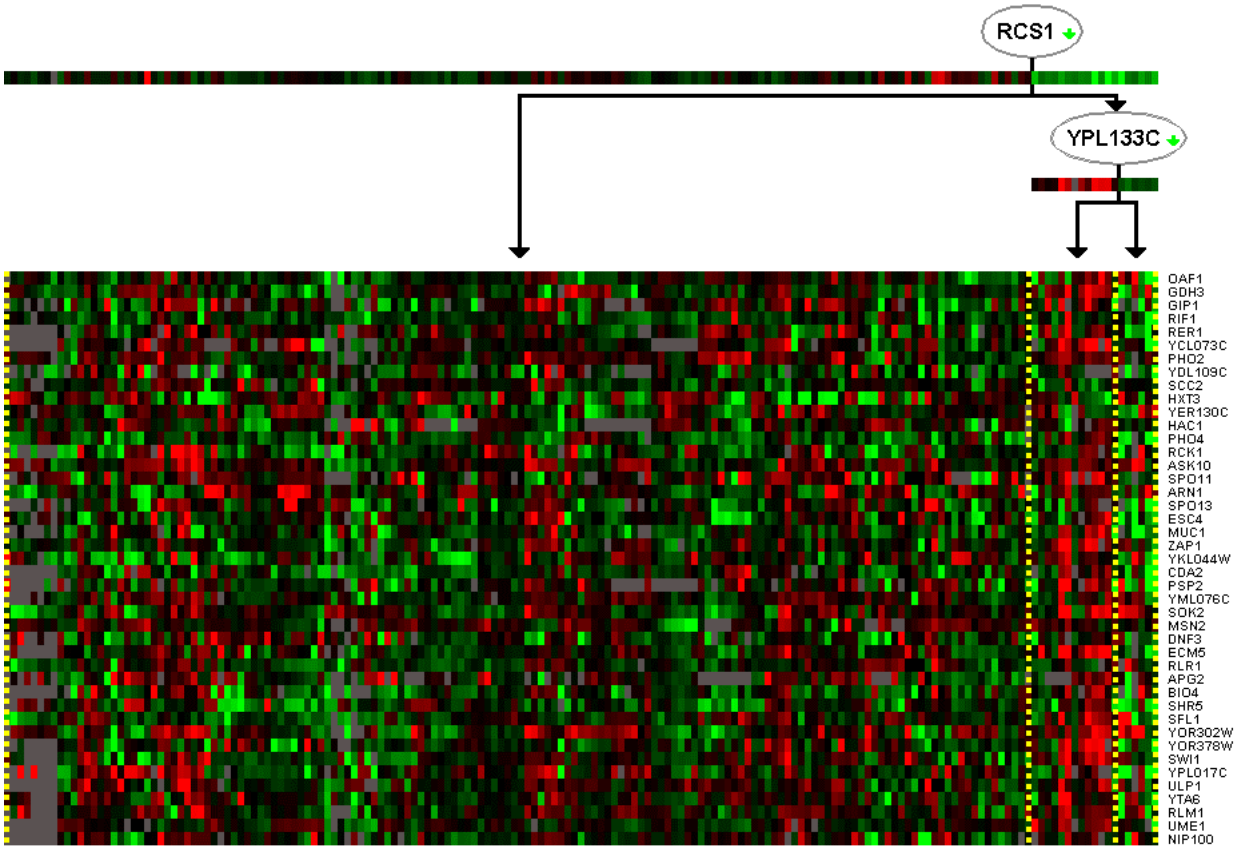
Module 21: TFs II



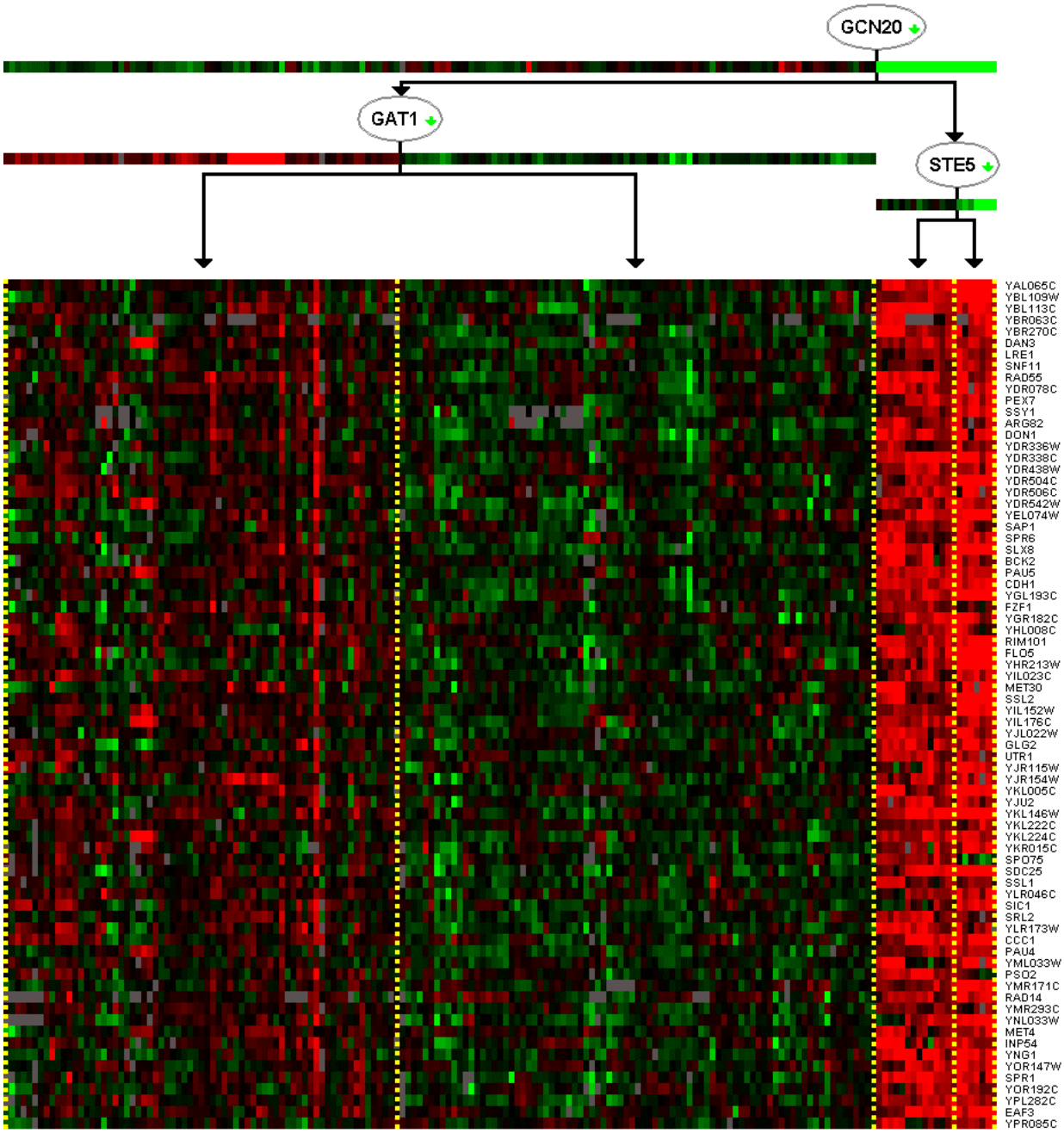
Module 22: TFs, cell wall and mating



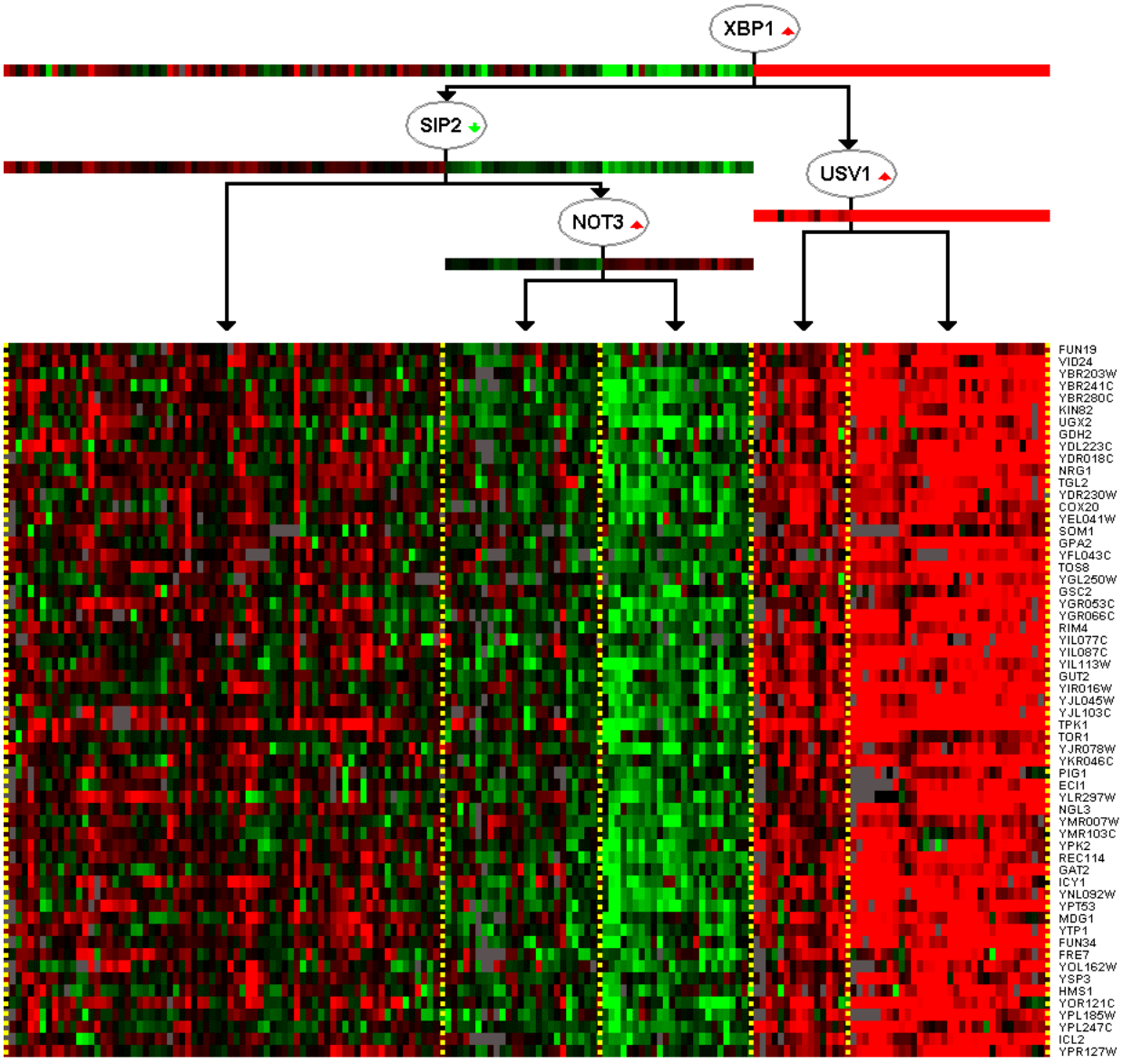
Module 23: TFs and sporulation



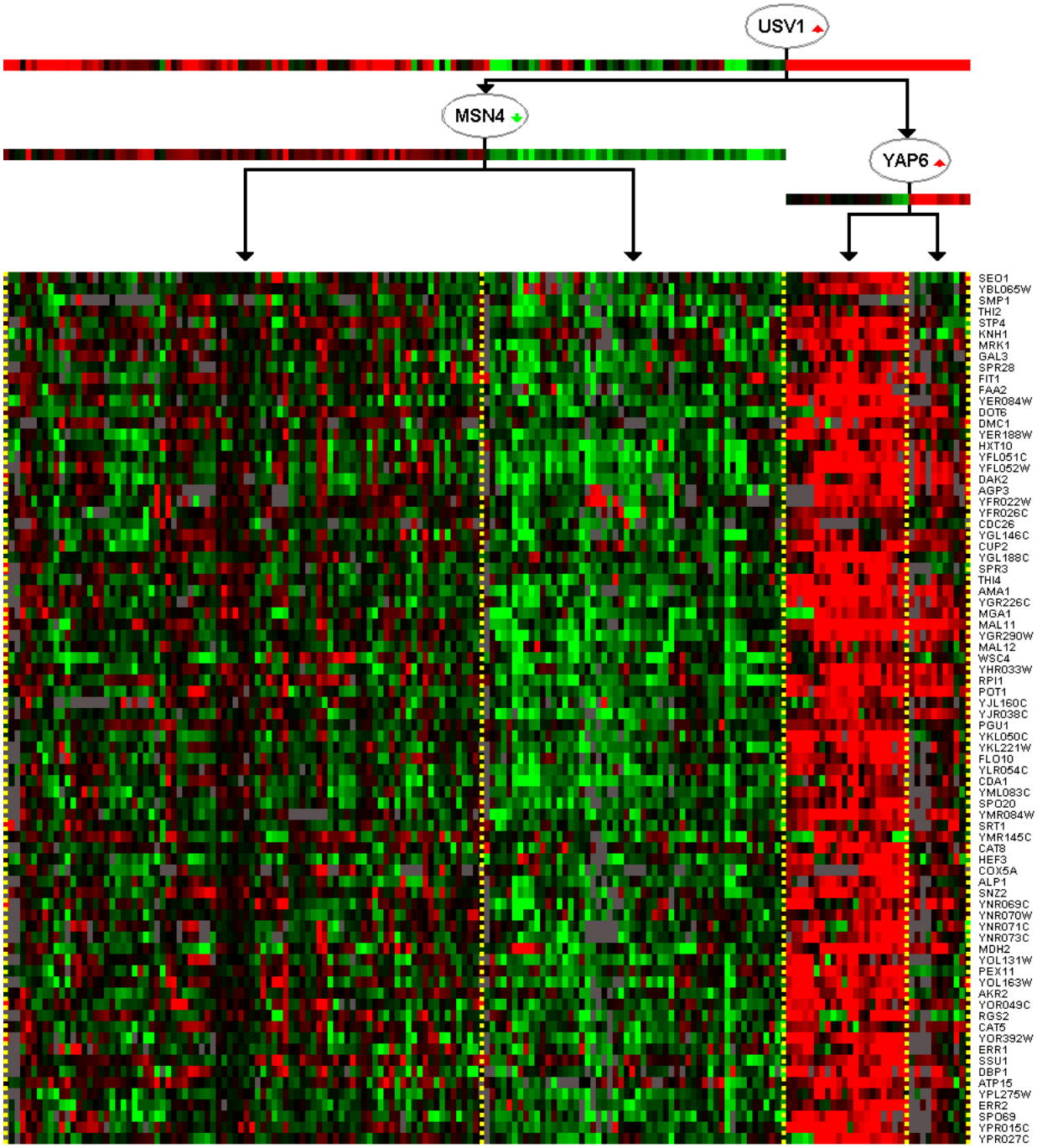
Module 24: Sporulation and TFs



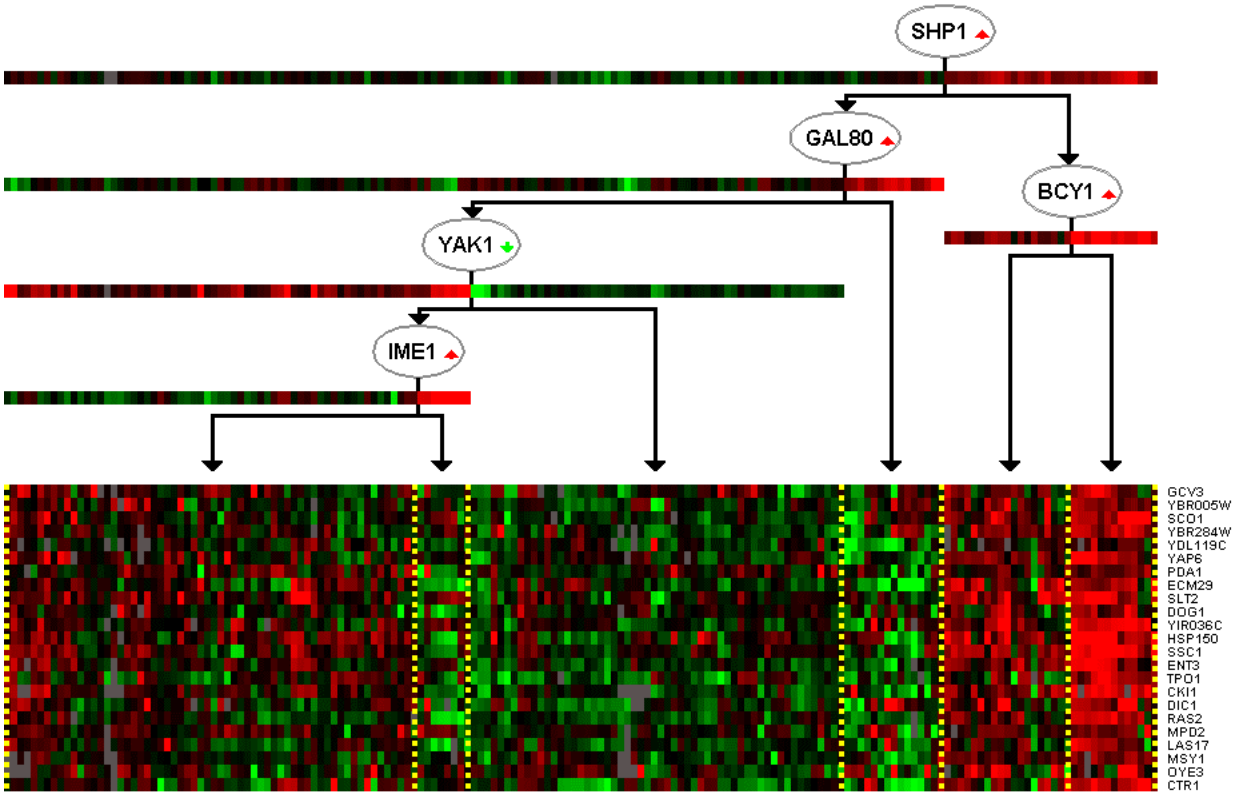
Module 25: Sporulation and cAMP pathway



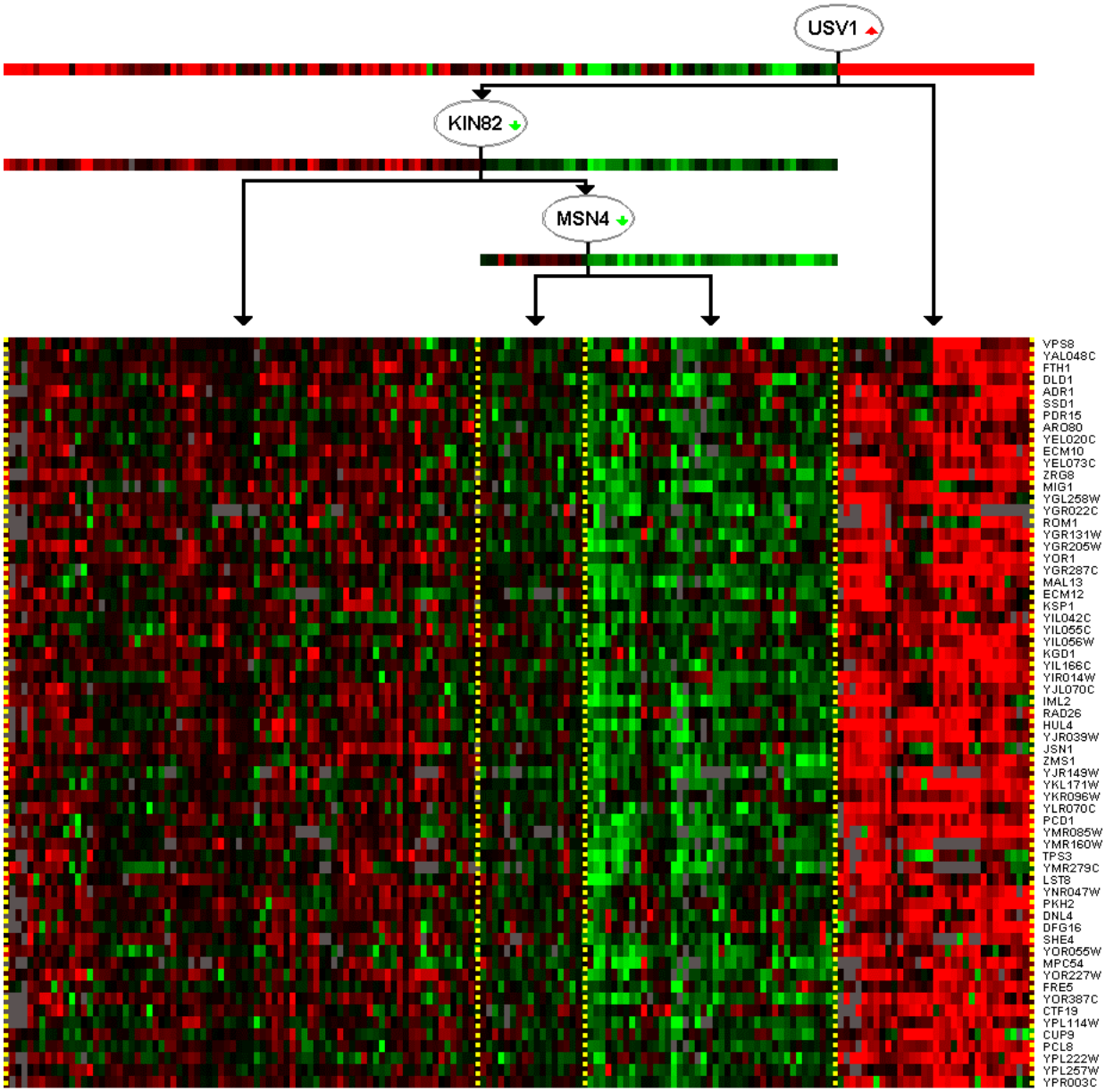
