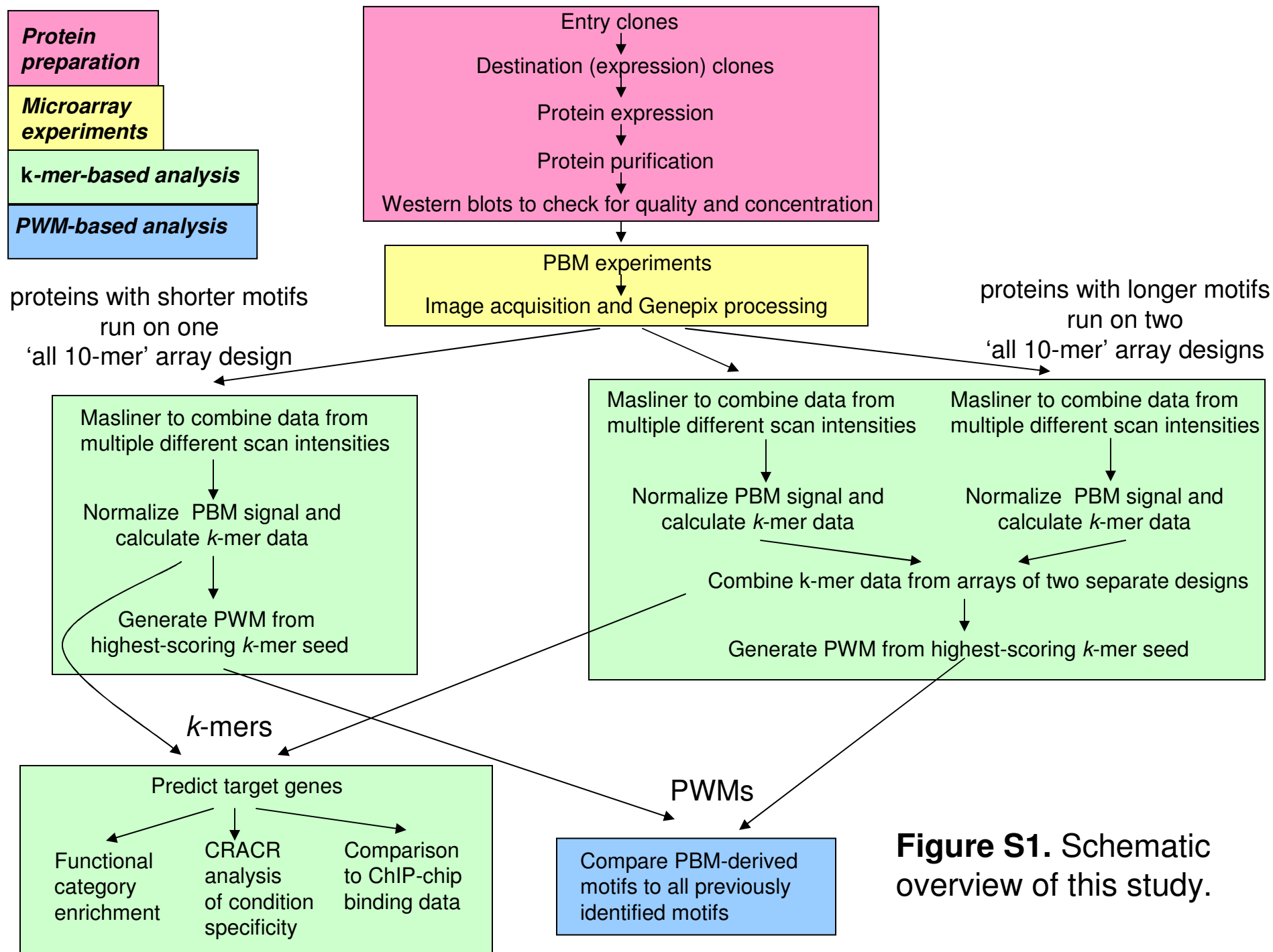