Module 26: Sporulation and Cell wall



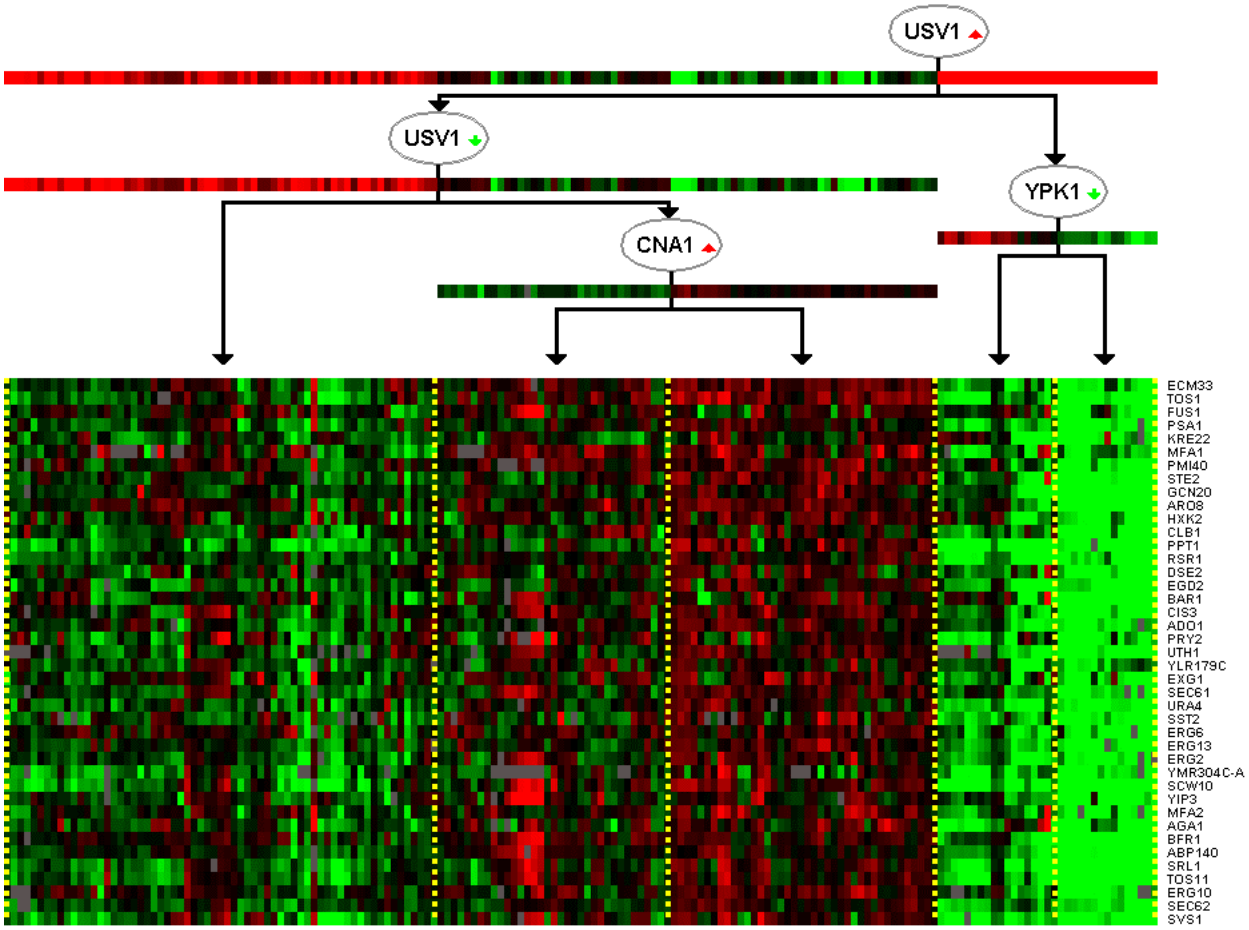
Module 27: Cell wall and transport I



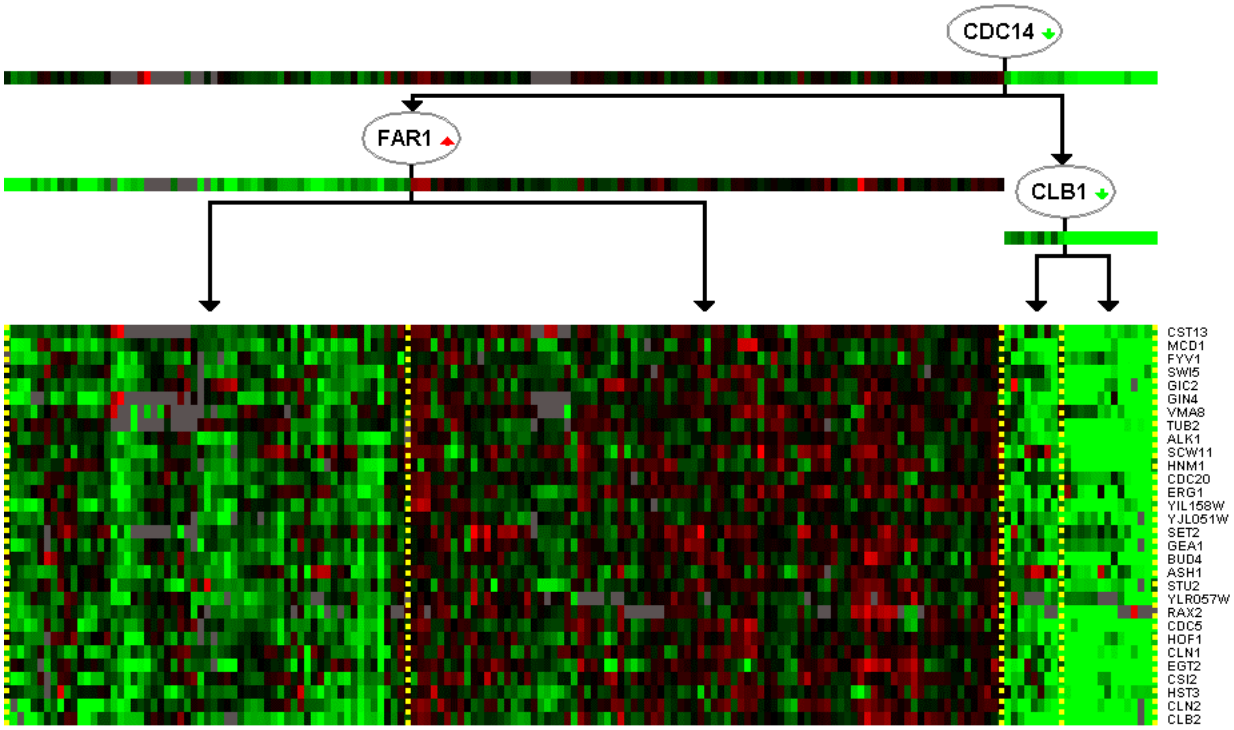
Module 28: Cell wall and Transport II



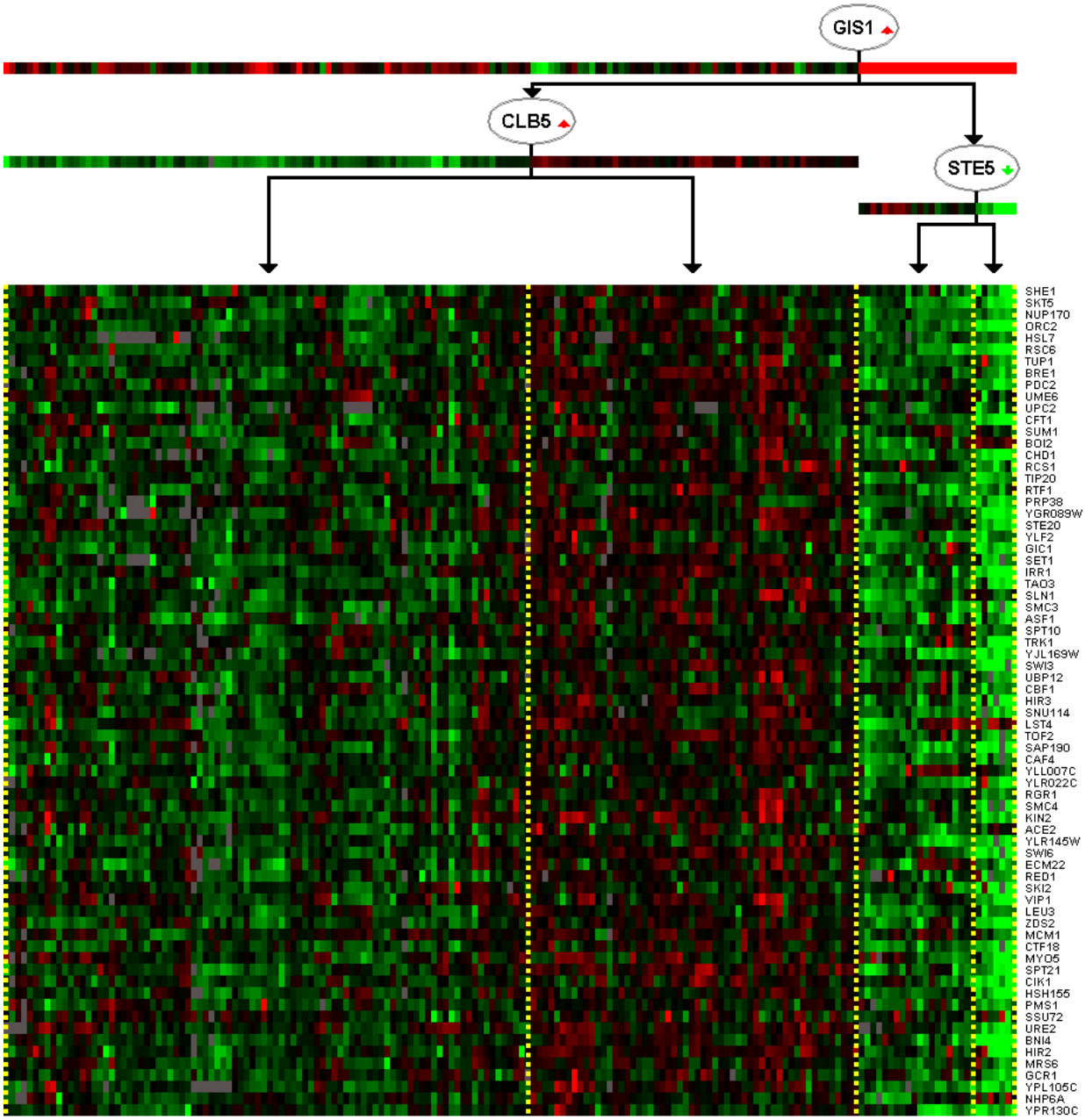
Module 29: Cell differentiation



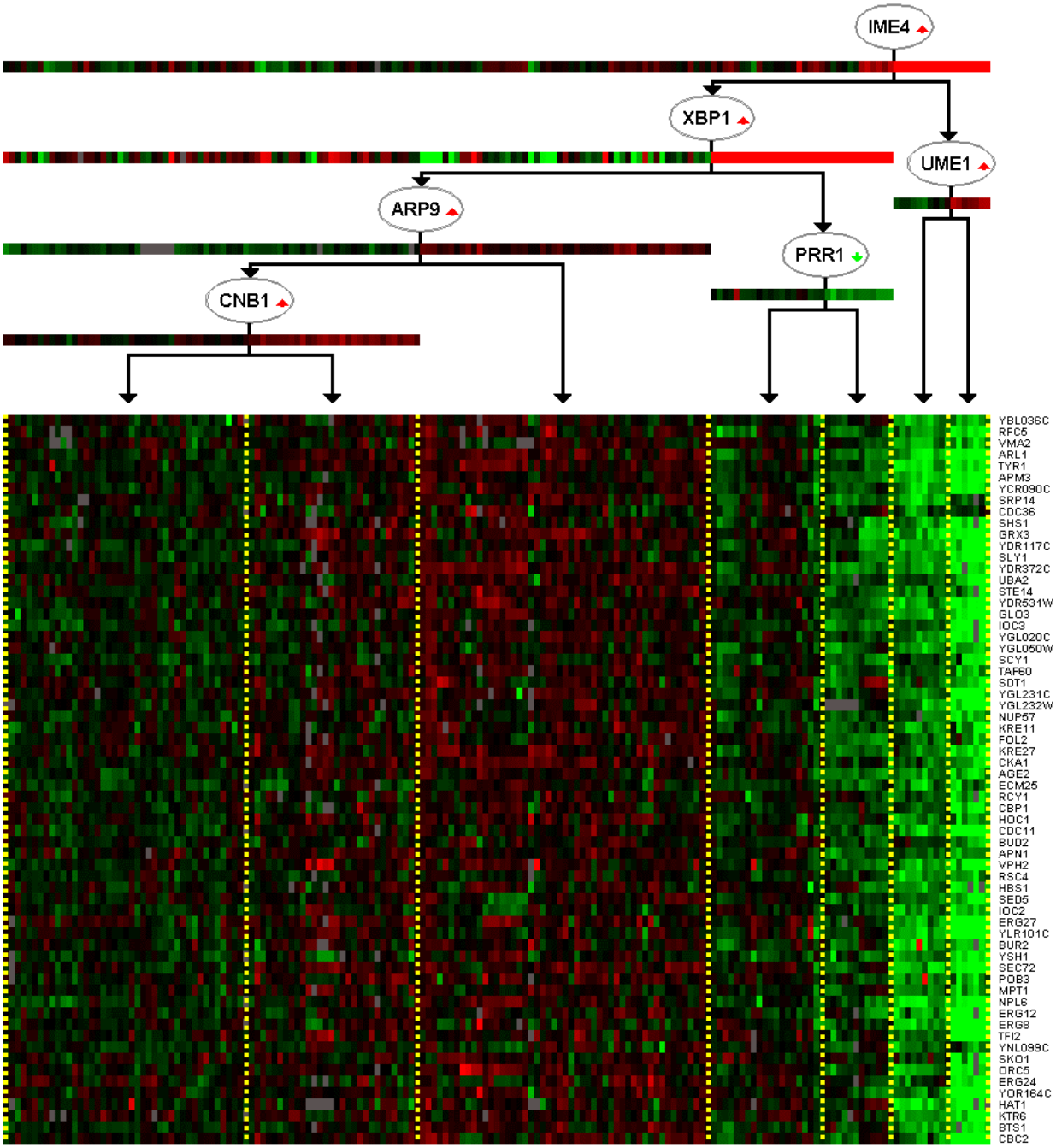
Module 30: Cell cycle (G2M)



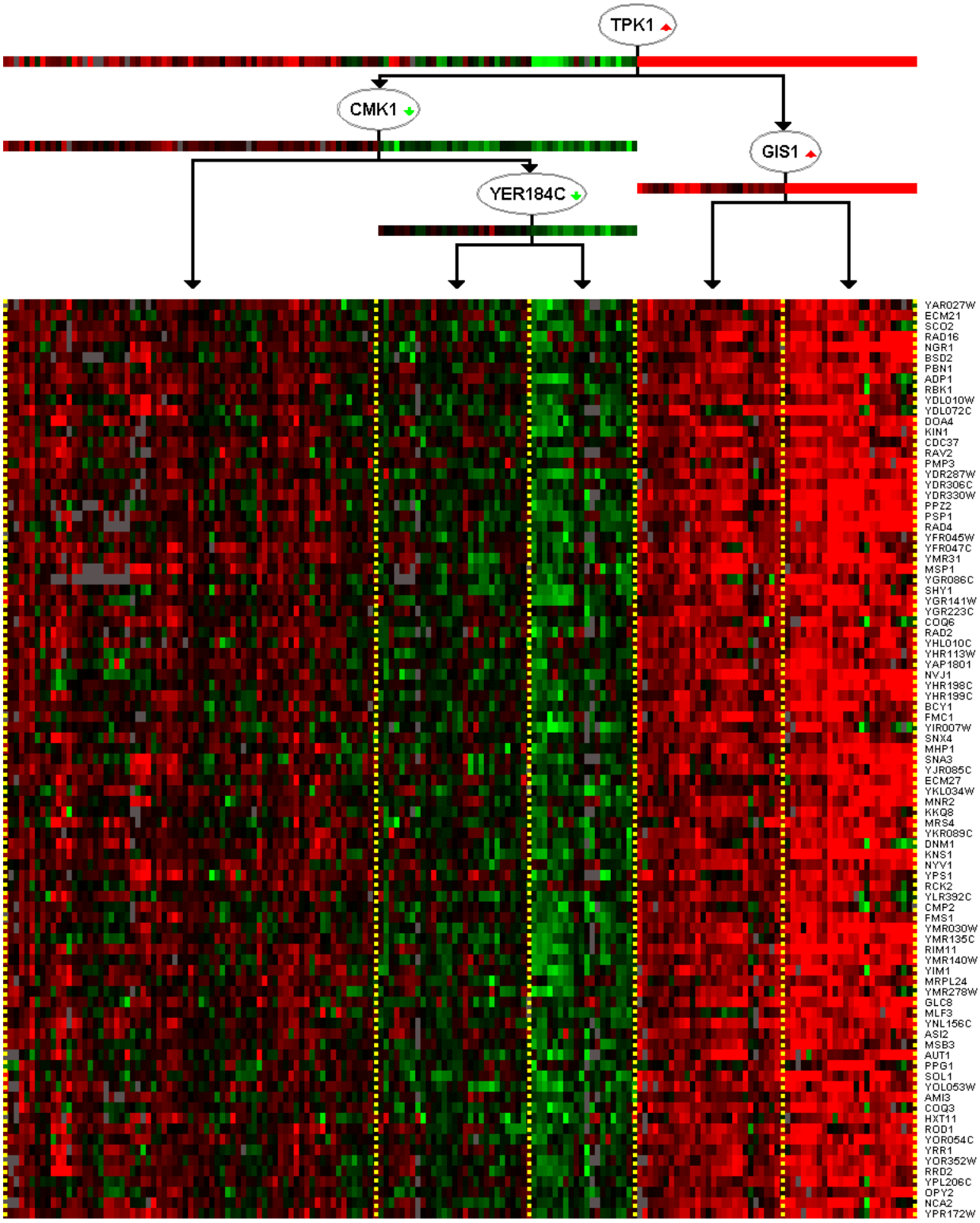
Module 31: Cell cycle, TFs and DNA metabolism



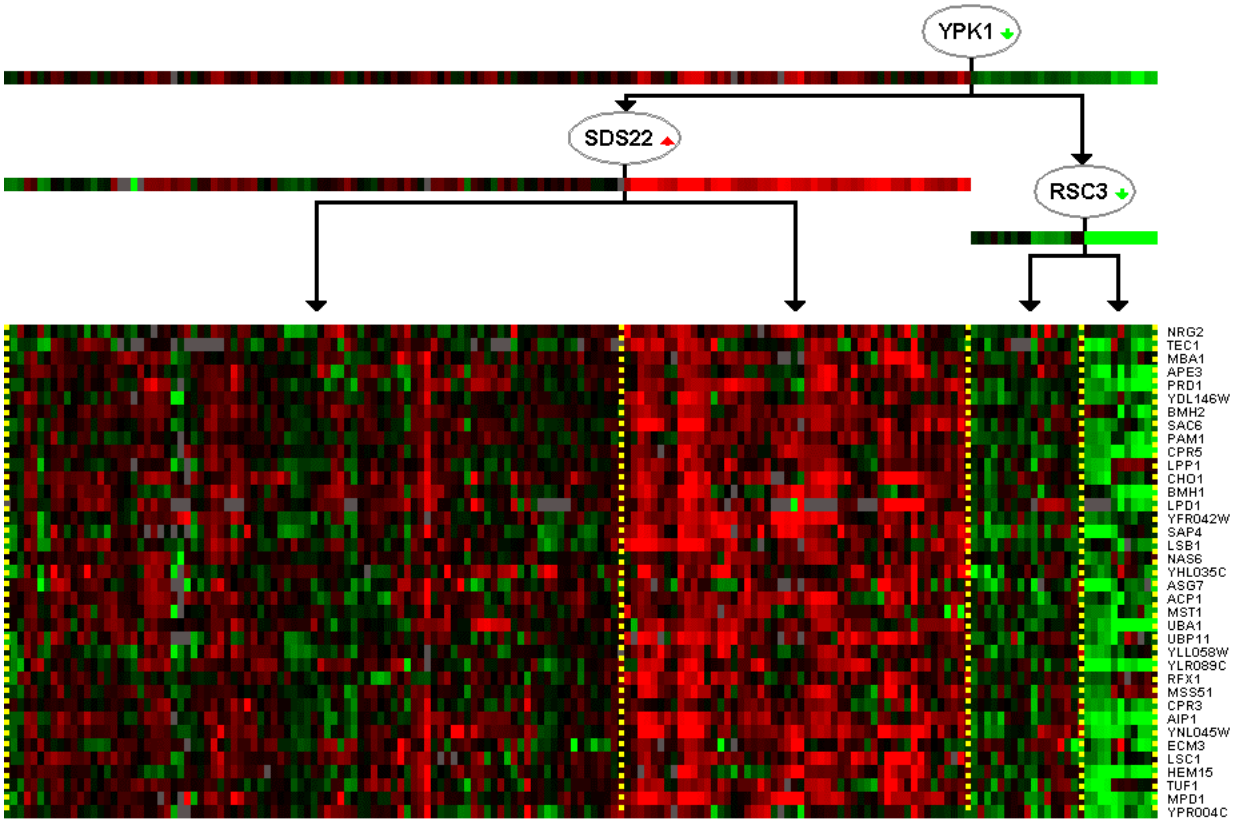
Module 32: Cell cycle and general TFs



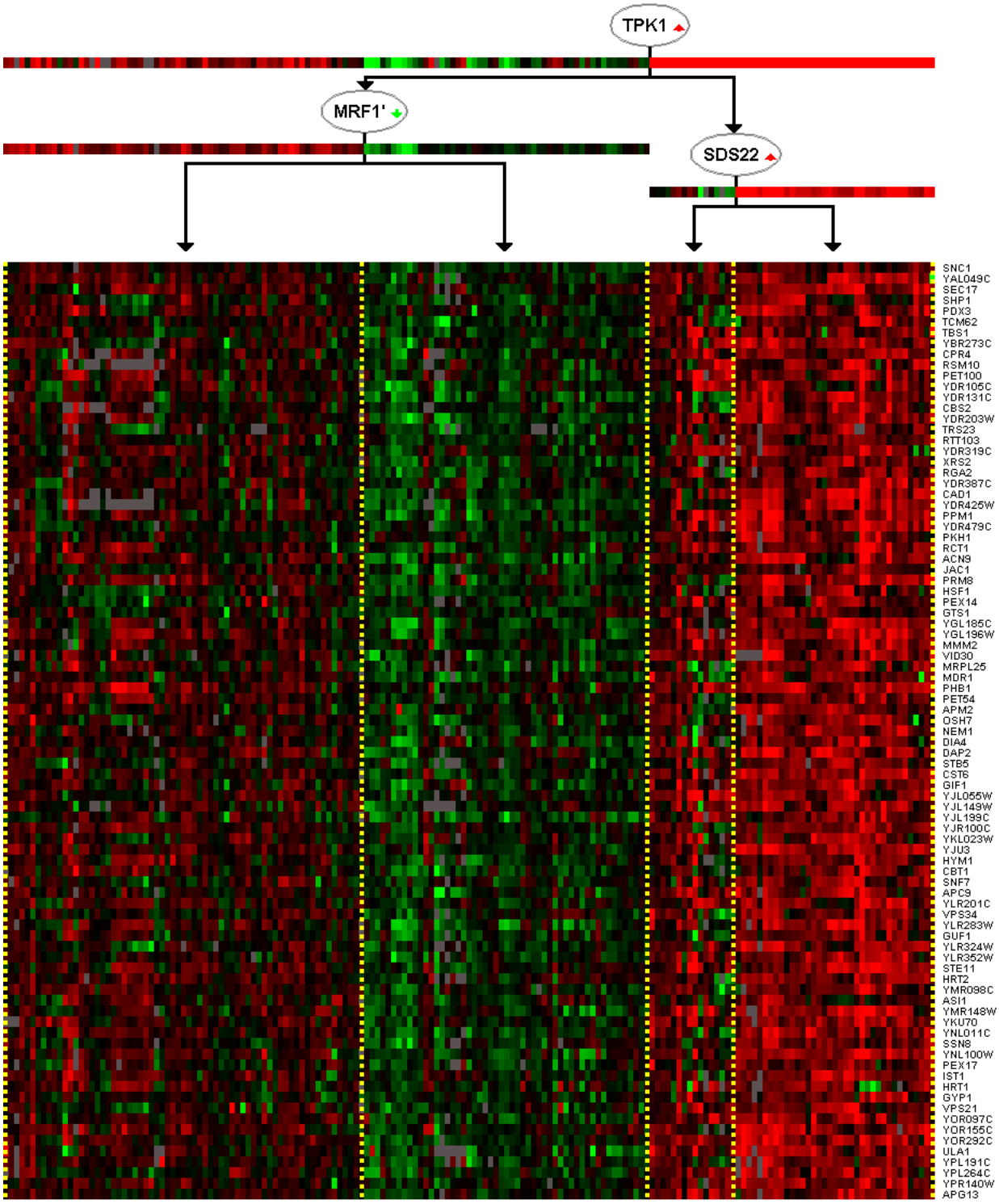
Module 33: Mitochondrial and Signaling



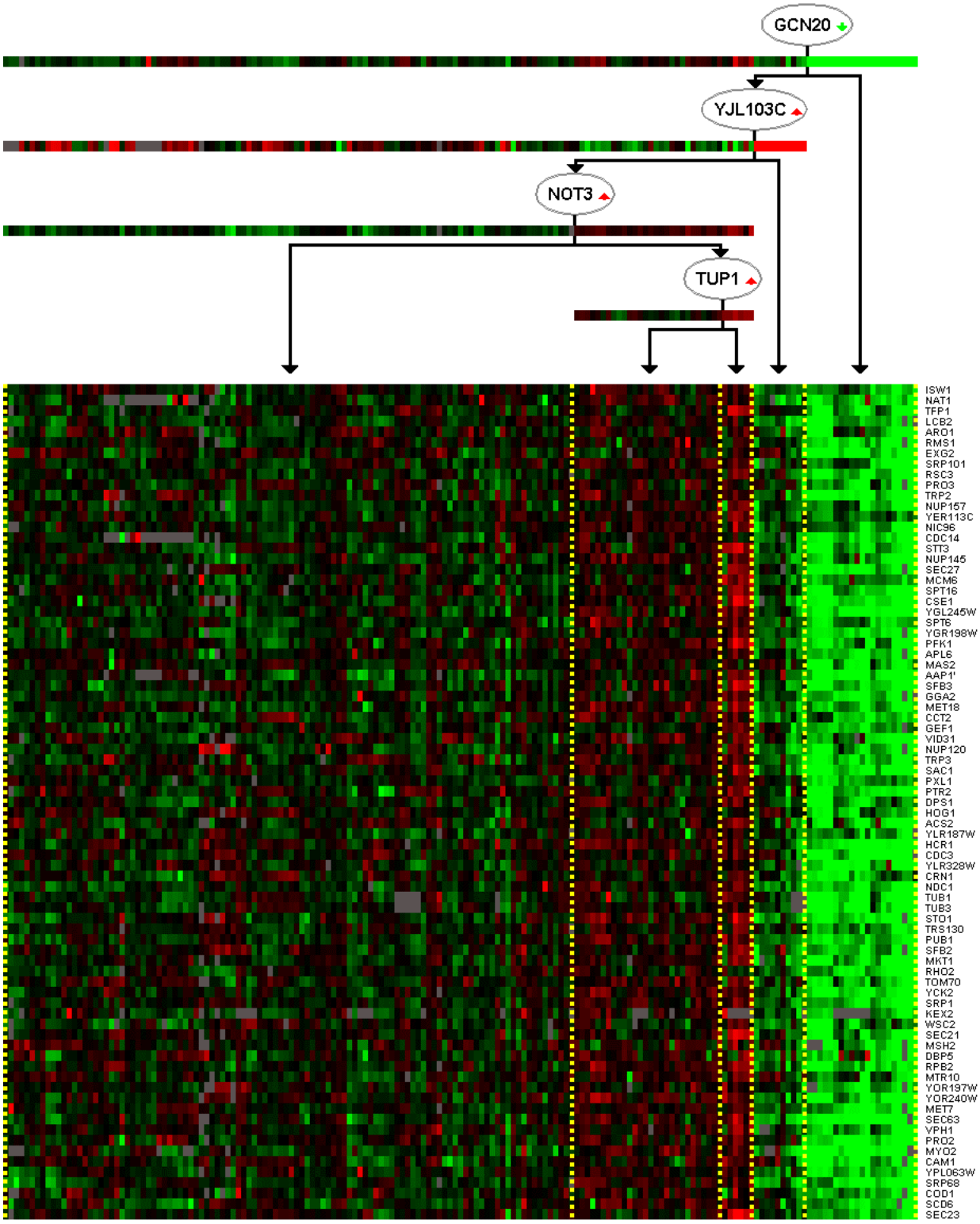
Module 34: Mitochondrial and Protein fate



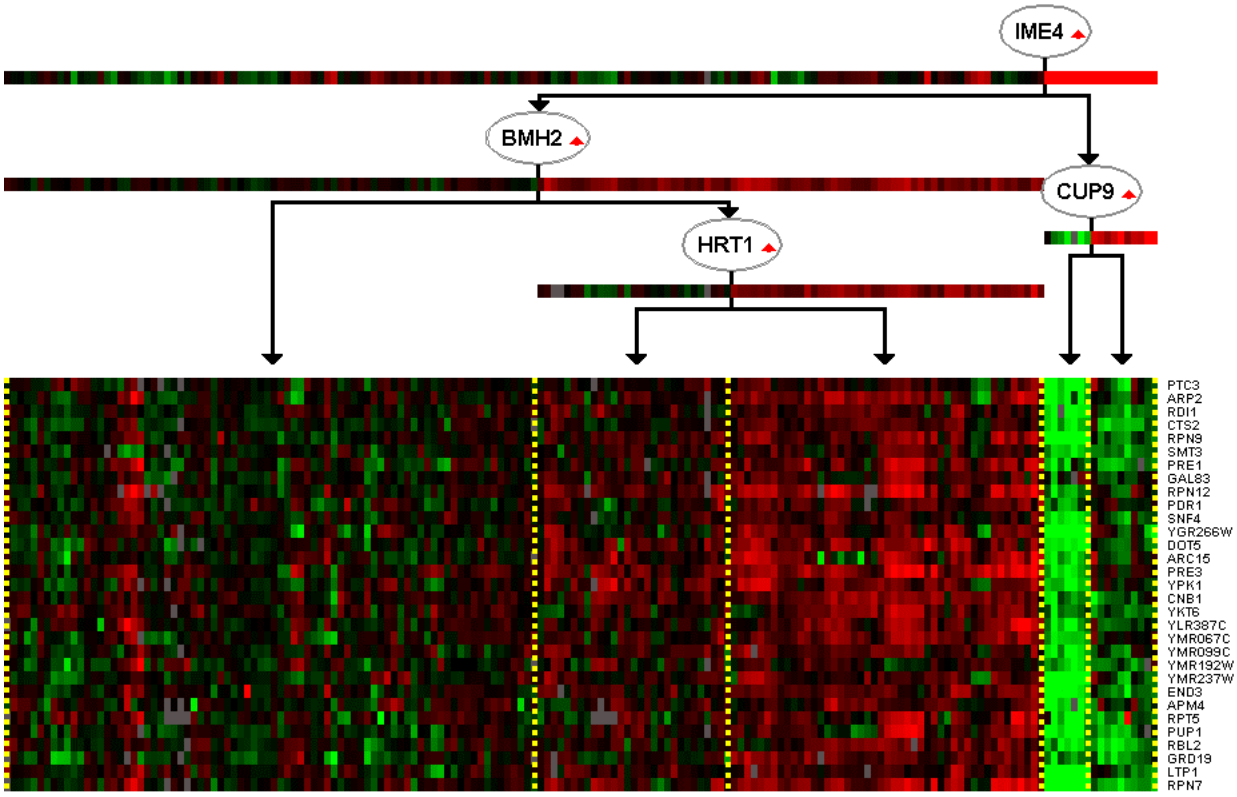
Module 35: Trafficking and Mitochondrial



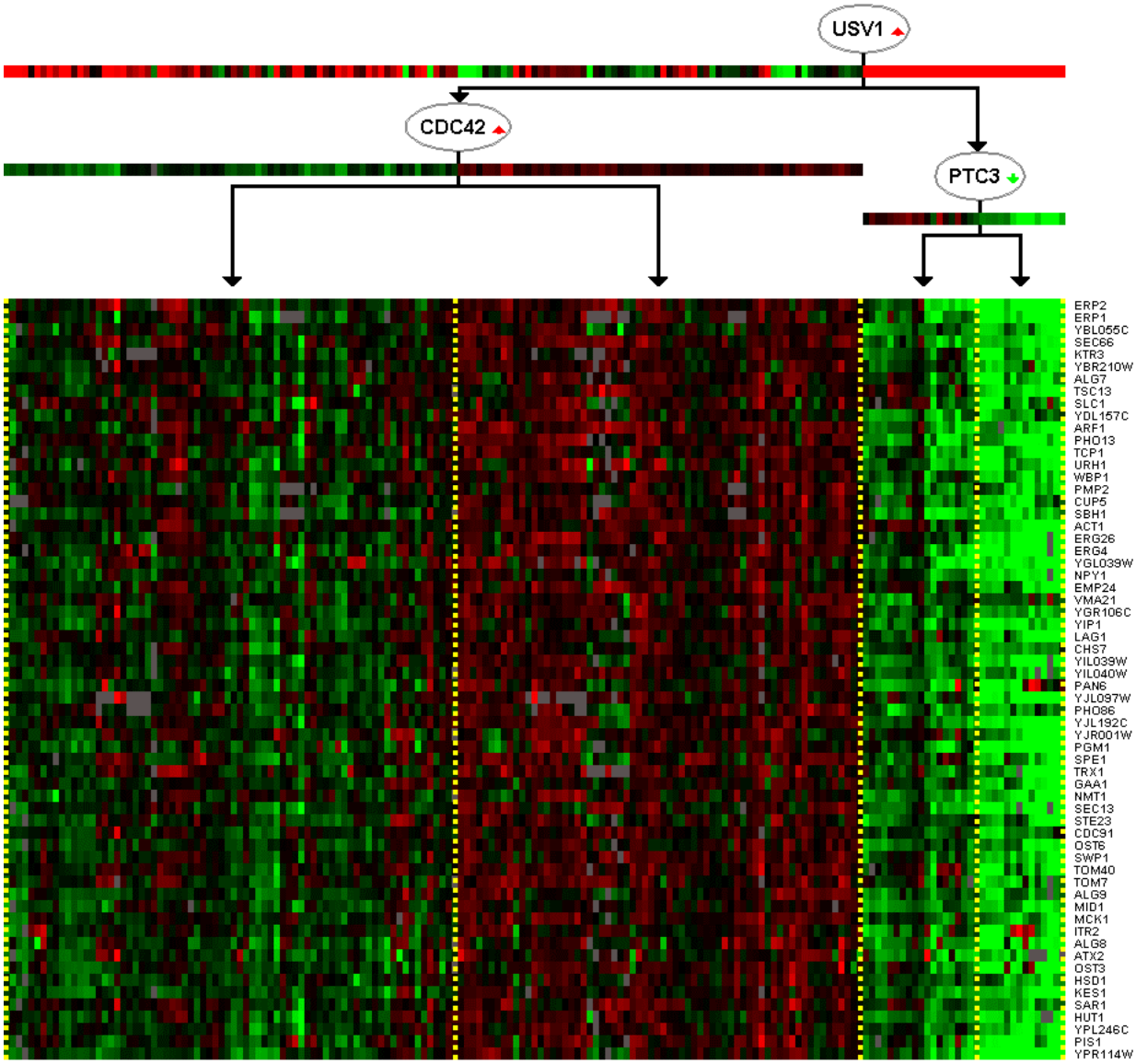
Module 36: ER and Nuclear



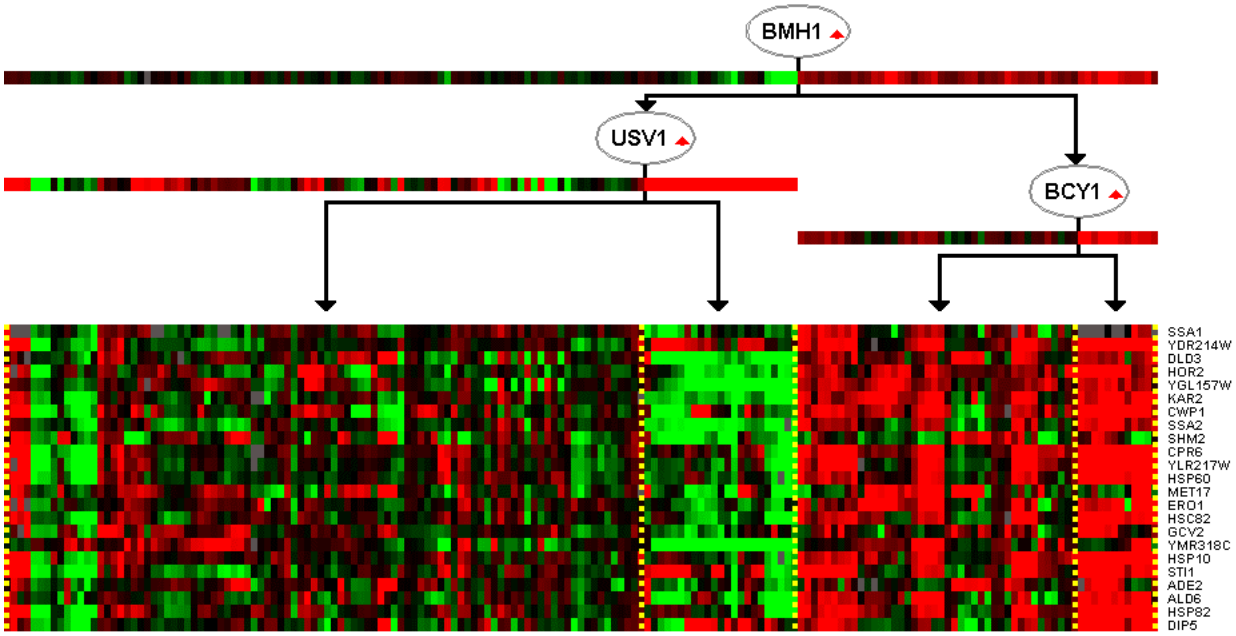
Module 37: Proteasome and Endocytosis



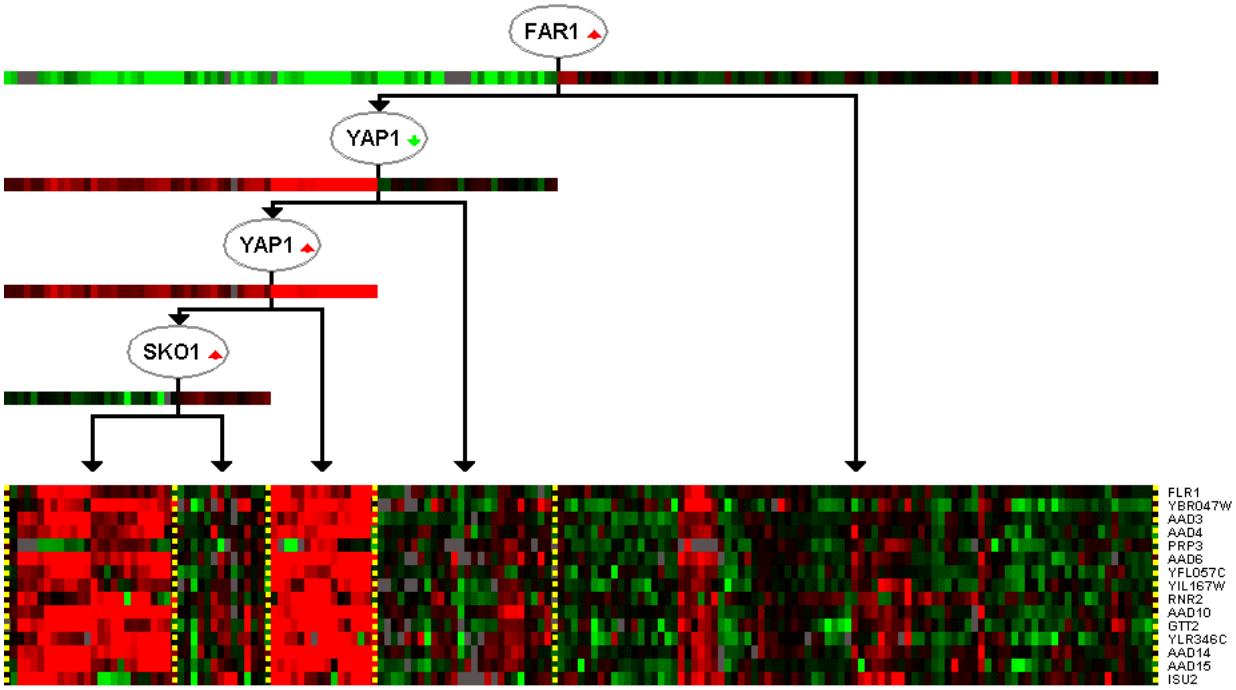
Module 38: Protein modification and trafficking