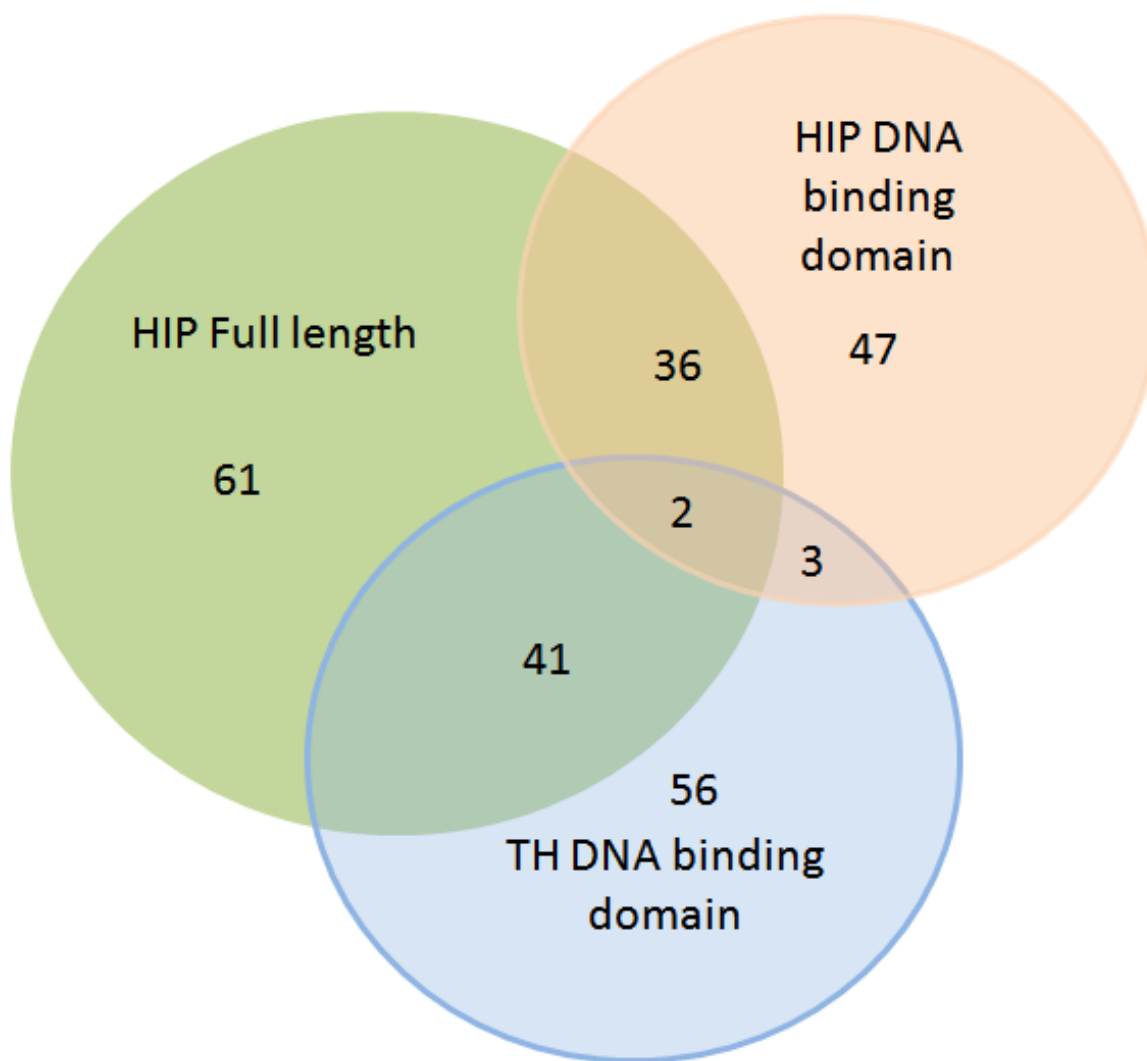


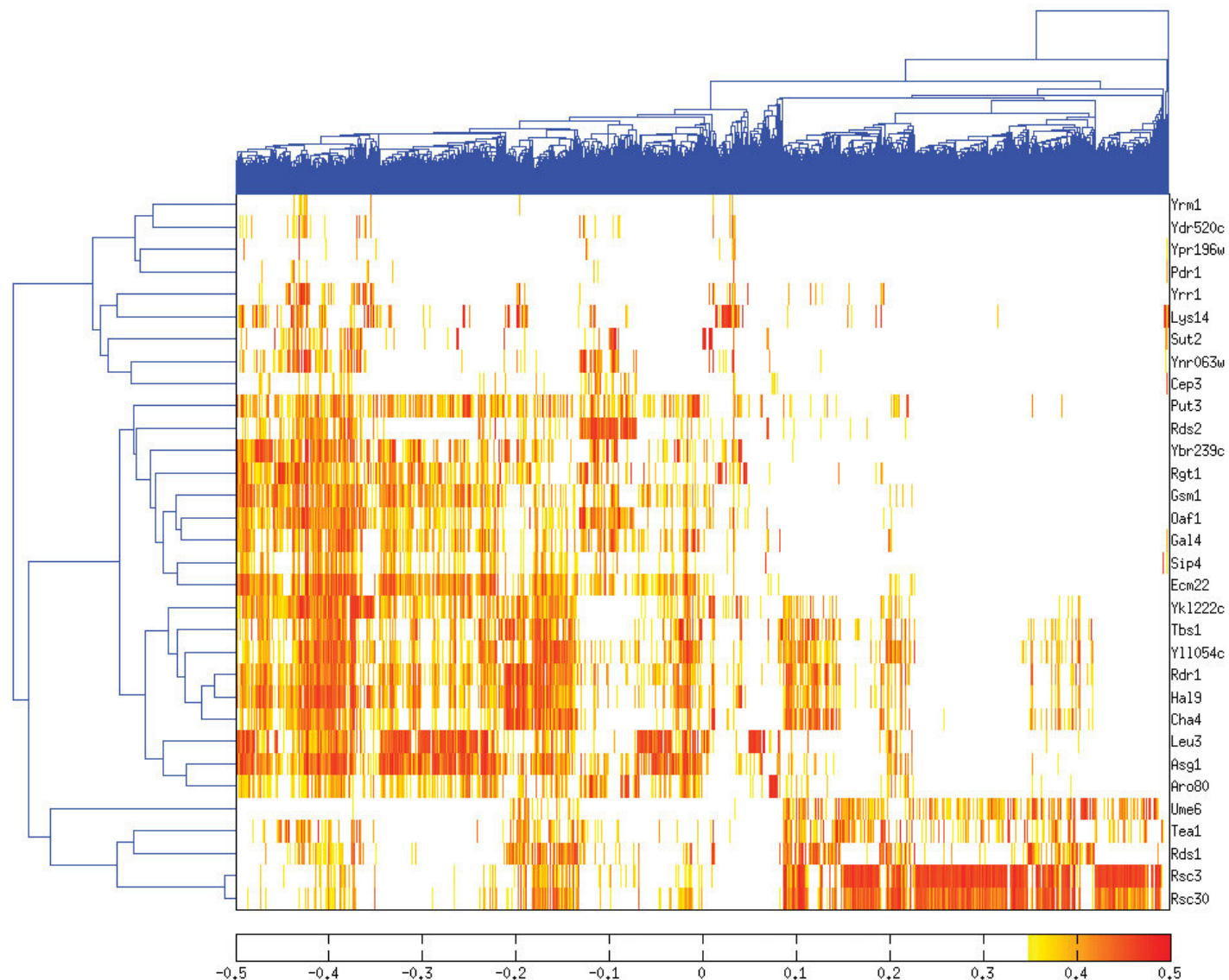


**Figure S1.** Schematic overview of this study.

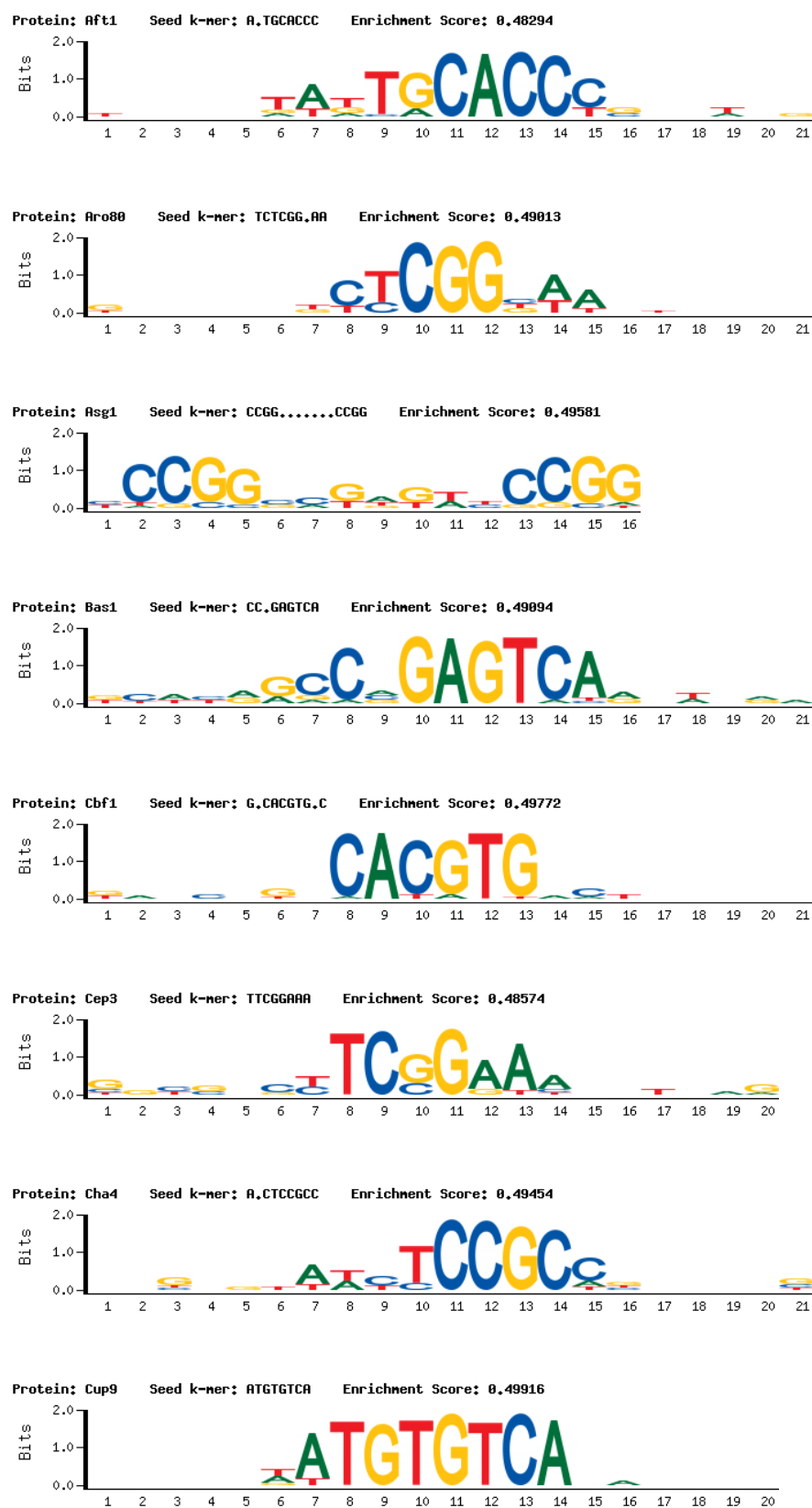


*Note: not to scale*

**Figure S2. Overview of all proteins tested on PBMs in this study.** All GSTTF fusion proteins that were deemed acceptable by Western blot (i.e., sufficient amount of protein of the appropriate size; see **Supplementary Experimental Procedures**) were first tested on 8x15K PBM arrays before subsequently applying them to 4x44K PBM arrays. These known and predicted TFs include those represented as: full-length ORFs cloned at the Harvard Institute of Proteomics as described in Hu *et al.*, *Genome Res.* '07 ("full-length"); DNA binding domains (DBDs) cloned at the Harvard Institute of Proteomics essentially as described in Hu *et al.*, *Genome Res.* '07 ("HIP DBD"); DBDs received as a gift from the laboratories of Timothy Hughes (U. Toronto) and Jason Lieb (U. North Carolina) ("TH DBD").