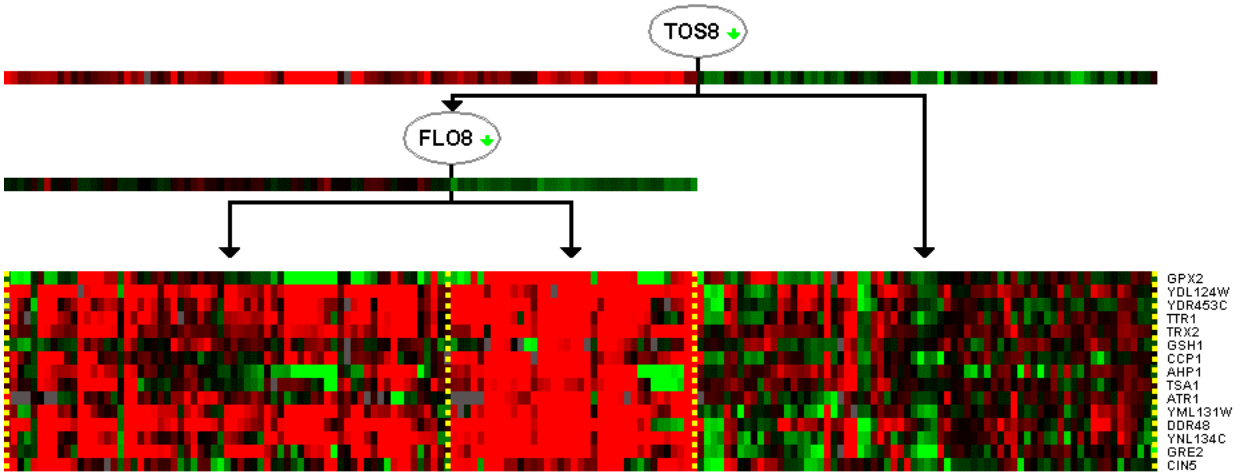
Module 39: Protein folding



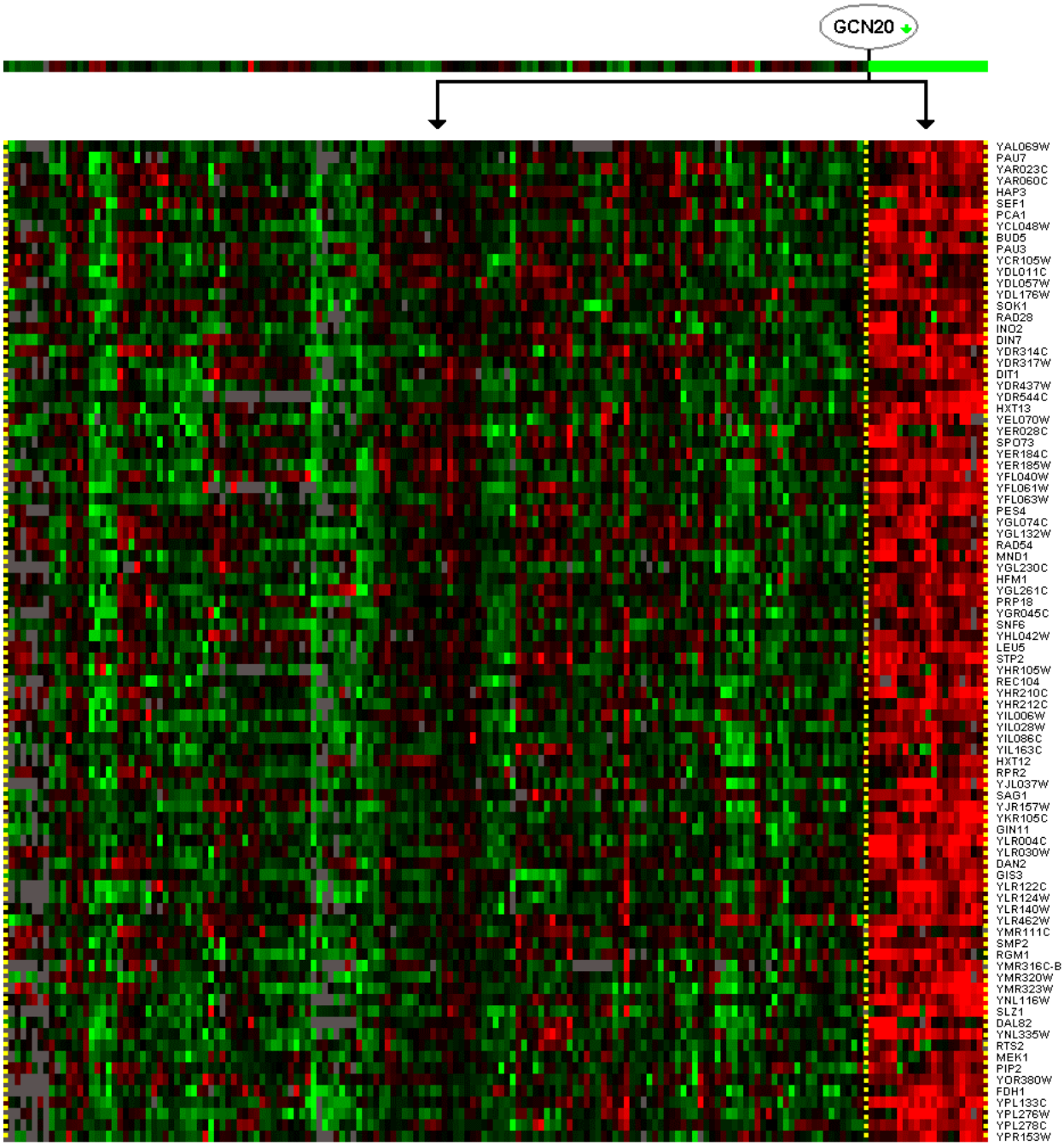
Module 40: Oxidative stress I



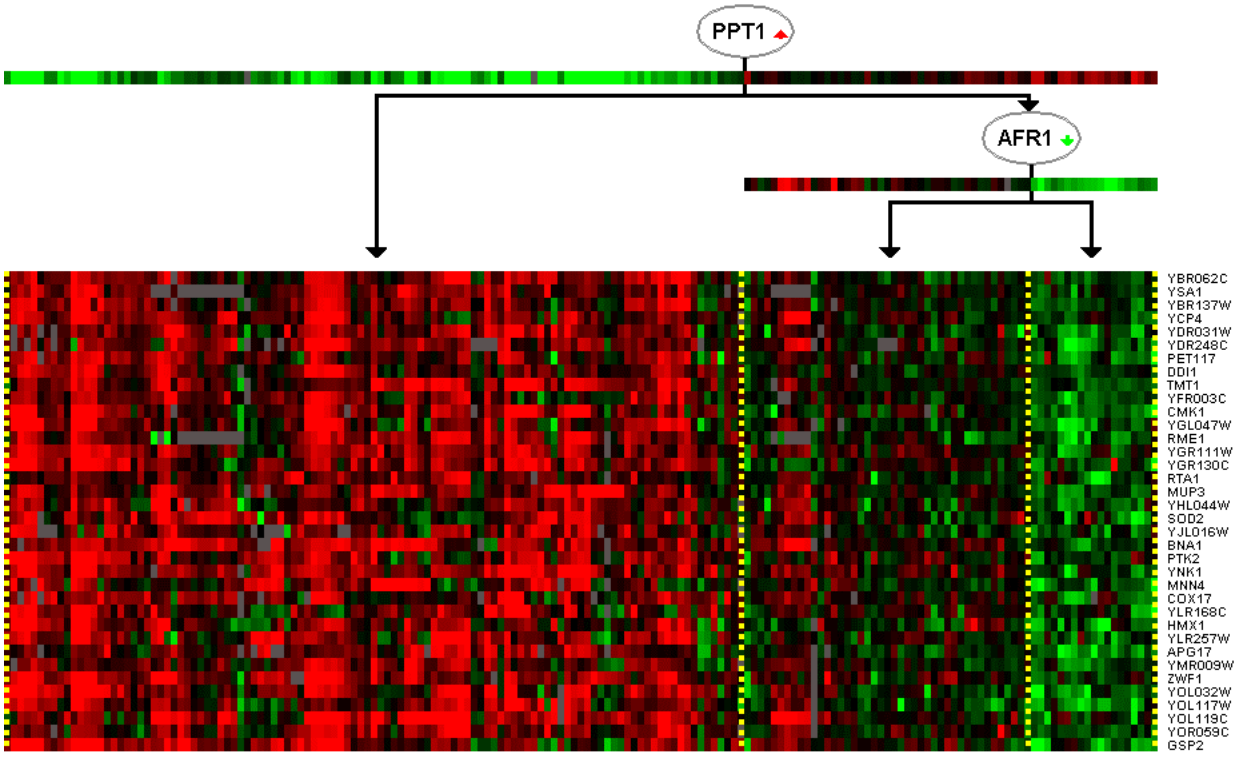
Module 41: Oxidative stress II



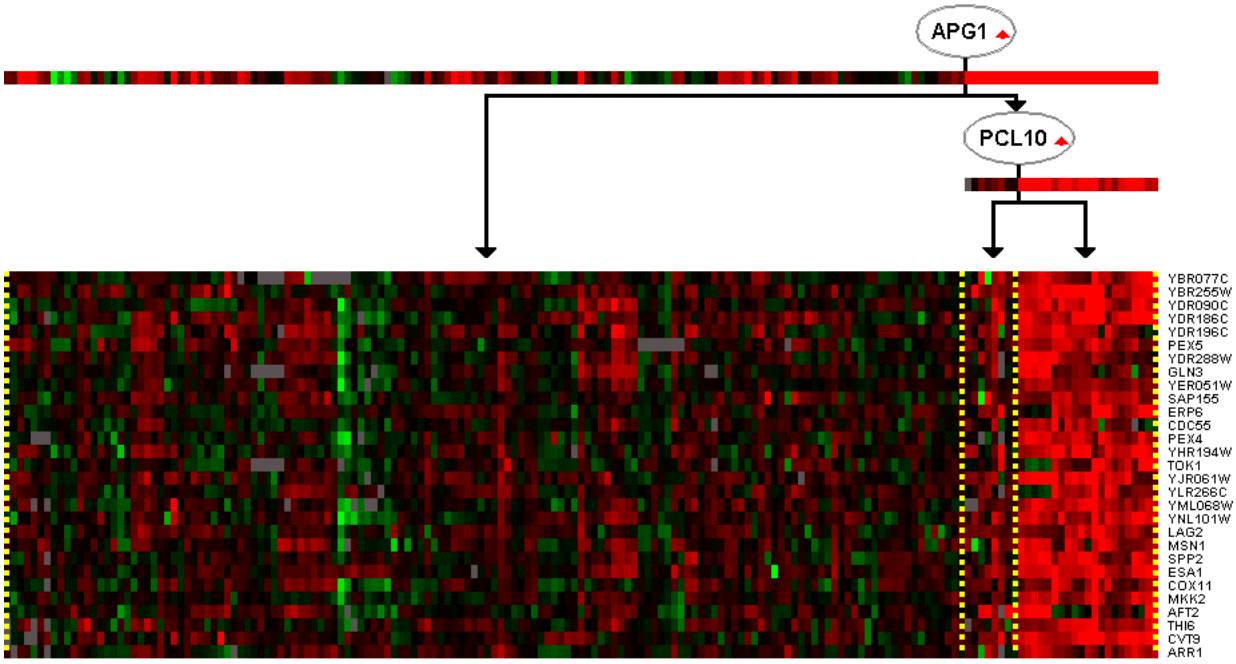
Module 42: Unkown (sub-telomeric)



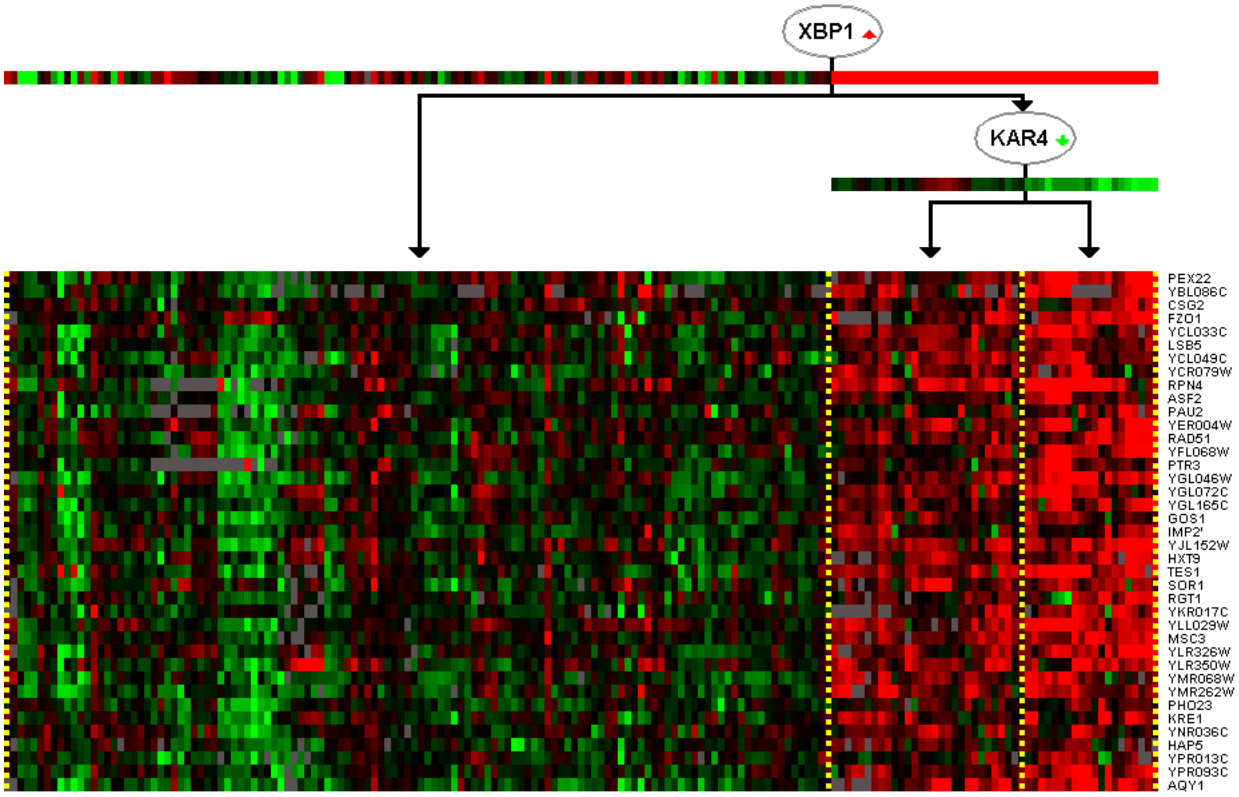
Module 43: Unknown genes I



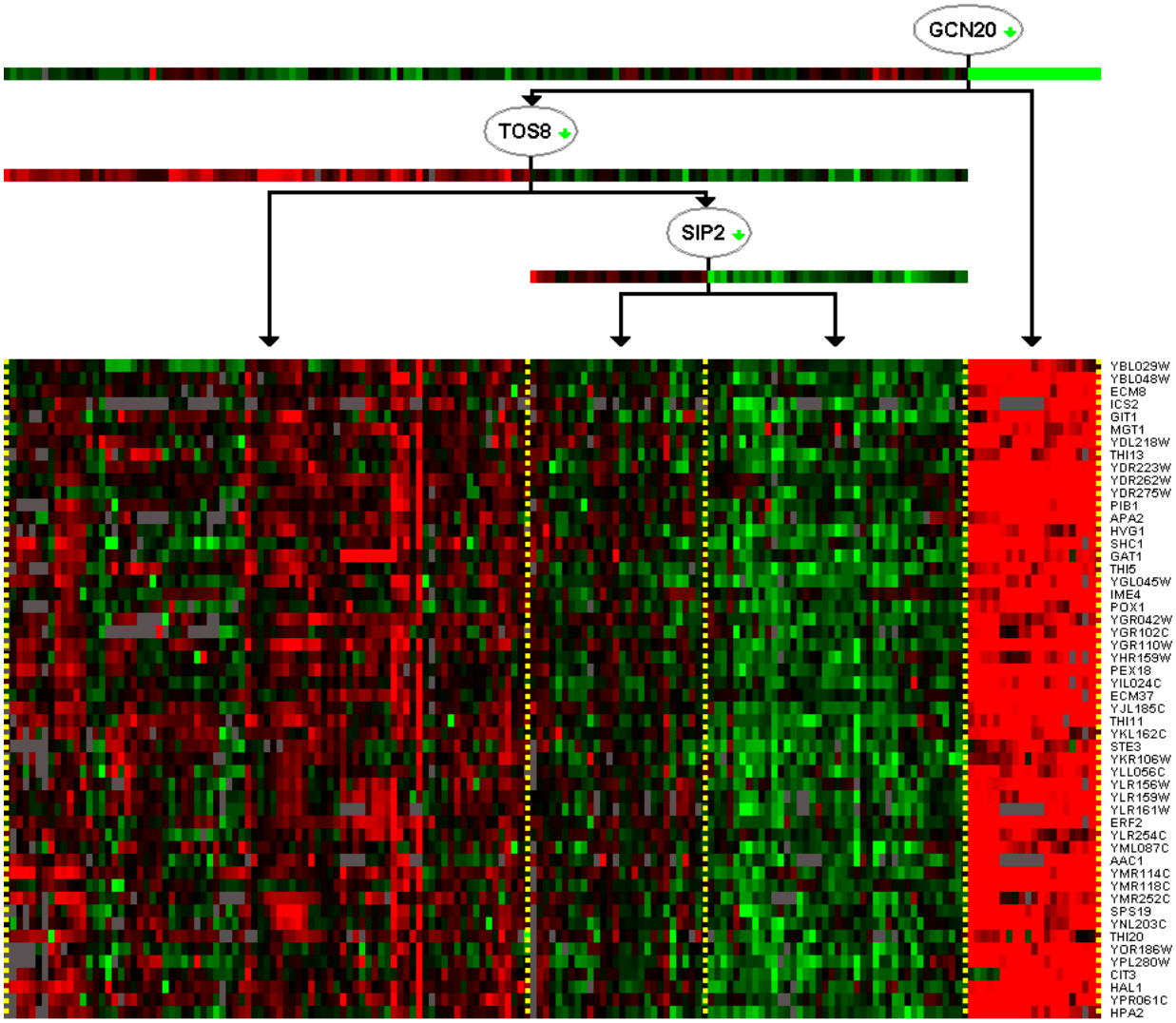
Module 44: Unknown genes II



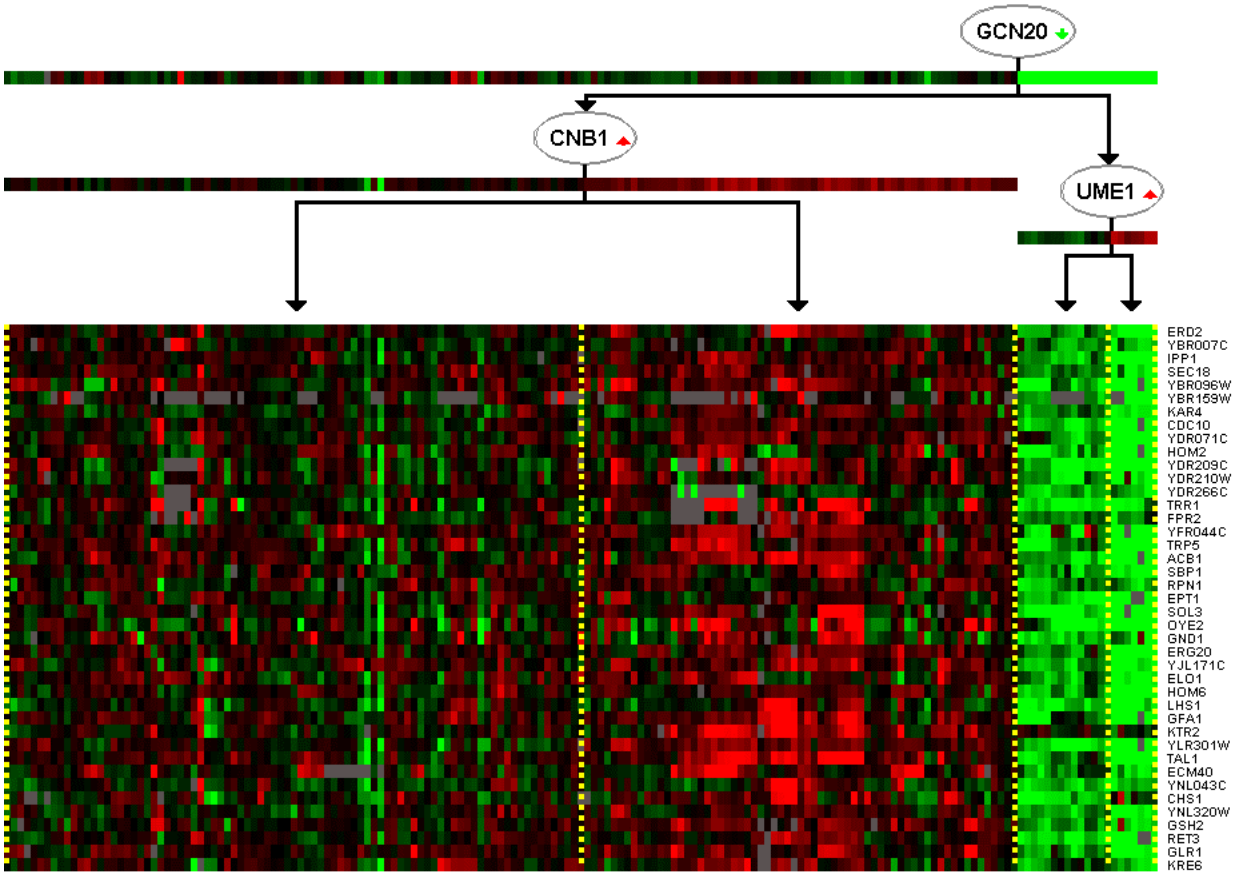
Module 45: Unknown genes III



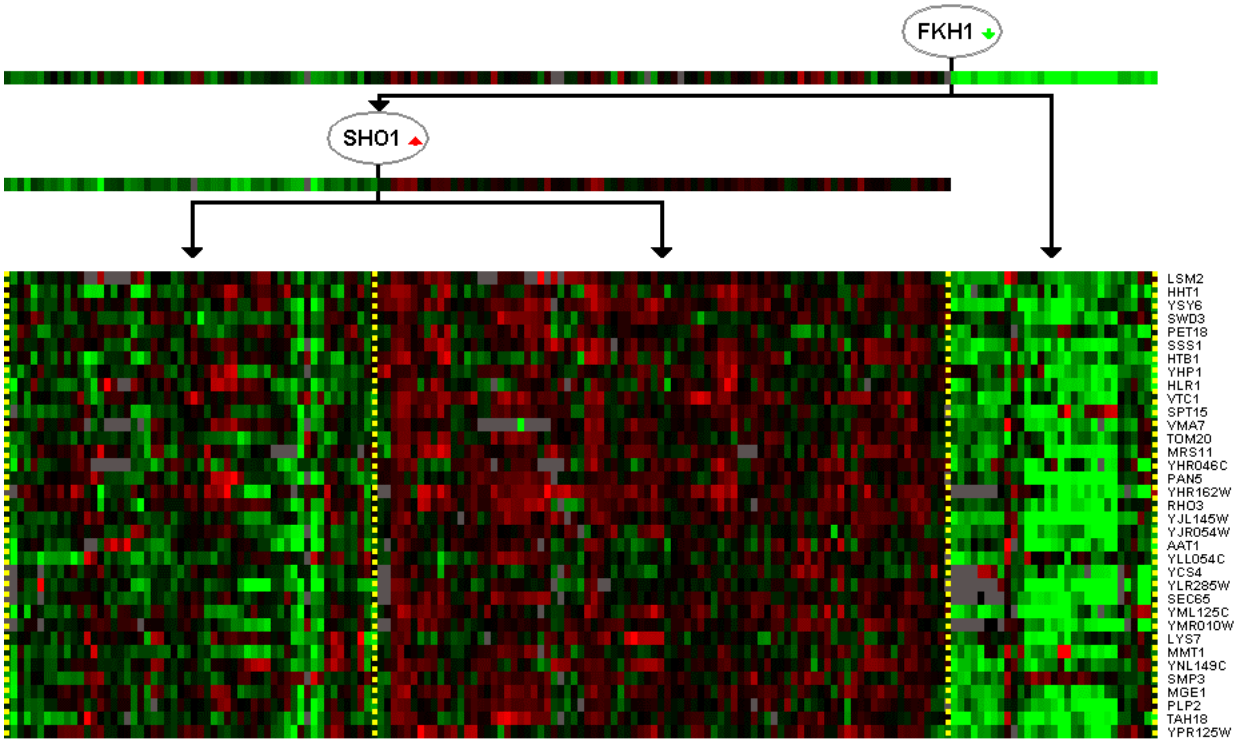
Module 46: Mixed II



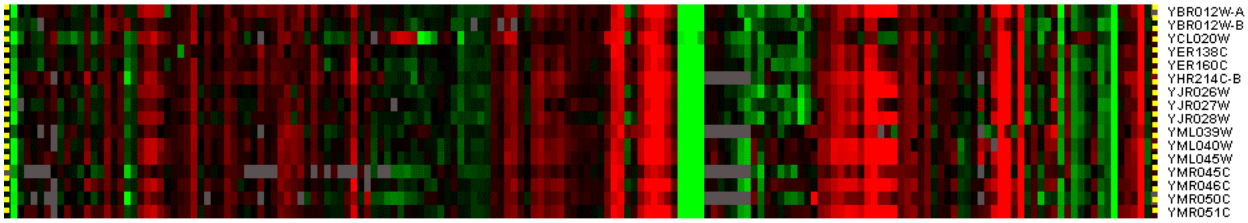
Module 47: Mixed III



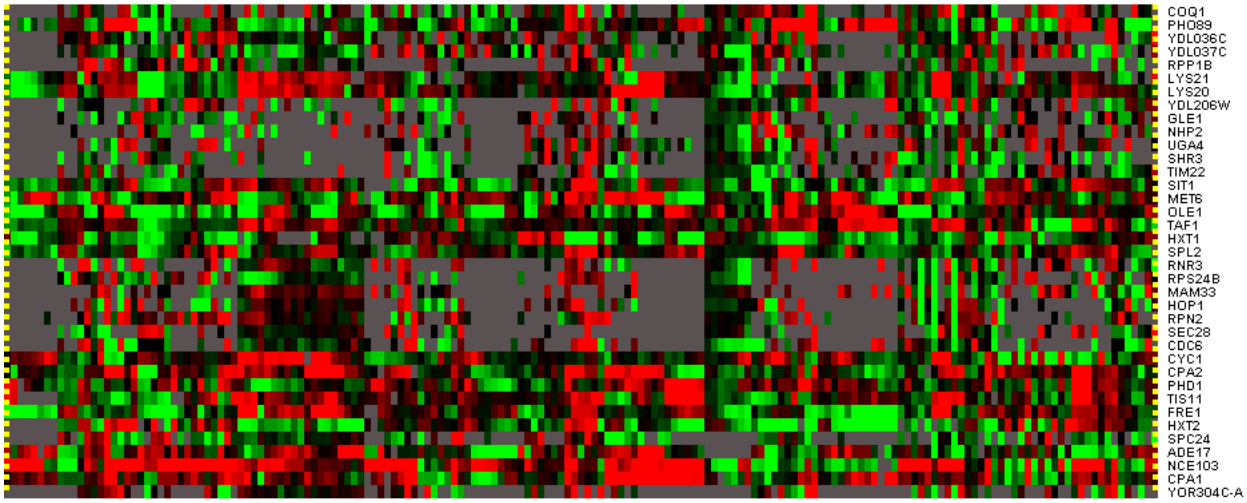
Module 48: Mixed IV



Module 49: Ty ORFs



Module 50: Missing values



Differentially Expressed Genes in Microarray Experiments.

We tested experimentally three of our method's hypotheses for a putative zinc-finger transcription factor, Ypl230w, and two putative signaling molecules, the protein kinase Kin82 and the phosphatase Ppt1. In concordance with the method's hypotheses, we tested ΔKin82 under heat shock conditions, ΔPpt1 during hypo-osmotic shift, and ΔYpl230w during the entry to stationary phase, a growth phase in which nutrients, primarily glucose, are depleted.

Below is a set of all genes that were found to be differentially expressed between the wild type and the mutant. We obtained these lists by applying a paired two-tailed t-test to compare the expression time series of mutant and wild-type. Genes with $p<0.05$ from the t-test were considered differentially expressed. Each time series was zero-transformed to enable comparison of the response to the tested condition. For Kin82 and Ppt1, we gave all time points as input to the t-test (5, 15, 30, and 60 minutes for Kin82; 7, 15, 30, and 60 minutes for Ppt1). For the experiments measuring response during stationary phase (Ypl230w), we used only the late time points (7, 9, and 24 hours for Ypl230w), as the response to this growth condition starts at this time. To ensure that only genes with large differences are included, we also required that at least half the time points compared are different by at least a 2-fold change in expression. The only exception was Ppt1, where we required a 1.3 fold difference, as the overall signal in these arrays was weaker.

Table 5. Differentially expressed genes in Ypl230w mutants

#	ORF	Name	*p*-value	#	ORF	Name	*p*-value	#	ORF	Name	*p*-value
1	Ydl017w	Cdc7	7.09E-05	51	Ykl156w	Rps27a	0.0041	101	Yjl066c	Mpm1	0.0097
2	Ydl001w	Rmd1	0.00021	52	Yer037w	Phm8	0.0041	102	Yil161w		0.0098
3	Yfl041w	Fet5	0.00022	53	Ybr103w	Sif2	0.0042	103	Ynl097c	Pho23	0.01
4	Ygr126w		0.00022	54	Ypl106c	Sse1	0.0043	104	Ypl251w		0.01
5	Ypl125w	Kap120	0.00029	55	Ylr438w	Car2	0.0044	105	Yor142w	Lsc1	0.01
6	Ygl013c	Pdr1	0.00033	56	Yol079w		0.0044	106	Ybr127c	Vma2	0.01
7	Ybr058c	Ubp14	0.00048	57	Ydl239c	Ady3	0.0044	107	Ybr057c	Mum2	0.01
8	Ygr232w	Nas6	0.00058	58	Ybr157c	Ics2	0.0045	108	Yhl034c	Sbp1	0.01
9	Ypl037c	Egd1	0.00067	59	Ynr051c	Bre5	0.0045	109	Ykl108w	Sld2	0.01
10	Ydr346c	Sgi1	0.0007	60	Ydl241w		0.0046	110	Ylr162w		0.011
11	Ygl127c	Soh1	0.00071	61	Yfl008w	Smc1	0.0046	111	Ydl130w	Rpp1b	0.011
12	Ynl211c		0.001	62	Yml013c-a		0.005	112	Ydr380w	Aro10	0.011
13	Yal004w		0.0012	63	Yjr059w	Ptk2	0.0051	113	Ykr033c		0.011
14	Ylr397c	Afg2	0.0012	64	Ybr263w	Shm1	0.0052	114	Yel049w	Pau2	0.011
15	Ypr182w	Smx3	0.0012	65	Ybr040w	Fig1	0.0052	115	Ybr205w	Ktr3	0.011
16	Yal005c	Ssa1	0.0013	66	Ycl075w		0.0053	116	Ycl076w		0.011
17	Ynl286w	Cus2	0.0013	67	Ypr133c	Iws1	0.0054	117	Ylr119w	Srn2	0.011
18	Ybr134w		0.0014	68	Yml078w	Cpr3	0.0057	118	Yel059w		0.011
19	Ydl226c	Gcs1	0.0016	69	Yhr122w		0.0057	119	Ygl011c	Scl1	0.011
20	Yfr029w	Ptr3	0.0016	70	Ydr082w	Stn1	0.0058	120	Yml100w	Tsl1	0.011
21	Yer072w	Vtc1	0.0017	71	Ylr214w	Fre1	0.0058	121	Yal068c		0.012
22	Ydr281c	Phm6	0.0019	72	Yal061w		0.0059	122	Yor298c-a	Mbf1	0.012
23	Ykl033w-a		0.0021	73	Yer133w	Glc7	0.0059	123	Yll007c		0.012
24	Ydr251w	Pam1	0.0022	74	Yfl013c	Ies1	0.0059	124	Yor240w		0.012
25	Yel003w	Gim4	0.0024	75	Yor140w	Sfl1	0.006	125	Yhr094c	Hxt1	0.013
26	Ydl180w		0.0025	76	Ygr156w	Pti1	0.0063	126	Ydr387c		0.013
27	Yhl001w	Rpl14b	0.0026	77	Ynl148c	Alf1	0.0063	127	Ydr416w	Syf1	0.013
28	Yhl031c	Gos1	0.0028	78	Yol052c	Spe2	0.0065	128	Ykl064w	Mnr2	0.013
29	Ygr019w	Uga1	0.0029	79	Yor117w	Rpt5	0.0066	129	Ydl224c	Whi4	0.013
30	Ybr230c		0.0029	80	Ylr451w	Leu3	0.0066	130	Ymr091c	Npl6	0.013
31	Yil154c	Imp2'	0.003	81	Ybr153w	Rib7	0.0067	131	Yhr134w	Wss1	0.013
32	Ypr200c	Arr2	0.0031	82	Ylr056w	Erg3	0.0068	132	Ypr138c	Mep3	0.014
33	Ylr136c	Tis11	0.0031	83	Yfr040w	Sap155	0.0069	133	Yer050c	Rsm18	0.014
34	Yjl213w		0.0033	84	Ygl054c	Erv14	0.007	134	Yjl008c	Cct8	0.014
35	Yil114c	Por2	0.0034	85	Ydl029w	Arp2	0.007	135	Ypr152c		0.014
36	Ylr323c	Cwc24	0.0034	86	Ypl082c	Mot1	0.0072	136	Ycr081w	Srb8	0.014
37	Ydr214w	Aha1	0.0034	87	Ybr087w	Rfc5	0.0072	137	Ylr299w	Ecm38	0.014
38	Ybr104w	Ymc2	0.0034	88	Yor141c	Arp8	0.0073	138	Yor068c		0.014
39	Ycl065w		0.0035	89	Ypl033c		0.0073	139	Ypl052w		0.014
40	Ypl265w	Dip5	0.0035	90	Yjl183w	Mnn11	0.0074	140	Yjl061w	Nup82	0.014
41	Yor312c	Rpl20b	0.0035	91	Ydr270w	Ccc2	0.0077	141	Yjl160c		0.014
42	Yfl012w		0.0036	92	Ynl124w	Naf1	0.0078	142	Yjl137c	Glg2	0.014
43	Yor248w		0.0037	93	Ybr014c		0.0082	143	Ydr171w	Hsp42	0.014
44	Ygr282c	Bgl2	0.0037	94	Ymr319c	Fet4	0.0085	144	Ymr291w		0.014
45	Ylr027c	Aat2	0.0038	95	Ygr085c	Rpl11b	0.0085	145	Ynl316c	Pha2	0.014
46	Ygl031c	Rpl24a	0.0038	96	Ymr272c	Scs7	0.0089	146	Ygr155w	Cys4	0.015
47	Ycr061w		0.0039	97	Ycr049c		0.0089	147	Ylr042c		0.015
48	Yil051c	Mmf1	0.0039	98	Ydr050c	Tpi1	0.0093	148	Ydl022w	Gpd1	0.015
49	Yfr034c	Pho4	0.0039	99	Yfr002w	Nic96	0.0093	149	Ypl101w	Elp4	0.015
50	Yir025w	Mnd2	0.004	100	Ydr258c	Hsp78	0.0095	150	Yor183w	Fyv12	0.015

#	ORF	Name	*p*-value	#	ORF	Name	*p*-value	#	ORF	Name	*p*-value
151	Yer051w		0.016	201	Ydr537c		0.022	251	Ynl188w	Kar1	0.032
152	Yer011w	Tir1	0.016	202	Ykl055c	Oar1	0.022	252	Ydr539w		0.032
153	Yal053w		0.016	203	Ydr161w	Tci1	0.022	253	Ycr025c		0.032
154	Yer136w	Gdi1	0.016	204	Ykl216w	Ura1	0.023	254	Yer094c	Pup3	0.032
155	Ykl051w		0.016	205	Ycl040w	Glk1	0.023	255	Yil159w	Bnr1	0.032
156	Ydr535c		0.016	206	Yir031c	Dal7	0.023	256	Ydr465c	Rmt2	0.032
157	Ymr121c	Rpl15b	0.016	207	Ymr158c-b		0.023	257	Ymr243c	Zrc1	0.032
158	Yer010c		0.016	208	Ykl137w		0.024	258	Yil009w	Faa3	0.032
159	Ynr035c	Arc35	0.017	209	Ydr083w	Rrp8	0.024	259	Ylr013w	Gat3	0.033
160	Yor093c		0.017	210	Ybr294w	Sul1	0.024	260	Yer182w		0.033
161	Ypr177c		0.017	211	Ylr444c		0.024	261	Ycr087c-a		0.033
162	Ycl074w		0.017	212	Ynl291c	Mid1	0.024	262	Yjl034w	Kar2	0.033
163	Ybr083w	Tec1	0.017	213	Ymr202w	Erg2	0.025	263	Yjr150c	Dan1	0.033
164	Yer181c		0.017	214	Yfl019c		0.025	264	Yll023c		0.033
165	Yjl190c	Rps22a	0.017	215	Yhl018w		0.025	265	Ydl210w	Uga4	0.033
166	Yjl085w	Exo70	0.017	216	Ymr138w	Cin4	0.025	266	Yer048w-a		0.033
167	Ybr152w	Spp381	0.017	217	Yel011w	Glc3	0.025	267	Yor316c	Cot1	0.034
168	Yer155c	Bem2	0.017	218	Ygr163w	Gtr2	0.025	268	Yel075c		0.034
169	Ypr010c	Rpa135	0.017	219	Yor382w	Fit2	0.025	269	Ybr065c	Ecm2	0.034
170	Ykl014c		0.017	220	Yol155c		0.025	270	Ygr038w	Orm1	0.034
171	Ydr467c		0.018	221	Yhr092c	Hxt4	0.026	271	Ygl248w	Pde1	0.034
172	Ykl096w	Cwp1	0.018	222	Ygr189c	Crh1	0.026	272	Ykl028w	Tfa1	0.034
173	Yjl095w	Bck1	0.018	223	Ynr076w	Pau6	0.026	273	Yhr140w		0.034
174	Ygr205w		0.018	224	Ydr327w		0.026	274	Yer178w	Pda1	0.035
175	Ykl027w		0.018	225	Ygr243w		0.026	275	Ypl230w		0.036
176	Ykr024c	Dbp7	0.018	226	Yfr044c		0.026	276	Ynl112w	Dbp2	0.036
177	Yfr041c		0.018	227	Ydr445c		0.026	277	Ynl100w		0.036
178	Yjl010c		0.019	228	Yer151c	Ubp3	0.026	278	Ycr006c		0.037
179	Yal060w	Bdh1	0.019	229	Ypl010w	Ret3	0.027	279	Ydl124w		0.037
180	Ygl012w	Erg4	0.02	230	Ydr525w	Api2	0.027	280	Ykr069w	Met1	0.037
181	Ydl027c		0.02	231	Ybr129c	Opy1	0.027	281	Yor243c	Pus7	0.037
182	Ynl309w	Stb1	0.02	232	Yll026w	Hsp104	0.027	282	Ydr409w	Siz1	0.037
183	Ynl172w	Apc1	0.02	233	Yml047c	Prm6	0.027	283	Ypr105c	Cog4	0.037
184	Ynl007c	Sis1	0.02	234	Yor247w	Srl1	0.027	284	Ykr039w	Gap1	0.038
185	Yfr052w	Rpn12	0.02	235	Ydl100c	Arr4	0.027	285	Ylr420w	Ura4	0.038
186	Yol154w	Zps1	0.02	236	Ybr158w	Cst13	0.027	286	Ylr189c	Ugt51	0.038
187	Ylr427w		0.02	237	Yor255w		0.027	287	Ycr028c	Fen2	0.039
188	Ygl189c	Rps26a	0.02	238	Ylr445w		0.028	288	Ydl083c	Rps16b	0.039
189	Ykl163w	Pir3	0.02	239	Yor333c	Swf5	0.029	289	Ynl071w	Lat1	0.039
190	Ydr331w	Gpi8	0.02	240	Yor383c	Fit3	0.029	290	Ycr057c	Pwp2	0.039
191	Ykl058w	Toa2	0.021	241	Ybl108w		0.029	291	Ybr111c	Ysa1	0.039
192	Ydl120w	Yfh1	0.021	242	Yfl026w	Ste2	0.03	292	Yhl027w	Rim101	0.039
193	Ykl002w	Did4	0.021	243	Ygl076c	Rpl7a	0.03	293	Ynl284c	Mrpl10	0.039
194	Ynl118c	Dcp2	0.021	244	Yor273c	Tpo4	0.03	294	Yhr100c		0.04
195	Ygr185c	Tys1	0.021	245	Yor021c		0.03	295	Ygr141w	Vps62	0.04
196	Yhr056c	Rsc30	0.022	246	Ylr177w		0.03	296	Ypl051w	Arl3	0.04
197	Yhr005c	Gpa1	0.022	247	Yjr141w		0.03	297	Ypl245w		0.04
198	Ygr063c	Spt4	0.022	248	Yjr022w	Lsm8	0.03	298	Ylr331c	Jip3	0.04
199	Ygr275w	Rtt102	0.022	249	Yol160w		0.03	299	Ydl130w-a	Stf1	0.041
200	Yjl158c	Cis3	0.022	250	Ybr287w		0.032	300	Yor039w	Ckb2	0.041

#	ORF	Name	*p*-value	#	ORF	Name	*p*-value	#	ORF	Name	*p*-value
301	Ygl261c		0.041	315	Ygr272c		0.044	329	Ypl155c	Kip2	0.046
302	Ydr519w	Fpr2	0.041	316	Ygl203c	Kex1	0.044	330	Ylr108c		0.046
303	Ydl090c	Ram1	0.042	317	Ydl182w	Lys20	0.044	331	Ycl028w	Rnq1	0.046
304	Yll047w		0.042	318	Ygr203w		0.045	332	Ygr146c		0.046
305	Ycr068w	Cvt17	0.042	319	Ydr008c		0.045	333	Yfr050c	Pre4	0.046
306	Ydl246c		0.042	320	Ygl263w	Cos12	0.045	334	Yir037w	Hyr1	0.047
307	Yfr053c	Hxk1	0.043	321	Ynl055c	Por1	0.045	335	Yir005w	Ist3	0.047
308	Yer156c		0.043	322	Yor227w		0.045	336	Ydr496c	Puf6	0.047
309	Ybr105c	Vid24	0.043	323	Ygl169w	Sua5	0.045	337	Ydr087c	Rrp1	0.049
310	Yll024c	Ssa2	0.043	324	Ylr181c	Vta1	0.045	338	Ydr395w	Sxm1	0.049
311	Yml113w	Dat1	0.043	325	Yll037w		0.045	339	Ygl068w		0.049
312	Ypl061w	Ald6	0.044	326	Ygl199c		0.045	340	Ynl315c	Atp11	0.049
313	Ybr253w	Srb6	0.044	327	Ydr106w	Arp10	0.046	341	Ykl060c	Fba1	0.049
314	Ykl085w	Mdh1	0.044	328	Ygl022w	Stt3	0.046				

Table 6. Differentially expressed genes in Ppt1 mutants

#	ORF	Name	*p*-value	#	ORF	Name	*p*-value	#	ORF	Name	*p*-value
1	Yjl078c	Pry3	1.52E-06	51	Yor056c	Nob1	0.0012	101	Ygl196w		0.0027
2	Ycl058c	Fyv5	6.12E-06	52	Yjr140c	Hir3	0.0012	102	Ydr033w	Mrh1	0.0028
3	Ykr069w	Met1	7.03E-06	53	Ydr381w	Yra1	0.0013	103	Ymr272c	Scs7	0.0028
4	Ylr449w	Fpr4	4.28E-05	54	Ynr034w	Sol1	0.0014	104	Ykl168c	Kkq8	0.0029
5	Yfr001w	Loc1	4.31E-05	55	Ydl093w	Pmt5	0.0014	105	Ynl124w	Naf1	0.0029
6	Ycr016w		8.68E-05	56	Ybr155w	Cns1	0.0015	106	Yir007w		0.003
7	Ykr024c	Dbp7	0.00015	57	Ylr414c		0.0015	107	Yor015w		0.003
8	Ygl110c	Cue3	0.00017	58	Yol080c	Rex4	0.0016	108	Ykl116c	Prr1	0.003
9	Ypl146c		0.00021	59	Yjr146w		0.0017	109	Ydl044c	Mtf2	0.003
10	Ycl069w		0.00021	60	Ydr169c	Stb3	0.0017	110	Ynl180c	Rho5	0.003
11	Ykl078w	Dhr2	0.00025	61	Yor132w	Vps17	0.0017	111	Ycr005c	Cit2	0.003
12	Ykr046c		0.00028	62	Yml100w-a		0.0017	112	Yer126c	Nsa2	0.003
13	Yol141w	Ppm2	0.00031	63	Ybl054w		0.0017	113	Ylr347c	Kap95	0.003
14	Ylr345w		0.00041	64	Ynl174w		0.0018	114	Ylr425w	Tus1	0.0031
15	Ygr096w	Tpc1	0.00046	65	Yjl087c	Trl1	0.0018	115	Ynl062c	Gcd10	0.0031
16	Yml130c	Ero1	0.00052	66	Ygl158w	Rck1	0.0018	116	Ydr099w	Bmh2	0.0032
17	Yfl031w	Hac1	0.00053	67	Yjr159w	Sor1	0.0019	117	Ymr086w		0.0033
18	Ypl032c	Svl3	0.00055	68	Yer112w	Lsm4	0.0019	118	Yjr126c	Vps70	0.0033
19	Yor223w		0.00056	69	Yclx10c		0.0019	119	Ymr081c	Isf1	0.0033
20	Yol155c		0.00057	70	Ynl266w		0.002	120	Yhr115c		0.0034
21	Yjr019c	Tes1	0.00058	71	Ydl014w	Nop1	0.002	121	Yol144w	Nop8	0.0034
22	Ygr292w	Mal12	0.00064	72	Ylr377c	Fbp1	0.002	122	Ydr039c	Ena2	0.0035
23	Ypr144c	Utp19	0.00066	73	Ymr128w	Ecm16	0.002	123	Yml040w		0.0035
24	Yil117c	Prm5	0.00066	74	Ykl215c		0.0021	124	Ygl162w	Sut1	0.0035
25	Ybr092c	Pho3	0.00067	75	Yhr213w		0.0021	125	Ylr273c	Pig1	0.0036
26	Ymr002w		0.0007	76	Yil158w		0.0023	126	Yhr049w	Fsh1	0.0036
27	Yjr092w	Bud4	0.00071	77	Yfr033c	Qcr6	0.0023	127	Ycr030c	Syp1	0.0037
28	Yhr169w	Dbp8	0.00071	78	Ypl203w	Tpk2	0.0023	128	Ydr394w	Rpt3	0.0037
29	Yir023w	Dal81	0.00074	79	Ypl111w	Car1	0.0023	129	Ykl026c	Gpx1	0.0037
30	Yjl148w	Rpa34	0.00074	80	Ynl337w		0.0023	130	Ykl202w		0.0037
31	Ydr324c	Utp4	0.00074	81	Ylr231c	Bna5	0.0024	131	Ylr198c		0.0038
32	Yjr048w	Cyc1	0.00081	82	Yjl160c		0.0024	132	Ybr238c		0.0038
33	Yhr201c	Ppx1	0.00087	83	Yor371c	Gpb1	0.0024	133	Yjr091c	Jsn1	0.0039
34	Ymr012w	Clu1	0.00088	84	Ynl196c	Slz1	0.0025	134	Ymr109w	Myo5	0.0039
35	Yol014w		0.0009	85	Yor031w	Crs5	0.0025	135	Ykr056w	Trm2	0.004
36	Ygl152c		0.00091	86	Yhr138c		0.0025	136	Ypl221w	Bop1	0.004
37	Yol142w	Rrp40	0.00094	87	Ybr257w	Pop4	0.0025	137	Ybr247c	Enp1	0.004
38	Ynl046w		0.001	88	Ycr054c	Ctr86	0.0025	138	Yjl197w	Ubp12	0.004
39	Ycr087w		0.001	89	Ynl127w		0.0025	139	Ylr200w	Yke2	0.004
40	Ylr346c		0.001	90	Ypr157w		0.0026	140	Ynr054c		0.0041
41	Ydr057w	Yos9	0.001	91	Yol098c		0.0026	141	Yor109w	Inp53	0.0041
42	Ycr072c		0.001	92	Ynl023c	Fap1	0.0026	142	Ydr298c	Atp5	0.0041
43	Ylr019w	Psr2	0.0011	93	Ypr182w	Smx3	0.0026	143	Ynr043w	Mvd1	0.0041
44	Ykl185w	Ash1	0.0011	94	Ybr279w	Paf1	0.0027	144	Yhr216w	Imd2	0.0042
45	Ygl171w	Rok1	0.0011	95	Ydr393w	She9	0.0027	145	Yjl196c	Elo1	0.0042
46	Ycr105w		0.0011	96	Yll053c		0.0027	146	Yor121c		0.0042
47	Ylr256w	Hap1	0.0011	97	Ykr081c	Rpf2	0.0027	147	Ypl061w	Ald6	0.0042
48	Yll031c	Gpi13	0.0012	98	Yjr023c		0.0027	148	Ypr079w	Mrl1	0.0042
49	Ypr026w	Ath1	0.0012	99	Yil067c		0.0027	149	Ygr075c	Prp38	0.0042
50	Ylr297w		0.0012	100	Ylr352w		0.0027	150	Yclx05c		0.0043

#	ORF	Name	*p*-value	#	ORF	Name	*p*-value	#	ORF	Name	*p*-value
151	Yhl048w	Cos8	0.0043	201	Yjl076w	Net1	0.0067	251	Yjr122w	Caf17	0.0095
152	Ycl003w		0.0043	202	Ynl065w	Aqr1	0.0067	252	Ymr173w	Ddr48	0.0096
153	Ynl215w	Ies2	0.0044	203	Ydr325w	Ycg1	0.0068	253	Yor209c	Npt1	0.0096
154	Ymr189w	Gcv2	0.0045	204	Yol099c		0.0068	254	Yor199w		0.0096
155	Yil152w		0.0046	205	Yll035w	Grc3	0.0071	255	Ylr286c	Cts1	0.0097
156	Ygr256w	Gnd2	0.0046	206	Yor013w		0.0071	256	Ykr025w	Rpc37	0.0097
157	Ykl040c	Nfu1	0.0046	207	Ybr130c	She3	0.0072	257	Ydr206w	Ebs1	0.0098
158	Ygl055w	Ole1	0.0046	208	Ypl062w		0.0073	258	Yor145c		0.0099
159	Ykr017c		0.0046	209	Yol001w	Pho80	0.0073	259	Ydr035w	Aro3	0.01
160	Ylr162w		0.0046	210	Ykl161c		0.0074	260	Ykl051w		0.01
161	Yil073c	Spo22	0.0047	211	Yil113w	Sdp1	0.0075	261	Ylr435w		0.01
162	Ybl042c	Fui1	0.0049	212	Ygr023w	Mtl1	0.0075	262	Yhr166c	Cdc23	0.01
163	Ygl077c	Hnm1	0.0049	213	Ybr034c	Hmt1	0.0075	263	Ydr433w	Kre22	0.01
164	Yer125w	Rsp5	0.0049	214	Yhl018w		0.0075	264	Ybr286w	Ape3	0.01
165	Yll062c	Mht1	0.005	215	Ymr239c	Rnt1	0.0076	265	Yjl104w	Mia1	0.01
166	Ymr037c	Msn2	0.005	216	Ynl059c	Arp5	0.0077	266	Ymr139w	Rim11	0.01
167	Yfl047w	Rgd2	0.0051	217	Ykr033c		0.0078	267	Ykl096w	Cwp1	0.01
168	Ygl222c	Edc1	0.0051	218	Yml074c	Fpr3	0.0078	268	Ynl236w	Sin4	0.01
169	Ydl175c	Air2	0.0052	219	Ynl142w	Mep2	0.0078	269	Yhr080c		0.01
170	Yml123c	Pho84	0.0052	220	Ymr049c	Erb1	0.0078	270	Yar010c		0.01
171	Yjl172w	Cps1	0.0053	221	Yer151c	Ubp3	0.0078	271	Ybr152w	Spp381	0.01
172	Ygl192w	Ime4	0.0054	222	Yor245c	Dga1	0.008	272	Ybl101w-a		0.01
173	Yor194c	Toa1	0.0054	223	Ydr009w	Gal3	0.008	273	Ylr276c	Dbp9	0.01
174	Ymr218c	Trs130	0.0054	224	Ylr105c	Sen2	0.008	274	Ydr284c	Dpp1	0.01
175	Ygr211w	Zpr1	0.0054	225	Ylr004c		0.0082	275	Ypl155c	Kip2	0.011
176	Yol118c		0.0054	226	Yml078w	Cpr3	0.0082	276	Ydl152w		0.011
177	Ygr138c	Tpo2	0.0055	227	Ybr121c	Grs1	0.0083	277	Ygl003c	Cdh1	0.011
178	Ypr015c		0.0056	228	Ybr064w		0.0083	278	Ycr029c		0.011
179	Yhl034c	Sbp1	0.0056	229	Ygr187c	Hgh1	0.0083	279	Yjl165c	Hal5	0.011
180	Ybr004c		0.0057	230	Ydr459c		0.0084	280	Yir029w	Dal2	0.011
181	Ypl149w	Apg5	0.0057	231	Yhr018c	Arg4	0.0084	281	Ypr152c		0.011
182	Yhr046c	Inm1	0.0058	232	Ydr382w	Rpp2b	0.0085	282	Ybr018c	Gal7	0.011
183	Ydr300c	Pro1	0.0059	233	Yor004w		0.0085	283	Ykl109w	Hap4	0.011
184	Yol125w		0.0059	234	Ygr229c	Smi1	0.0086	284	Yml043c	Rrn11	0.011
185	Ylr011w	Lot6	0.0059	235	Ymr085w		0.0087	285	Yjr132w	Nmd5	0.011
186	Ykr038c	Kae1	0.006	236	Yor113w	Azf1	0.0088	286	Yor086c		0.011
187	Ydl213c	Fyv14	0.0061	237	Ybr285w		0.0088	287	Yil175w		0.012
188	Ygl087c	Mms2	0.0061	238	Ymr300c	Ade4	0.0088	288	Ygr291c		0.012
189	Yil169c		0.0062	239	Ylr249w	Yef3	0.0088	289	Ykr053c	Ysr3	0.012
190	Ybl007c	Sla1	0.0062	240	Ycr021c	Hsp30	0.009	290	Ynl256w	Fol1	0.012
191	Yer090w	Trp2	0.0062	241	Ydr096w	Gis1	0.009	291	Ylr051c		0.012
192	Yor334w	Mrs2	0.0063	242	Yjl125c	Gcd14	0.0091	292	Yil112w		0.012
193	Ygl099w	Lsg1	0.0064	243	Ypl058c	Pdr12	0.0091	293	Ydr415c		0.012
194	Ybl111c		0.0064	244	Ymr247c		0.0091	294	Ydr098c	Grx3	0.012
195	Ynl001w	Dom34	0.0064	245	Ylr117c	Clf1	0.0093	295	Ybr040w	Fig1	0.012
196	Yol077c	Brx1	0.0065	246	Ydr443c	Ssn2	0.0094	296	Yil151c		0.012
197	Yjr032w	Cpr7	0.0065	247	Ynl151c	Rpc31	0.0094	297	Ygl062w	Pyc1	0.012
198	Ylr020c		0.0066	248	Ymr224c	Mre11	0.0095	298	Ygr280c	Pxr1	0.012
199	Yel028w		0.0067	249	Ydl204w	Rtn2	0.0095	299	Ygl219c	Mmm2	0.012
200	Ykl099c	Utp11	0.0067	250	Yjl083w		0.0095	300	Ykl179c	Coy1	0.012