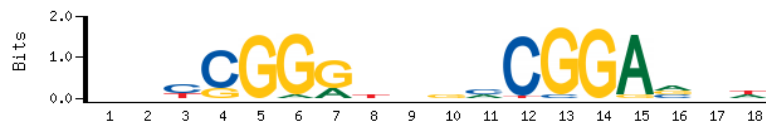


**Figure S3. 8mer binding profile for 32 Zn<sub>2</sub>Cys<sub>6</sub> TFs.** Two dimension clustergram was generated for Zn<sub>2</sub>Cys<sub>6</sub> TFs using their enrichment score for all un-gapped 8mers and 8mers consist of 4 bp half sites on both side and with gaps of 1 through 12. 8-mer data were filtered at enrichment score cut-off value of 0.45.

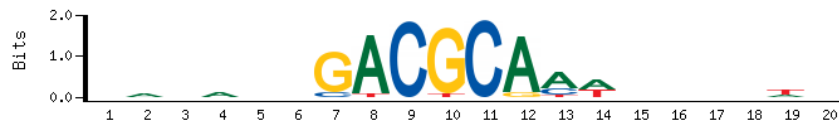


**Figure S4. PBM-derived yeast TF DNA binding site motifs determined in this study.**

Protein: Ecm22 Seed k-mer: CGGG....CCGA Enrichment Score: 0.49307



Protein: Fhl1 Seed k-mer: GACGC AAA Enrichment Score: 0.49223



Protein: Fkh1 Seed k-mer: GTAACAA Enrichment Score: 0.49902



Protein: Fkh2 Seed k-mer: GTAACAA Enrichment Score: 0.49839



Protein: Gal4 Seed k-mer: TCGG.....CCGA Enrichment Score: 0.49782



Protein: Gat1 Seed k-mer: CCTTATCG Enrichment Score: 0.49700

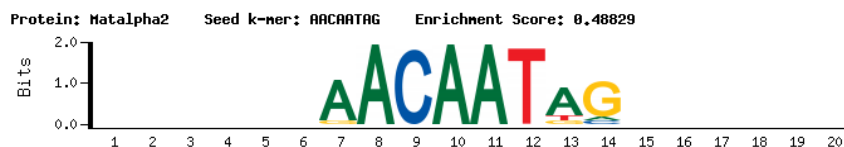


Protein: Gat3 Seed k-mer: AGATCTAC Enrichment Score: 0.49893



Protein: Gat4 Seed k-mer: TAGATCTA Enrichment Score: 0.49914

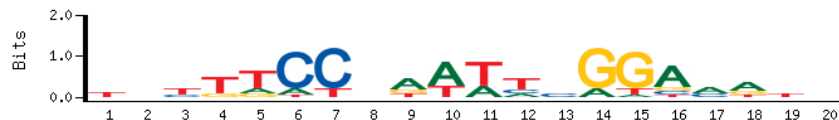




Protein: Mbp1    Seed k-mer: ACGCGTCA    Enrichment Score: 0.49873



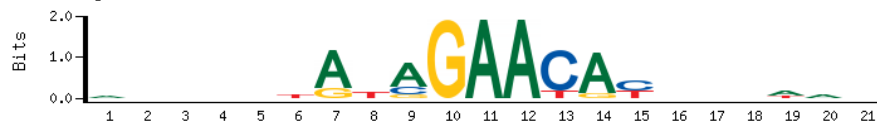
Protein: Mcn1    Seed k-mer: CC.AATT.GG    Enrichment Score: 0.49395



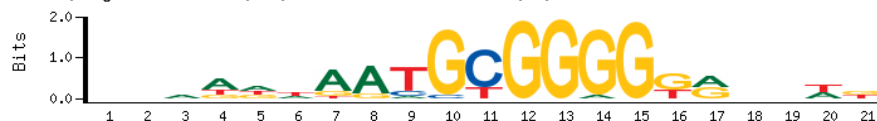
Protein: Met32    Seed k-mer: A.TGTGGCG    Enrichment Score: 0.49924