#	ORF	Name	*p*-value	#	ORF	Name	*p*-value	#	ORF	Name	*p*-value
301	Ymr014w	Bud22	0.012	351	Ykl055c	Oar1	0.016	401	Ydr398w	Utp5	0.02
302	Yal034w-a	Mtw1	0.012	352	Ybr288c	Apm3	0.016	402	Yhr133c		0.02
303	Ydl039c	Prm7	0.013	353	Ygl031c	Rpl24a	0.017	403	Ygl261c		0.02
304	Yor083w	Whi5	0.013	354	Yll013c	Puf3	0.017	404	Yel051w	Vma8	0.021
305	Yar073w	Imd1	0.013	355	Ybr091c	Mrs5	0.017	405	Yhr170w	Nmd3	0.021
306	Ynl227c		0.013	356	Yol126c	Mdh2	0.017	406	Ycl027w	Fus1	0.021
307	Yor261c	Rpn8	0.013	357	Yor048c	Rat1	0.017	407	Yir039c	Yps6	0.021
308	Ylr351c	Nit3	0.013	358	Ynl061w	Nop2	0.017	408	Ycr060w		0.021
309	Ybr267w		0.013	359	Yer082c	Utp7	0.017	409	Ypr032w	Sro7	0.021
310	Yol010w	Rcl1	0.013	360	Yjr037w		0.017	410	Ynl269w		0.021
311	Yer002w	Nop16	0.013	361	Ypr200c	Arr2	0.017	411	Yml002w		0.021
312	Ypr083w		0.013	362	Ypr089w		0.017	412	Ykl110c	Kti12	0.021
313	Ybr154c	Rpb5	0.013	363	Yfl007w	Blm3	0.017	413	Ydr429c	Tif35	0.021
314	Ydr157w		0.014	364	Yil096c		0.017	414	Ybr075w		0.021
315	Yor287c		0.014	365	Yhr021c	Rps27b	0.017	415	Yll067c		0.021
316	Ydl063c		0.014	366	Yhr050w	Smf2	0.017	416	Ybr002c	Rer2	0.021
317	Ybr183w	Ypc1	0.014	367	Ycr101c		0.018	417	Ycrx01w		0.022
318	Ykl172w	Ebp2	0.014	368	Ykl001c	Met14	0.018	418	Ybr093c	Pho5	0.022
319	Yfl055w	Agp3	0.014	369	Ynl193w		0.018	419	Ydr231c	Cox20	0.022
320	Ycr106w	Rds1	0.014	370	Ykl139w	Ctk1	0.018	420	Yer020w	Gpa2	0.022
321	Ykr021w		0.014	371	Ynl015w	Pbi2	0.018	421	Ybr114w	Rad16	0.022
322	Ydr183w	Plp1	0.014	372	Ydl238c		0.018	422	Ynr009w		0.022
323	Yhr014w	Spo13	0.014	373	Yil127c		0.018	423	Yar015w	Ade1	0.022
324	Yor087w	Yvc1	0.014	374	Ydr449c	Utp6	0.018	424	Ygl250w		0.022
325	Yer127w	Lcp5	0.014	375	Yer179w	Dmc1	0.018	425	Ymr304w	Ubp15	0.023
326	Ypr195c		0.014	376	Ynr053c	Nog2	0.018	426	Yjl159w	Hsp150	0.023
327	Yol154w	Zps1	0.014	377	Ygl049c	Tif4632	0.018	427	Yor215c		0.023
328	Ydr379w	Rga2	0.014	378	Ypl249c-a	Rpl36b	0.018	428	Yor262w		0.023
329	Yfl012w		0.015	379	Yhr218w		0.018	429	Ygl116w	Cdc20	0.024
330	Ycr047c	Bud23	0.015	380	Ydr184c	Atc1	0.019	430	Yol004w	Sin3	0.024
331	Ydr037w	Krs1	0.015	381	Yml129c	Cox14	0.019	431	Ydr313c	Pib1	0.024
332	Yclx07w		0.015	382	Ynl332w	Thi12	0.019	432	Ygr022c		0.024
333	Ydl210w	Uga4	0.015	383	Yhr092c	Hxt4	0.019	433	Yor018w	Rod1	0.024
334	Yar074c		0.015	384	Yil045w	Pig2	0.019	434	Ybr117c	Tkl2	0.024
335	Ygr026w		0.015	385	Ylr063w		0.019	435	Yol037c		0.025
336	Yor222w	Odc2	0.016	386	Ymr034c		0.019	436	Ygr109c	Clb6	0.025
337	Ypr111w	Dbf20	0.016	387	Ynl043c		0.019	437	Ypl140c	Mkk2	0.025
338	Yll061w	Mmp1	0.016	388	Yjr028w		0.019	438	Ymr318c	Adh6	0.025
339	Ygr145w	Enp2	0.016	389	Ydl050c		0.019	439	Yer071c		0.025
340	Ydl021w	Gpm2	0.016	390	Ylr152c		0.02	440	Yjl008c	Cct8	0.025
341	Ykl124w	Ssh4	0.016	391	Ydr075w	Pph3	0.02	441	Ygl016w	Kap122	0.025
342	Ykr042w	Uth1	0.016	392	Ygl096w	Tos8	0.02	442	Yjl111w	Cct7	0.025
343	Ygr245c	Sda1	0.016	393	Ynl182c		0.02	443	Ynl192w	Chs1	0.025
344	Ylr139c	Sls1	0.016	394	Ygl058w	Rad6	0.02	444	Ycl016c	Dcc1	0.025
345	Ydl079c	Mrk1	0.016	395	Ykl197c	Pex1	0.02	445	Ybr269c		0.025
346	Ybl075c	Ssa3	0.016	396	Ykr005c		0.02	446	Ycl059c	Krr1	0.025
347	Ylr407w		0.016	397	Ydr234w	Lys4	0.02	447	Yer006w	Nug1	0.026
348	Ydl187c		0.016	398	Ycr103c		0.02	448	Ydl150w	Rpc53	0.026
349	Yol147c	Pex11	0.016	399	Ylr337c	Vrp1	0.02	449	Ylr265c	Nej1	0.026
350	Ydr016c	Dad1	0.016	400	Yor345c		0.02	450	Ymr018w		0.026

#	ORF	Name	*p*-value	#	ORF	Name	*p*-value	#	ORF	Name	*p*-value
451	Ybl027w	Rpl19b	0.026	502	Ypl099c		0.033	553	Ynl118c	Dcp2	0.041
452	Yhr207c	Set5	0.026	503	Ygr070w	Rom1	0.033	554	Ygl181w	Gts1	0.041
453	Ypr061c		0.026	504	Ygr137w		0.033	555	Ygl072c		0.042
454	Ynl110c	Nop15	0.027	505	Yml100w	Tsl1	0.033	556	Ybr024w	Sco2	0.042
455	Ypl126w	Nan1	0.027	506	Ygr104c	Srb5	0.034	557	Yhr211w	Flo5	0.042
456	Ydl097c	Rpn6	0.027	507	Ybr294w	Sul1	0.034	558	Yer044c-a	Mei4	0.042
457	Yil012w		0.027	508	Yol070c		0.034	559	Ygl237c	Hap2	0.042
458	Yor366w		0.027	509	Ygl033w	Hop2	0.034	560	Yil100w		0.042
459	Yor339c	Ubc11	0.027	510	Yjr014w		0.034	561	Ylr013w	Gat3	0.042
460	Ygl117w		0.027	511	Ycl001w-a		0.034	562	Ypr131c	Nat3	0.042
461	Yhr064c	Ssz1	0.027	512	Yor178c	Gac1	0.035	563	Ylr039c	Ric1	0.042
462	Ylr006c	Ssk1	0.027	513	Yor141c	Arp8	0.035	564	Ygl073w	Hsf1	0.043
463	Ynr070w	Pdr18	0.027	514	Ybr027c		0.035	565	Ydr014w	Rad61	0.043
464	Ypl097w	Msy1	0.027	515	Ylr058c	Shm2	0.035	566	Ypr143w		0.044
465	Yhr055c	Cup1-2	0.027	516	Ydr425w		0.035	567	Yfr055w		0.044
466	Ypl223c	Gre1	0.027	517	Yir032c	Dal3	0.035	568	Yhr069c	Rrp4	0.044
467	Yhr024c	Mas2	0.027	518	Ybr140c	Ira1	0.036	569	Ylr037c	Dan2	0.044
468	Yhr096c	Hxt5	0.027	519	Ygr283c		0.036	570	Ybr203w		0.044
469	Ynl176c		0.028	520	Ynl103w	Met4	0.037	571	Ycr050c		0.044
470	Ydl190c	Ufd2	0.028	521	Ygr175c	Erg1	0.037	572	Ypr156c	Tpo3	0.044
471	Ylr149c		0.028	522	Ydr504c		0.037	573	Yor190w	Spr1	0.044
472	Yil173w	Vth1	0.028	523	Ybl046w		0.037	574	Ygl221c	Nif3	0.045
473	Ygl001c	Erg26	0.028	524	Yhl038c	Cbp2	0.037	575	Ylr074c	Bud20	0.045
474	Yhl030w	Ecm29	0.028	525	Ygl177w		0.037	576	Yer099c	Prs2	0.045
475	Ymr095c	Sno1	0.029	526	Yil160c	Pot1	0.037	577	Ypr202w		0.045
476	Ygr272c		0.029	527	Ygl215w	Clg1	0.038	578	Ynl299w	Trf5	0.045
477	Ybl005w-a		0.029	528	Ykl093w	Mbr1	0.038	579	Ydl025c		0.045
478	Yor114w		0.029	529	Ybr141c		0.038	580	Yjl069c	Utp18	0.045
479	Ygr030c	Pop6	0.029	530	Ygr105w	Vma21	0.038	581	Ylr413w		0.046
480	Yor077w	Rts2	0.029	531	Yor135c		0.038	582	Yjr111c		0.046
481	Ycl014w	Bud3	0.029	532	Ykl143w	Ltv1	0.038	583	Ydr165w	Trm82	0.046
482	Ylr009w	Rlp24	0.029	533	Yel058w	Pcm1	0.038	584	Yol056w	Gpm3	0.046
483	Yer042w	Mxr1	0.03	534	Ybr095c	Rxt2	0.038	585	Ydl234c	Gyp7	0.046
484	Ycr037c	Pho87	0.03	535	Yjr108w	Abm1	0.038	586	Yhr099w	Tra1	0.046
485	Ybr296c	Pho89	0.03	536	Ygr160w	Fyv13	0.039	587	Ypl238c		0.046
486	Yer030w		0.03	537	Yer153c	Pet122	0.039	588	Ydr201w	Spc19	0.046
487	Ygr139w		0.03	538	Yol124c		0.039	589	Ygl149w		0.047
488	Ydl070w	Bdf2	0.031	539	Yjr056c		0.039	590	Ydr130c	Fin1	0.047
489	Yjr055w	Hit1	0.031	540	Ydl121c		0.039	591	Ynl052w	Cox5a	0.047
490	Yor208w	Ptp2	0.031	541	Yjl042w	Mhp1	0.039	592	Yfr020w		0.047
491	Ydr156w	Rpa14	0.031	542	Yjl016w		0.039	593	Ylr419w		0.047
492	Ydr438w		0.032	543	Ybr243c	Alg7	0.039	594	Ydr045c	Rpc11	0.047
493	Ykl126w	Ypk1	0.032	544	Ydr533c		0.039	595	Ynl139c	Rlr1	0.047
494	Ylr289w	Guf1	0.032	545	Ybr142w	Mak5	0.04	596	Yhl043w	Ecm34	0.047
495	Ybl062w		0.032	546	Ygr228w		0.04	597	Ymr023c	Mss1	0.047
496	Ykl218c	Sry1	0.033	547	Yjr026w		0.04	598	Yer096w	Shc1	0.048
497	Ykl095w	Yju2	0.033	548	Ybl074c	Aar2	0.04	599	Yfl061w		0.048
498	Ynl212w	Vid27	0.033	549	Ydr093w	Dnf2	0.041	600	Ymr175w	Sip18	0.048
499	Yer178w	Pda1	0.033	550	Ygl074c		0.041	601	Yol100w	Pkh2	0.048
500	Ygl240w	Doc1	0.033	551	Ybr128c	Apg14	0.041	602	Ycl075w		0.049
501	Ynr052c	Pop2	0.033	552	Ydr409w	Siz1	0.041				

Table 7. Differentially expressed genes in Kin82 mutants

#	ORF	Name	*p*-value	#	ORF	Name	*p*-value	#	ORF	Name	*p*-value
1	Yor273c	Tpo4	7.80E-05	51	Ygr028w	Msp1	0.0042	101	Yll056c		0.01
2	Ygr250c		9.02E-05	52	Ygl101w		0.0042	102	Ygr248w	Sol4	0.01
3	Ydl024c	Dia3	0.00026	53	Ydr352w		0.0048	103	Ydl153c	Sas10	0.01
4	Ypl088w		0.00027	54	Yjl208c	Nuc1	0.0048	104	Ykl089w	Mif2	0.01
5	Yhr069c	Rrp4	0.00028	55	Ydr088c	Slu7	0.0049	105	Yor002w	Alg6	0.011
6	Ymr291w		0.00047	56	Ygr198w		0.005	106	Yhr138c		0.011
7	Ygl134w	Pcl10	0.00055	57	Ymr043w	Mcm1	0.005	107	Yor197w	Mca1	0.011
8	Yil022w	Tim44	0.00059	58	Ycl016c	Dcc1	0.005	108	Ynl128w	Tep1	0.011
9	Yjl161w		0.00067	59	Ygr088w	Ctt1	0.0051	109	Yel021w	Ura3	0.011
10	Ycr020c-a	Mak31	0.0007	60	Yjl140w	Rpb4	0.0053	110	Yhr007c	Erg11	0.011
11	Ybr116c		0.00076	61	Ypl143w	Rpl33a	0.0054	111	Yel042w	Gda1	0.012
12	Yol016c	Cmk2	0.00078	62	Yer073w	Ald5	0.0054	112	Ykr080w	Mtd1	0.012
13	Yll028w	Tpo1	0.00099	63	Ygl179c		0.0055	113	Yjl017w		0.012
14	Ygr043c		0.0011	64	Yel060c	Prb1	0.0055	114	Ymr136w	Gat2	0.012
15	Yar060c		0.0012	65	Ygl037c	Pnc1	0.0057	115	Ynl036w	Nce103	0.012
16	Yor343c		0.0012	66	Ygr191w	Hip1	0.006	116	Ydr222w		0.012
17	Ymr220w	Erg8	0.0012	67	Ymr104c	Ypk2	0.0062	117	Yhl014c	Ylf2	0.012
18	Ylr149c		0.0013	68	Ycl026c		0.0062	118	Ykl160w		0.012
19	Yjr066w	Tor1	0.0014	69	Yar050w	Flo1	0.0063	119	Yer096w	Shc1	0.013
20	Yer051w		0.0015	70	Yil136w	Om45	0.0065	120	Ydr464w	Spp41	0.013
21	Yjl144w		0.0017	71	Ykl038w	Rgt1	0.0065	121	Ycl046w		0.013
22	Ygr237c		0.0018	72	Ynl319w		0.0066	122	Ymr189w	Gcv2	0.013
23	Yhr099w	Tra1	0.0019	73	Yer080w		0.0067	123	Yhr136c	Spl2	0.014
24	Ydr062w	Lcb2	0.0021	74	Yer149c	Pea2	0.0067	124	Ybr196c	Pgi1	0.014
25	Ycrx18c		0.0022	75	Yhr087w		0.007	125	Ygl204c		0.014
26	Ygr036c	Cax4	0.0023	76	Ydr085c	Afr1	0.0072	126	Ybl012c		0.014
27	Ypl135w	Isu1	0.0025	77	Yll008w	Drs1	0.0072	127	Ynl242w	Apg2	0.014
28	Yfl014w	Hsp12	0.0026	78	Ycr048w	Are1	0.0073	128	Ybr297w	Mal33	0.014
29	Yhl035c		0.0026	79	Ydl104c	Qri7	0.0074	129	Ypr157w		0.014
30	Ylr453c	Rif2	0.0027	80	Ygr022c		0.0075	130	Yor152c		0.015
31	Ygr238c	Kel2	0.0028	81	Ygr128c	Utp8	0.0075	131	Ylr167w	Rps31	0.015
32	Yol153c		0.0028	82	Ydl166c	Fap7	0.0076	132	Ykl091c		0.016
33	Yer045c	Aca1	0.0028	83	Yml004c	Glo1	0.0076	133	Yjl050w	Mtr4	0.016
34	Ylr336c	Sgd1	0.0029	84	Yfl065c		0.0076	134	Ymr288w	Hsh155	0.016
35	Ybl011w	Sct1	0.0031	85	Ygr048w	Ufd1	0.0076	135	Yer012w	Pre1	0.016
36	Ycl042w		0.0031	86	Yol121c	Rps19a	0.0077	136	Ydr034w-b		0.016
37	Ygl243w	Tad1	0.0033	87	Ydl030w	Prp9	0.0082	137	Ydl222c		0.016
38	Ynl108c		0.0033	88	Ygr213c	Rta1	0.0083	138	Ydl130w	Rpp1b	0.016
39	Ymr158w-a		0.0034	89	Ydr232w	Hem1	0.0085	139	Ymr268c	Prp24	0.016
40	Ygr121c	Mep1	0.0035	90	Ygl191w	Cox13	0.0089	140	Ygr257c		0.016
41	Yjl169w		0.0035	91	Ynl061w	Nop2	0.009	141	Yhr200w	Rpn10	0.016
42	Ygr192c	Tdh3	0.0036	92	Ygr259c		0.0092	142	Yjr089w	Bir1	0.017
43	Ynl110c	Nop15	0.0036	93	Yfl031w	Hac1	0.0094	143	Ymr224c	Mre11	0.017
44	Ygr146c		0.0037	94	Ygl252c	Rtg2	0.0094	144	Ymr304w	Ubp15	0.017
45	Yal035c-a		0.0037	95	Ymr085w		0.0097	145	Ypr154w	Pin3	0.017
46	Yml035c	Amd1	0.0039	96	Ynl077w		0.0097	146	Ydr285w	Zip1	0.017
47	Ygr047c	Tfc4	0.004	97	Yer176w	Ecm32	0.0097	147	Ykl222c		0.017
48	Ykl036c		0.0041	98	Ydr030c	Rad28	0.0099	148	Yjl134w	Lcb3	0.018
49	Yfr003c		0.0041	99	Yer026c	Cho1	0.01	149	Yor091w		0.018
50	Ydl160c	Dhh1	0.0042	100	Yjl122w		0.01	150	Yjl034w	Kar2	0.018

#	ORF	Name	*p*-value	#	ORF	Name	*p*-value	#	ORF	Name	*p*-value
151	Yar062w		0.018	195	Ypl223c	Gre1	0.027	239	Ykl037w		0.038
152	Ygr031w		0.018	196	Ydr055w	Pst1	0.027	240	Yhr140w		0.038
153	Yor272w	Ytm1	0.018	197	Ylr010c	Ten1	0.028	241	Yfr055w		0.038
154	Ycr040w	Matalph	0.018	198	Ygr211w	Zpr1	0.028	242	Ydr138w	Hpr1	0.038
155	Ydl071c		0.019	199	Ygl226c-a	Ost5	0.028	243	Ybr238c		0.038
156	Ycrx19w		0.019	200	Yer068w	Mot2	0.028	244	Ymr278w		0.039
157	Ynl132w	Kre33	0.019	201	Ydr007w	Trp1	0.028	245	Ycrx01w		0.039
158	Yer067w		0.019	202	Ypr139c	Vps66	0.03	246	Ymr117c	Spc24	0.039
159	Yml017w	Psp2	0.019	203	Ylr185w	Rpl37a	0.03	247	Yal002w	Vps8	0.039
160	Ylr127c	Apc2	0.02	204	Yor383c	Fit3	0.03	248	Yjl219w	Hxt9	0.039
161	Yhr080c		0.02	205	Ybr011c	Ipp1	0.03	249	Ypr184w	Gdb1	0.039
162	Yel026w	Snu13	0.02	206	Yer061c	Cem1	0.031	250	Yel064c		0.039
163	Ynr051c	Bre5	0.021	207	Ydl015c	Tsc13	0.031	251	Yjr150c	Dan1	0.04
164	Ydl121c		0.021	208	Ybl071c		0.031	252	Ymr239c	Rnt1	0.04
165	Ygl184c	Str3	0.021	209	Ygl055w	Ole1	0.031	253	Ynl227c		0.04
166	Ygr067c		0.021	210	Ykl043w	Phd1	0.032	254	Ygr272c		0.04
167	Yjr037w		0.021	211	Ygl100w	Seh1	0.032	255	Ymr213w	Cef1	0.04
168	Ygl073w	Hsf1	0.021	212	Yjr157w		0.032	256	Ycl040w	Glk1	0.041
169	Ykl207w		0.021	213	Ydl039c	Prm7	0.032	257	Ybr048w	Rps11b	0.041
170	Ybr263w	Shm1	0.021	214	Yor374w	Ald4	0.032	258	Ypl075w	Gcr1	0.041
171	Ygr284c	Erv29	0.022	215	Ymr120c	Ade17	0.033	259	Ylr122c		0.042
172	Ypr112c	Mrd1	0.022	216	Ynr054c		0.033	260	Ylr359w	Ade13	0.042
173	Ypl166w		0.022	217	Ynl293w	Msb3	0.034	261	Ygl067w	Npy1	0.042
174	Ypl138c	Spp1	0.022	218	Ydr276c	Pmp3	0.034	262	Ymr153c-a		0.043
175	Ygl262w		0.023	219	Ydr392w	Spt3	0.034	263	Ybr286w	Ape3	0.043
176	Yfl034w		0.023	220	Yhr112c		0.034	264	Ydr393w	She9	0.043
177	Ymr003w		0.023	221	Yjl037w		0.035	265	Ynl308c	Kri1	0.043
178	Ydl021w	Gpm2	0.023	222	Yer023w	Pro3	0.035	266	Yer126c	Nsa2	0.043
179	Yel071w	Dld3	0.023	223	Ydl218w		0.035	267	Yml054c	Cyb2	0.043
180	Yer054c	Gip2	0.023	224	Ypl014w		0.035	268	Ylr112w		0.043
181	Ynl299w	Trf5	0.023	225	Ymr078c	Ctf18	0.035	269	Ylr143w		0.043
182	Yer156c		0.024	226	Yfr011c		0.036	270	Ylr369w	Ssq1	0.044
183	Yor275c	Rim20	0.024	227	Ygr153w		0.036	271	Yhr158c	Kel1	0.044
184	Ygr035c		0.024	228	Ybl005w-b		0.036	272	Ypl230w		0.044
185	Ykl044w		0.024	229	Ypl092w	Ssu1	0.036	273	Ynl060c		0.044
186	Ydl152w		0.025	230	Ylr086w	Smc4	0.036	274	Yml010w-a		0.044
187	Yer132c	Pmd1	0.025	231	Ynl016w	Pub1	0.036	275	Ygr142w	Btn2	0.046
188	Yor120w	Gcy1	0.026	232	Yfl068w		0.036	276	Ynl013c		0.048
189	Ycr030c	Syp1	0.026	233	Ykr093w	Ptr2	0.036	277	Ydr227w	Sir4	0.048
190	Ypl142c		0.026	234	Ylr327c		0.036	278	Ydr390c	Uba2	0.048
191	Yir009w	Msl1	0.027	235	Yor341w	Rpa190	0.037	279	Ynl075w	Imp4	0.049
192	Ycr049c		0.027	236	Yjr159w	Sor1	0.037	280	Ycr042c	Taf2	0.049
193	Yjl121c	Rpe1	0.027	237	Yor009w	Tir4	0.037	281	Ymr154c	Rim13	0.049
194	Ymr156c	Tpp1	0.027	238	Ygr080w	Twf1	0.038				

Full Details of Experimental Procedures

Strains and growth conditions. Strains used in this study are listed in Table 8. Unless otherwise mentioned, cells were grown with shaking (295 rpm) in rich medium (YPD), in a volume no more than 20% of the vessel maximum, at 30°C; henceforth referred to as normal conditions.

Table 8. Strains used in this study

Name	Genotype	Source
DBY8778(BY4741)	MATa ura3Δ leu2Δ hisΔ1 met15Δ1	Invitrogen, Carlsbad CA
DBY10058	DBY8778 ypl230w::Kan^R	Invitrogen, Carlsbad CA
DBY10089	DBY8778 kin82::Kan^R	Invitrogen, Carlsbad CA
DBY10090	DBY8778 ppt1::Kan^R	Invitrogen, Carlsbad CA

Cell Density Measurements . Cell densities in all experiments were measured at OD_{600} using a Pharmacia Ultrospec III spectrophotometer. All experiments, excluding those during the stationary phase, were carried out with early log phase cultures (OD 0.2-0.4).

Heat shock. Following dilution of saturated inoculates, cells were grown for 2-3 generations at 25°C. They were then collected by centrifugation, resuspended in an equal volume of 37°C medium, and returned to 37°C for growth. Samples were collected at 0, 5, 15, 30 and 60 minutes after transfer to 37°C.
Stationary Phase. Cultures were grown to OD_{600} of 0.27 (Ypl230w mutants) and 0.4 (congenic wildtype, DBY8778), at which point time zero samples were collected. Samples were further collected at 2/3, 5, 7, 9, and 24 hours.
Hypo-osmotic shock. Cultures were grown with 1M sorbitol for ~20 hours, cells collected by centrifugation and resuspended in YPD at time zero. Samples were collected at 0, 7, 15, 30 and 60 minutes after transfer to YPD.

For each environmental stress, mutants and their congenic wild-type strains were subjected to the same conditions and procedures, preferably side by side (this was not true for the Kin82 mutant heat shock experiment which was performed at a different occasion than its wildtype).

RNA Preparation. Samples for RNA isolation (25-35 ml aliquots) were vacuum-collected onto a 0.45 micron filter (Osmonics), snap-frozen in liquid nitrogen and kept at -80°C until use. RNA was prepared by adding 4 ml Lysis buffer (10 mM Tris-Hcl pH 7.5, 1 mM EDTA, 0.5 % SDS) and 4 ml of phenol saturated with 0,1 M citrate buffer pH 4.3 (Sigma; P4682) to each filter. Each mixture was incubated at 65°C for 1 hour, vortexing vigorously every 10 min. Mixture was then transferred without the filter, for better phase separation, to a new 15-ml conical tube and incubated for10 min on ice. After spinning at 3000 *g* for 10 min, the aqueous phase was transferred to another 15-ml tube containing 4 ml of saturated phenol. Samples were vortexed, and the spin was repeated. Aqueous phases were again transferred to a new 15-ml tube and 4 ml of chloroform were added, followed by a 10-min spin. RNA was precipitated by adding the aqueous phase 1/10

volume of 3 M sodium acetate and 2.5 volumes of ethanol. Samples were spun for 10 min at 3000 *g* to pellet the RNA. Pellets were washed twice with 70% ethanol and dried at room temperature. RNA pellets were dissolved in water to ~4 mg/ml.
Poly-(A)+ mRNA, was extracted from total RNA using the Oligotex midi kit (Qiagen) according to the manufacturer instructions, and dissolved in water to ~0.15 mg/ml

Probe Preparation. Poly-(A)+ mRNA (1.5 µg) and 4 µg of oligo-dT-VN 3'-anchored primer were combined in a total volume of 15 µl. RNA oligo-dT mixtures were heated to 70°C for 2 min and then cooled on ice. Three microliters of 1 mM Cy3- or Cy5-conjugated dUTP (Amersham Biosciences), 3 µl of 1 M DTT, 6 µl of first-strand buffer (Invitrogen), 0.6 µl of dNTPs (25 mM each dATP, dCTP, and dGTP and 15 mM dTTP), and 2 µl of Superscript II (Invitrogen) were added. Each sample was then incubated at 42°C for 1 h to generate Cy-labeled cDNA. A 1 µl boost of Superscript II was added, and the mixture was incubated for another hour. Starting mRNA was degraded by addition of 15 µl of 0.1 N NaOH and incubation at 70°C for 10 min. Samples were neutralized by addition of 15 µl of 0.1 N HCl and 380 µl of TE (10 mM Tris, 1 mM EDTA, pH 7.4). Labeled cDNA was separated from unbound dyes and concentrated to ≤30 µl using a Centricon-30 column (Amicon) according to the manufacturer instructions.

Microarray Hybridizations. A probe mixture (37 µl) consisting of Cy3- and Cy5-labeled cDNAs, 3XSSC, 0.3% SDS, and 4 µg/µl yeast polyA RNA (Sigma; P9403) was applied to each microarray. The microarray was covered by a 24X60-mm coverslip (Fisher Scientific) and placed in a custom-manufactured hybridization chamber (Monterey Industries). Twenty microliters of water were placed inside the hybridization chamber before sealing, and the chamber was placed in a 65°C water bath. The microarrays were allowed to hybridize 16-20 hours. Microarrays were removed from the chambers and placed in standard histochemistry slide holders where they were washed by plunging 2 minutes in each of the following solutions, respectively: 1X SSC, 0.06% SDS (followed by a plunge in a 1XSSC solution); 0.2X SSC; and 0.05X SSC.

Data acquisition and analysis. Microarrays were scanned using the GenePix 4000 microarray scanner (Axon instruments) at a resolution of 10 µm/pixel. This resulted in two images of fluorescence signals, one for each channel (red or green). Fluorescence intensity for each spot, in both channels, was extracted after semi-automatically superimposing a grid of circles onto the array images, using GenePix Pro 3.0. Data was subjected to quality control filters, flagging spots of poor quality as such. Fluorescence ratios were calibrated independently for each array by applying a single scaling factor to all fluorescent ratios from each array; this scaling factor was computed so that the mean fluorescence ratio of well-measured spots on each array was 1. Data was then stored in the Stanford Microarray Database (http://genome-www5.stanford.edu/MicroArray/SMD/). Subsequent analyses used only spots representing successfully amplified genes, with fluorescent intensity in both channels that was greater than 1.2 times the local background and ORFs for which more than 80% of the intensity ratios in each time series were following this rule. Analyses used the log-transformed (base 2) ratios. Raw data files for each array including flagging information,

and the actual filtered data files used for analysis can be downloaded from http://www.cs.stanford.edu/~eran/module_nets.

Verifying chromosomal integrity of deletion strains. For each deletion strain, the reference RNA pool was compared to that of the congenic wildtype strain to observe for gross chromosomal rearrangements reflected in locus-associated gene expression biases. None of the strains used in this study showed such a bias.

Identifying Differentially Expressed Genes in Microarray Experiments for Putative Regulators. We applied a paired two-tailed t-test to compare the expression time series of mutant and wild-type. Genes with $p<0.05$ from the t-test were considered differentially expressed. Each time series was zero-transformed to enable comparison of the response to the tested condition. For Kin82 and Ppt1, we gave all time points as input to the t-test (5, 15, 30, and 60 minutes for Kin82; 7, 15, 30, and 60 minutes for Ppt1). For the experiment measuring response during stationary phase (Ypl230w), we used only the late time points (7, 9, and 24 hours), since the response to this growth condition starts at this time. To ensure that only genes with large differences are included, we also required that at least half the time points compared are different by at least 2-fold change in expression. The only exception was Ppt1, where we required a 1.3 fold difference, since the overall signal in these arrays was weaker.

Algorithmic Details and Statistical Performance

A technical report describing the full details of the *module networks* method is available at: http://www.cs.stanford.edu/~eran/module_nets/tech.html.

Learning Module Networks

Here, we present a simplified version, which captures the algorithm's essence. Our approach is model based, following an integration of the ideas and rationale of Pe'er *et al.* and of Segal *et al.*: We define a space of possible models and use a statistically based likelihood score called the Bayesian score to evaluate a model's fit to the data. Our iterative learning procedure attempts to search for the model with the highest score by using the Expectation Maximization (EM) algorithm. An important property of the EM algorithm is that each iteration is guaranteed to improve the likelihood of the model, until convergence to a local maximum of the score. Each iteration of the algorithm consists of two steps: an *E-step* and an *M-step*. In the *M-step*, the procedure is given a partition of the genes into modules and learns the best regulation program (regression tree) for each module. For computational efficiency, some *M-steps* only optimize the parameters of the normal distributions at the leaves of the regulation tree and leave the tree structure unchanged. An *M-step* that relearns the regulation tree structure is employed only after iterations of *E-steps* and parameter optimizing *M-steps* converge.

The regulation program is learned via a combinatorial search over the space of trees. The tree is grown from the root to its leaves. At any given node, the query which best partitions the gene expression into two distinct distributions is chosen, until no such split exists. In the *E-step*, given the inferred regulation programs, we determine the module whose associated regulation program best predicts each gene's behavior. Recall that each regulation program defines a probability distribution over the gene's expression levels in each array. We can test the probability of a gene's measured expression values in the dataset under each regulatory program as follows: We evaluate, for each array, the probability of the associated expression measurement in the array's context, as specified by the regression tree; we then multiply the probabilities for the different arrays, obtaining an overall probability that this gene's expression profile was generated by this regulation program. We then select the module whose program gives the gene's expression profile the highest probability, and re-assign the gene to this module. We take care not to assign a regulator gene to a module in which it is also a regulatory input, since it is not surprising that a gene can predict its own gene expression. Overall, each iteration of this procedure requires computation time which is linear in the size of the expression matrix (number of genes times number of experiments).

In order to allow the method to discover as many regulatory relationships as possible, we incorporated only minimal regularization when learning each regulation tree, allowing for the construction of very deep trees. As is common in decision tree learning (J.R. Quinlan, *C4.5: Programs for Machine Learning*, Morgan Kaufmann, 1993), spurious

splits further down the tree were pruned in a post-processing phase based on a statistical significance test for the resulting split.

Performance of EM (number of iterations, initialization, change from starting point)

We initialized our module network procedure with 50 clusters using PCluster, a hierarchical agglomerative clustering (see technical report in web site). The cost of the initialization step is quadratic in the number of experiments, and linear in the number of genes. We then applied the iterative EM algorithm to to this starting point , refining both the gene partition and the regulatory programs. Our procedure converged after 23 iterations (four tree structure change iterations) to the 50 modules we analyzed, changing the initial module assignment for 49% of the genes. To characterize the trajectory of the algorithm, we plot its improvement in performance across the EM iterations (Fig. 1), measured as the log-likelihood of the data given our model across the different EM iterations (normalized by the number of genes). *M-steps* in which the structure of the regression trees were also changed are marked by red vertical dashed lines. We also plot the gene module assignment changes (Fig. 2), showing both the change in assignment between consecutive iterations (pink line) and the change in assignment compared to the starting point. As a more biological performance criterion, we compared the starting point to the final module assignments in terms of their enrichment for gene annotations from GO. For each annotation, we computed its enrichment in the starting point and in the final module assignment using the hypergeometric distribution. A comparison of all such enrichments is shown (Fig. 3), where each dot compares the negative log of the *p*-value for one annotation between the two models. This plot shows a clear improvement in the significance of the annotations found between the initial starting point and the final modules.

Sensitivity of EM to initial starting point

The EM algorithm is sensitive to the starting point and is only guaranteed to converge to a local maximum of the score. We assessed the quality of our convergence point and the degree to which our variant of EM is indeed sensitive to the initial clustering. We generated 100 random clusterings and applied the module networks procedure 100 times, using each of the random clusterings as a starting point. As expected, different initialization points led to different convergence points. However, in all of the random runs, between 40-50 of the learned modules had an overlap of 30% or more with their matched module in the target run; this degree of overlap is significantly greater than the overlap we would expect to see by chance. (Specifically, in 100 randomly generated clusterings that preserved the same sizes as the modules obtained from these 100 runs, approximately 0-4 clusters demonstrated the same degree of overlap with the target run.). We used this overlap to pair modules between the randomized and target runs. With this match, between 41% and 52% of the total number of genes were placed in the same module in the target run and in the one initialized from the random clustering. A plot of the sorted percentage of consistently placed genes is shown in Fig. 4. Furthermore, a

large number of genes are placed consistently in the same module across many of the random runs, as shown in Fig. 5. We conclude that, while our method is clearly sensitive to the initialization, this dependence is in fact weaker than may have been expected.

Quality of our initial starting point

To apply the procedure in practice, we need a general method for selecting a specific initialization. Although initialization from random starting points is possible, generating a number of random initialization points required to obtain a high-quality answer is computationally prohibitive. We believe that a deterministic initialization derived from the data is more likely to give high-quality answers consistently. We chose to use a probabilistic hierarchical clustering algorithm to initialize the procedure. We evaluated this proposed initialization method by comparing the log-likelihood of the data in the final model using both our initialization and the 100 random initializations. A plot of the sorted log-likelihood of the data for each of the 100 runs initialized from random clusterings is shown in the supplementary information, Fig. 6. Encouragingly, the score for our method's output was better than that of 98/100 of the runs initialized from random clusters, and the 2/100 random runs that performed better are only incrementally better. We also compared the biological coherence of the modules obtained from our clustering with those of the resulting clusters from the two runs that achieved an incrementally better log-likelihood score than ours. This was done by comparing the enrichment of each GO annotation in our clustering and in random clustering. In both cases, the number of GO annotations that were more significantly enriched in the target run was greater than the number of annotations that were more significantly enriched in the randomly initialized runs: 219 annotations more significant in the target run versus 181 more significant in the best log-likelihood run, and 218 more significant in the target run versus 182 more significant in the second-best log-likelihood run. Overall, our results indicate that our initialization approach provides a high-quality local maximum, which tends to provide results that are more biologically meaningful that those obtained by initializing with random clusterings.

Selecting the number of modules

The number of modules is a parameter to our algorithm. As for any clustering algorithm, the choice of parameters is important, and can make a difference to the results. However, as in most clustering problems, there is no clear "right" choice of this parameter. We selected 50 based on the biological rule of thumb that the average number of genes in a module is around 50. We note that an average of 50 genes per module is consistent with the average number of genes per module found by the approach of Ihmels *et al* (*Nat Genet* **31**, 370-7 (2002)). To verify that this choice was a reasonable one, we also did statistical validation, using five-fold cross-validation: We compared three values for the number of modules: 20, 50, 80. We randomly partitioned the original set of 173 arrays into five equally sized sets (two sets had one array less that the other three sets), and applied the module network procedure to each of the five possible combinations of four

of these array sets. In each case, we evaluated performance by measuring the log-likelihood that the learned model assigns to the array set that was held-out. The mean and standard deviation of the test-set log-likelihood per gene, across the five different runs were as follows: -31.54 +/- 1.71 for the 20 module model, -30.65 +/- 1.85 for the 50 module model, and -31.12 +/- 1.92 for the 80 module model. These results suggest that a module network model with 50 modules is a better fit to the underlying distribution than models with 20 or 80 modules.

We note that other heuristics could be employed for selecting the number of modules. A more formally motivated *Bayesian* approach is to employ a prior over models, which would typically be designed to favor models with fewer number of modules, and then compare models by their posterior probability given the data. Using such criteria, it would then be possible to select the number of modules as part of the learning algorithm. This extension is an interesting direction for future work.

Figure 1

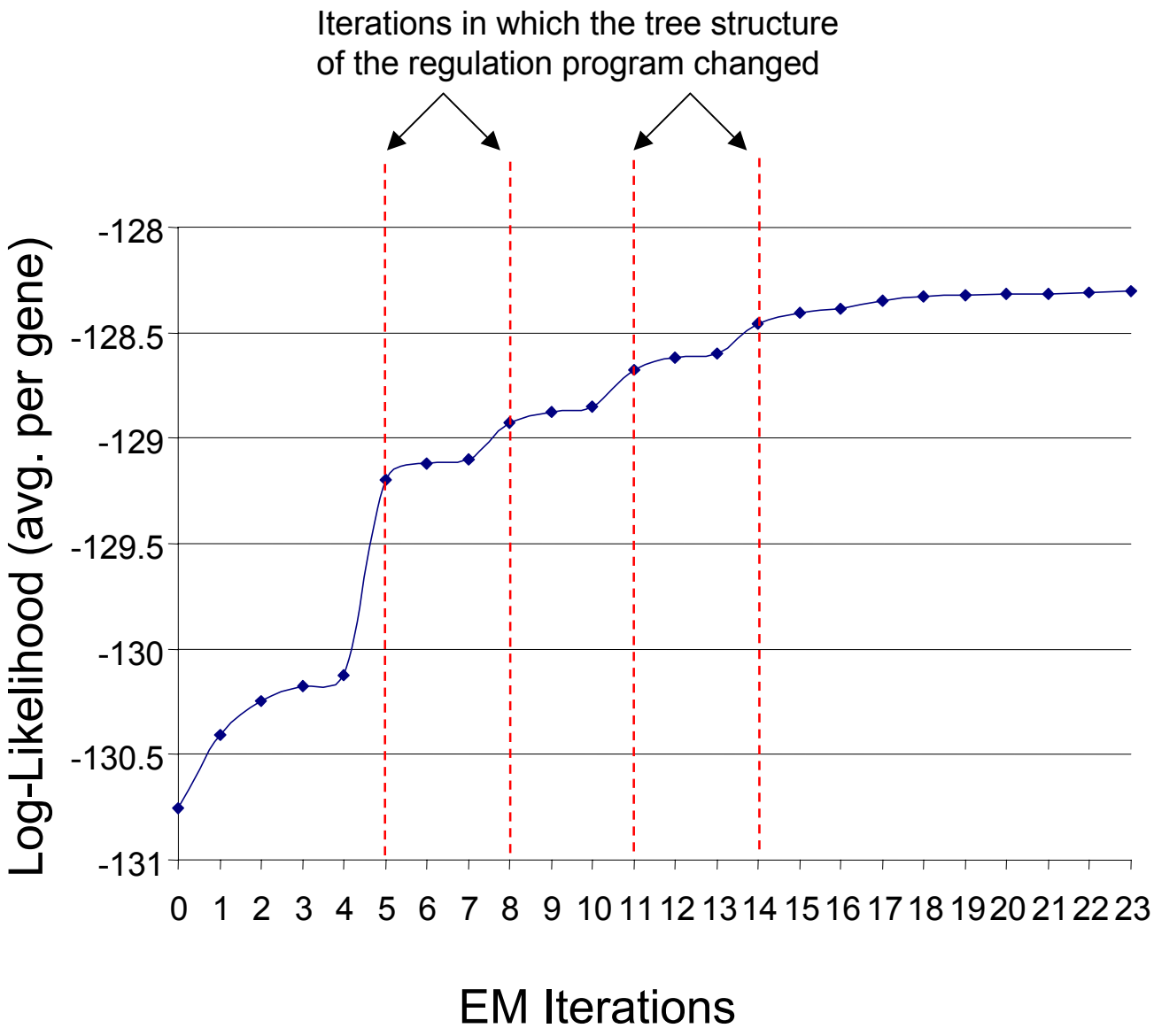


Figure 1. Characterization of EM across the 23 iterations. Plotted is the log-likelihood of the data across the different EM iterations. The EM algorithm is guaranteed to improve the log-likelihood of the data in each iteration until convergence. Iterations in which the structure of the regulation trees were also changed are indicated by red dashed lines (in other iterations only the parameters of the normal distributions associated with each context were changed).

Figure 2

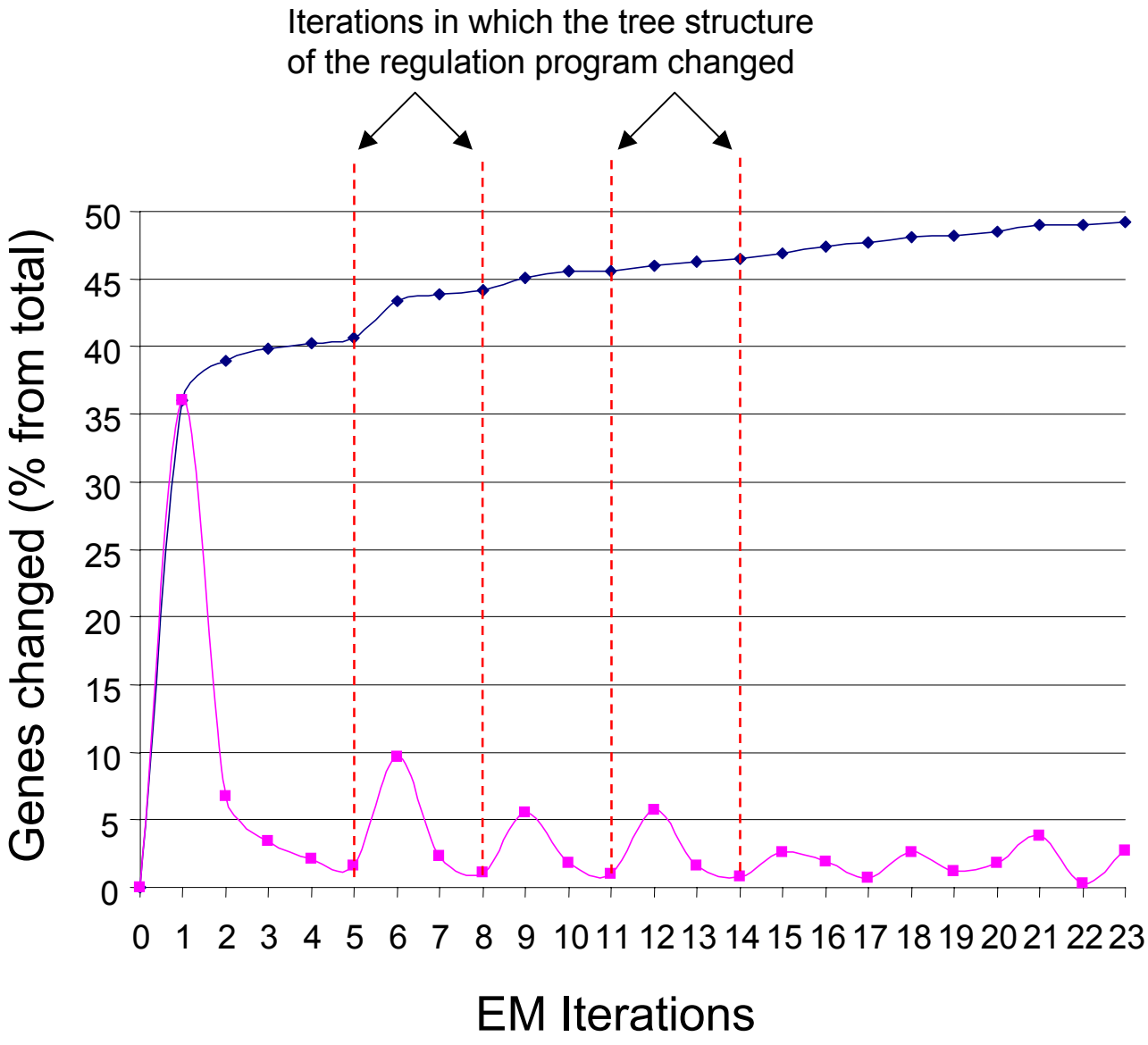


Figure 2. Characterization of EM across the 23 iterations. Plotted is the fraction of genes that changed their module assignment between consecutive iterations (pink line) or compared to the starting point (blue line). Iterations in which the structure of the regulation trees were also changed are indicated by red dashed lines (in other iterations only the parameters of the normal distributions associated with each context were changed).

Figure 3

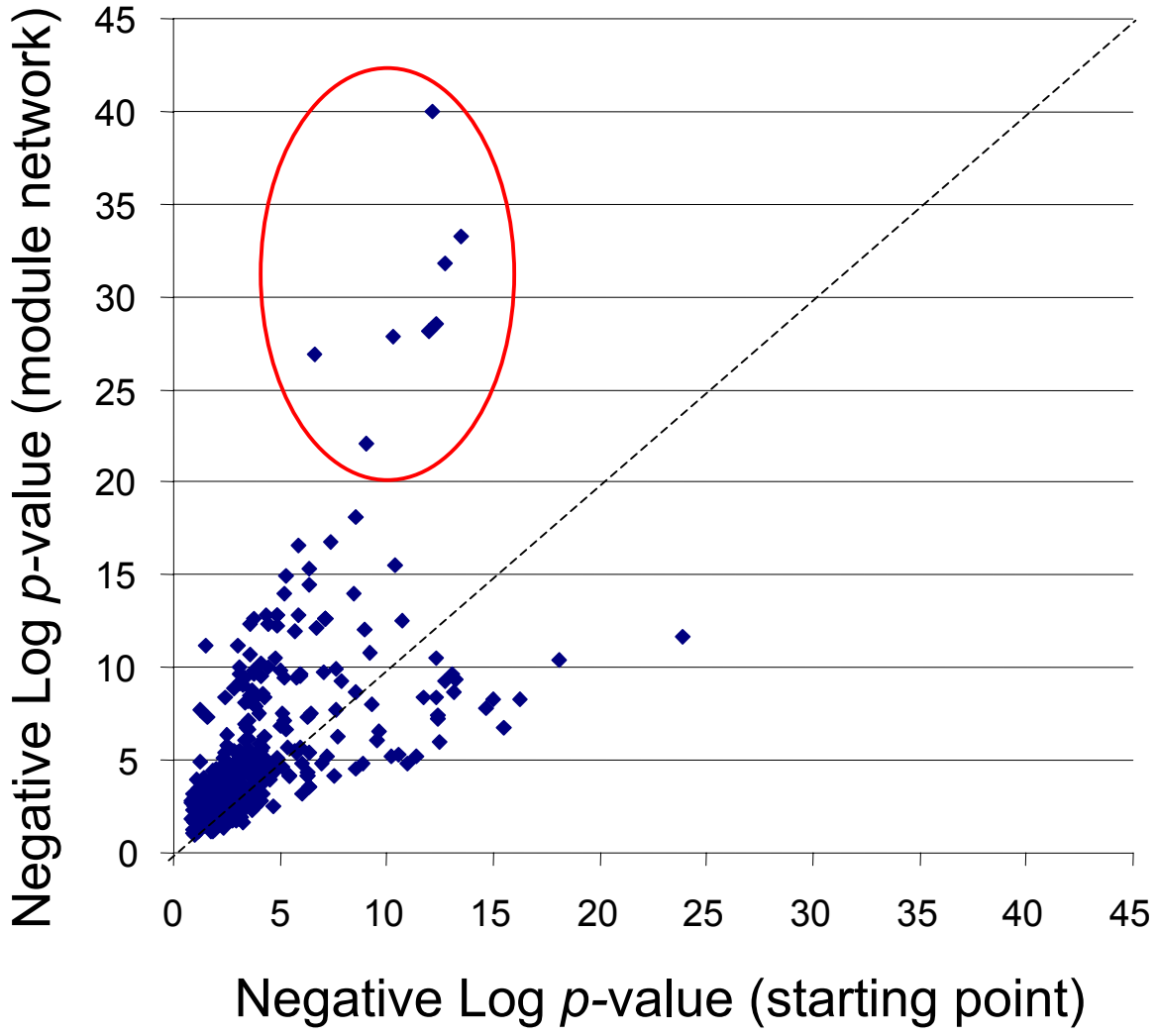


Figure 3. Comparison of the enrichment for GO annotations between the starting point initialized from PCluster (x-axis), and the model resulting from applying the module networks procedure to this starting point (y-axis). Each dot corresponds to the best *p*-value of the enrichment of the annotation in any of the clusters of each model. Circled in red are the annotations that were most strongly enriched in the analyzed model and much less enriched in the starting point. Dots above the diagonal line are more significantly enriched in the model analyzed in the manuscript

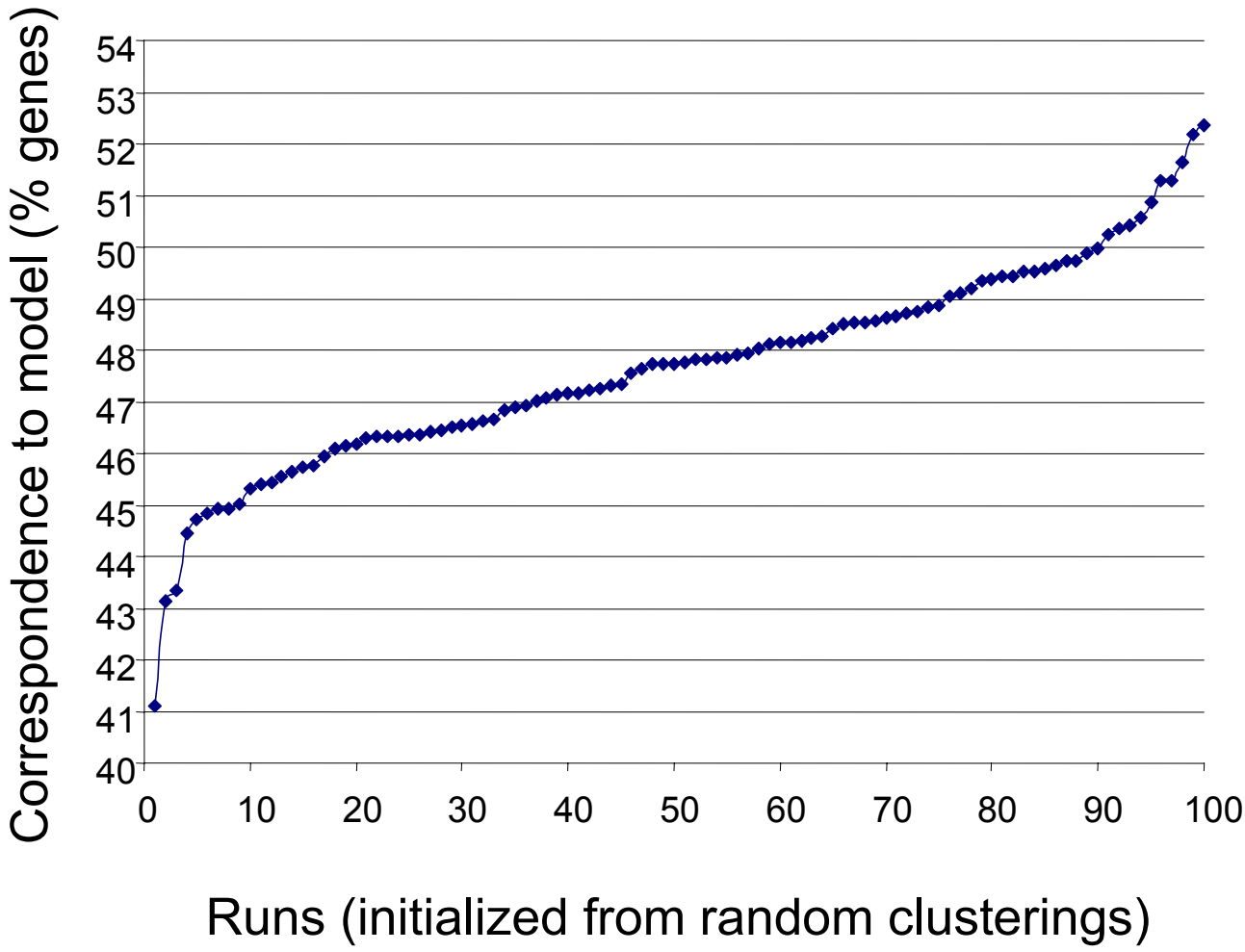


Figure 4. Evaluation of the sensitivity of the method to the starting point. Since EM is initialized from some clustering, we wanted to evaluate the how sensitive it is to the choice of starting point. We thus applied the module network procedure 100 times, where each run was initialized from a random clustering of the genes. In all 100 comparisons, between 46 and 50 of the modules in the analyzed run could clearly be matched to a module in the run initialized from a random clustering. For this mapping, we computed the fraction of genes that are placed in the same module between the analyzed model and the randomly initialized models. This is shown in this figure, where the runs are sorted according to the percentage of genes that matched between the run initialized from the random clustering and the analyzed model.

Figure 5

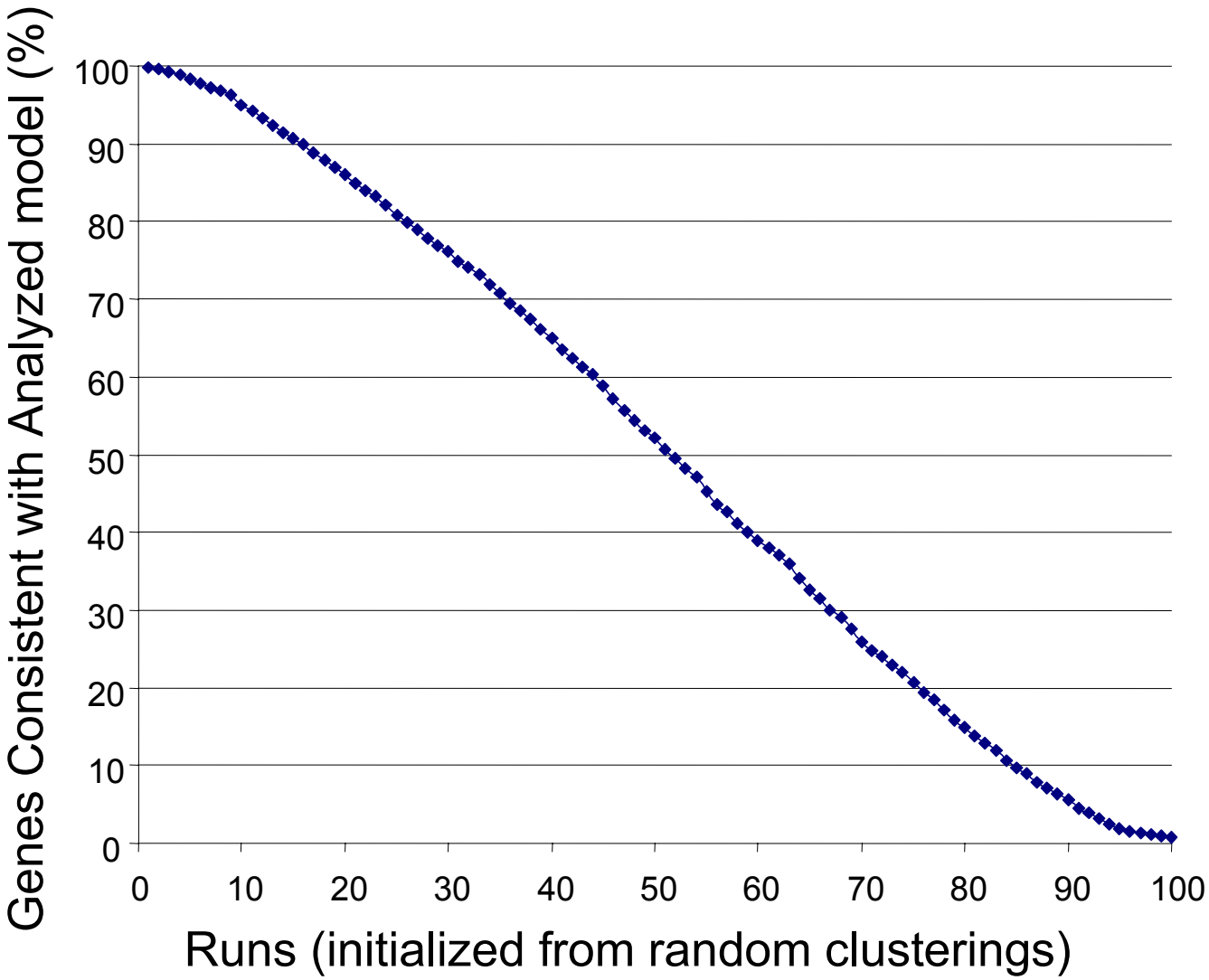


Figure 5. Evaluation of the sensitivity of the method to the starting point. Since EM is initialized from some clustering, we wanted to evaluate the how sensitive it is to the choice of starting point. We thus applied the module network procedure 100 times, where each run was initialized from a random clustering of the genes. In all 100 comparisons, between 46 and 50 of the modules in the analyzed run could clearly be matched to a module in the run initialized from a random clustering. For this mapping, we computed the fraction of genes that are placed in the same module between the analyzed model and the randomly initialized models. This figure shows the fraction of genes that were consistently placed in the same module across 'x' or more of the 100 runs, where we range x from 1 to 100.

Figure 6

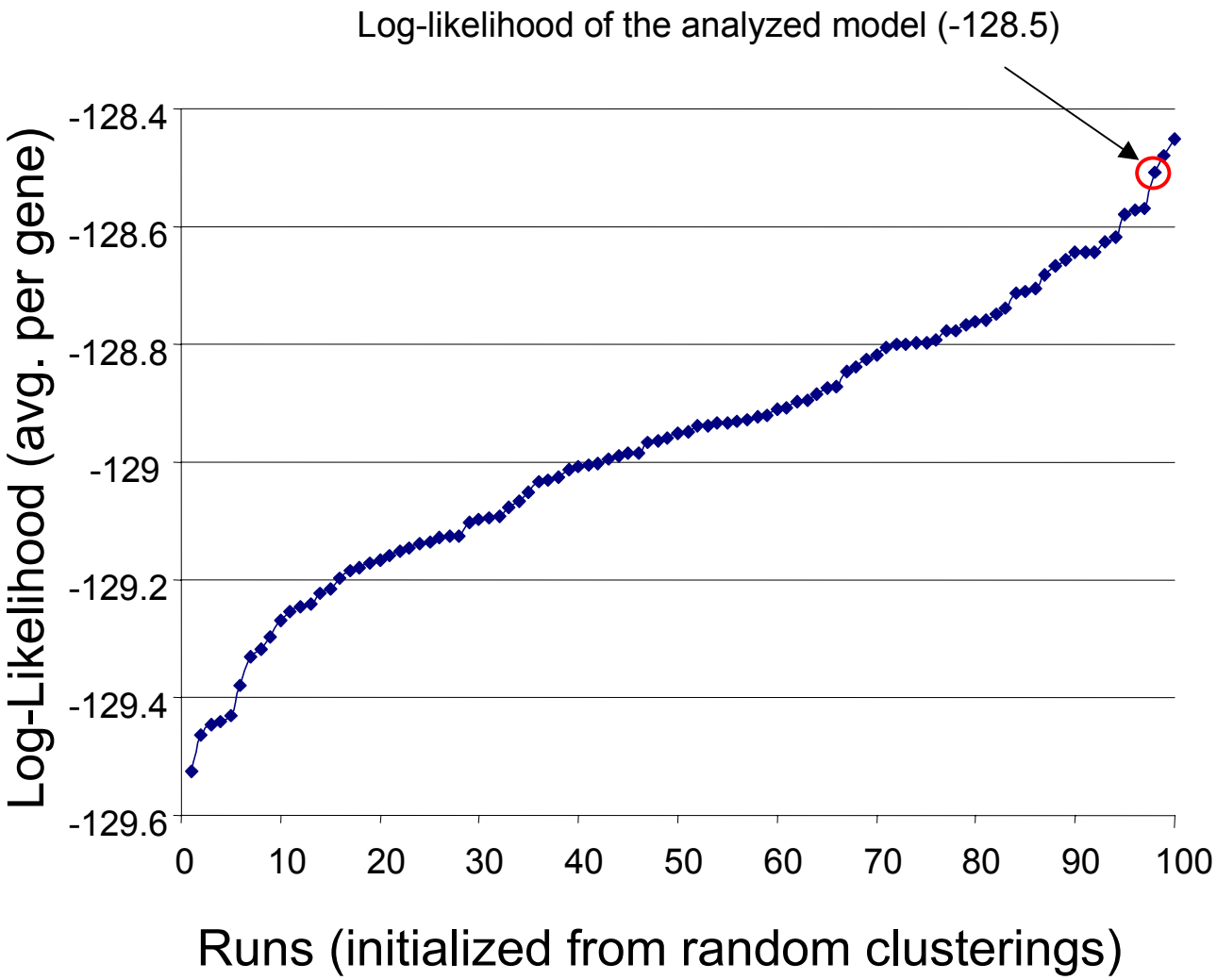


Figure 6. Evaluation of the quality of the convergence point of the algorithm. Since EM only converges to a local maximum of the score, we wanted to evaluate the quality of this local maximum. We thus applied the module network procedure 100 times, where each run was initialized from a random clustering of the genes. The sorted log-likelihood of all the randomized runs are shown, and the convergence point analyzed throughout the paper is marked with an arrow. Only two randomized runs converged to a better point than the analyzed model, indicating that the analyzed model converged to a strong local maximum.

Figure 7

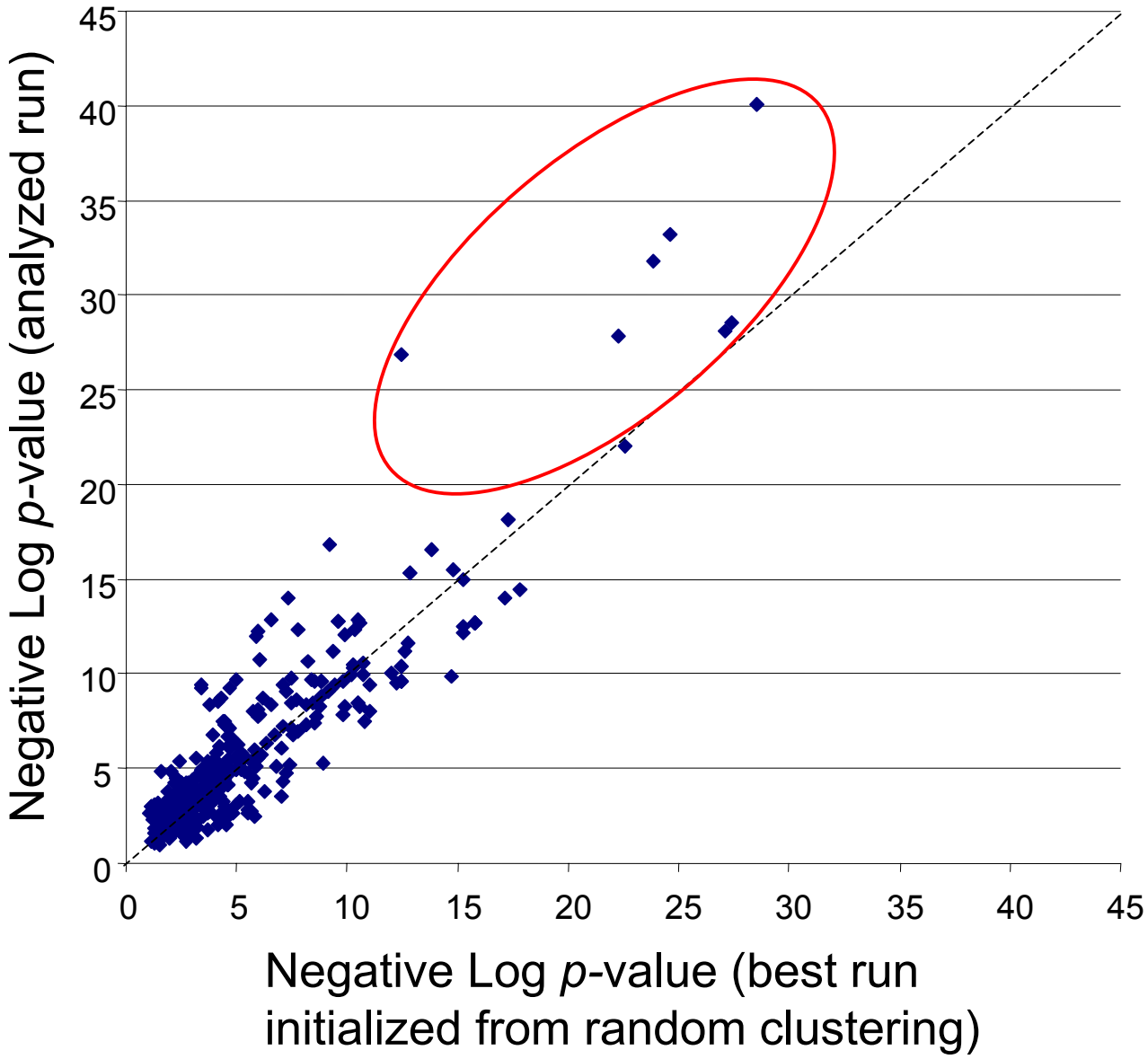


Figure 7. Comparison of the enrichment for GO annotations between the modules analyzed in the manuscript (y-axis), and the run that achieved the best log-likelihood from all 100 runs initialized from a random clustering (x-axis). Each dot corresponds to the best *p*-value of the enrichment of the annotation in any of the clusters of each model. Circled in red are the annotations that were most strongly enriched in the analyzed model and much less enriched in the starting point. Dots above the diagonal line are more significantly enriched in the model analyzed in the manuscript.

URLs

The supplementary web site is http://www.cs.stanford.edu/~eran/module_nets (username: modnet, password: modnet-review). The site contains all the information presented here, as well as the full raw expression data obtained from the four different microarray experiments.

All of the statistical evaluations in the paper were done and visualized in GeneXPress, a cluster analysis and visualization tool we developed for this purpose. The tool can evaluate the output of any clustering program for enrichment of gene annotations and motifs and is freely available for academic use at http://GeneXPress.stanford.edu/. GeneXPress files for the learned module network and the annotations we used are available from the supplementary web site.

The main yeast stress data set that we analyzed in the paper can be downloaded from: http://genome-www.stanford.edu/yeast_stress/.

A technical report describing the probabilistic clustering used to initially partition the genes to modules is available at http://www.cs.stanford.edu/~eran/module_nets/tech.html

A technical report describing the full details of the *module networks* method is available at: http://www.cs.stanford.edu/~eran/module_nets/tech.html.

All experimental data is available at the Stanford Microarray Database: http://genome-www5.stanford.edu/MicroArray/SMD/.