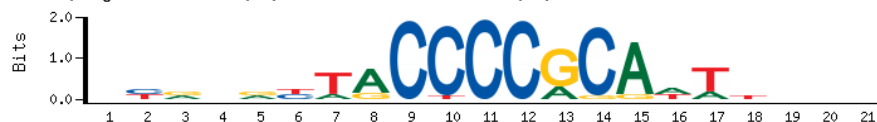
Protein: Mga1    Seed k-mer: A.AGAACAC    Enrichment Score: 0.49231



Protein: Mig1    Seed k-mer: AA.GCGGGG    Enrichment Score: 0.49690



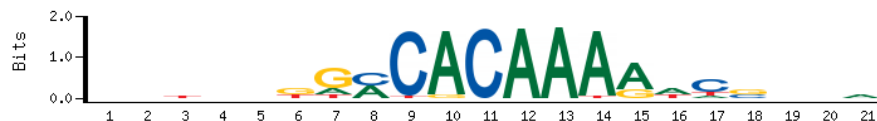
Protein: Mig2    Seed k-mer: T.CCCCGCA    Enrichment Score: 0.49896



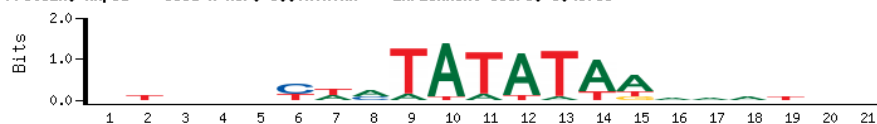
Protein: Mig3    Seed k-mer: T.CCCCGCA    Enrichment Score: 0.49866



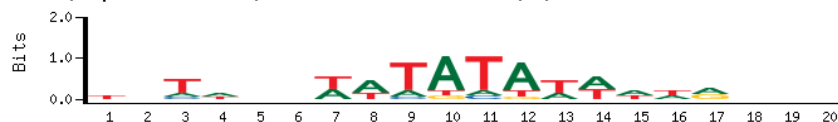
Protein: Ndt80    Seed k-mer: G.CACAAAA    Enrichment Score: 0.49876



Protein: Nhp6a Seed k-mer: C..TATATAA Enrichment Score: 0.48753



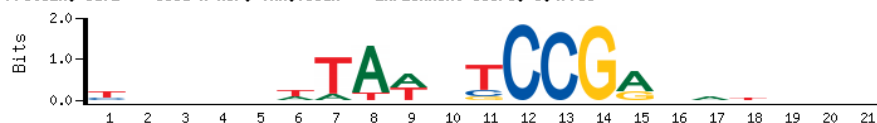
Protein: Nhp6b Seed k-mer: TATATATA Enrichment Score: 0.48166



Protein: Nrg1 Seed k-mer: CAGGGTCC Enrichment Score: 0.49926



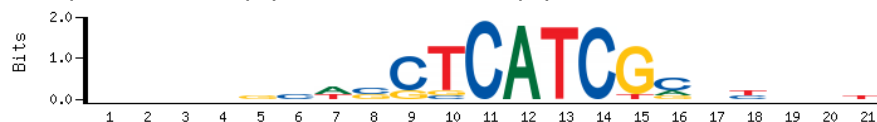
Protein: Oaf1 Seed k-mer: TAA.TCCGA Enrichment Score: 0.47756



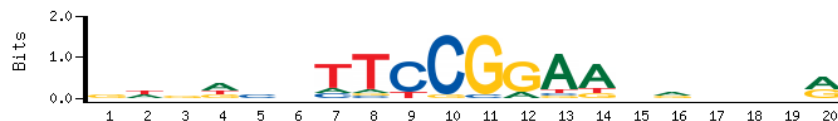
Protein: Pbf1 Seed k-mer: A.CTCATCG Enrichment Score: 0.49719



Protein: Pbf2 Seed k-mer: A.CTCATCG Enrichment Score: 0.49615



Protein: Pdr1 Seed k-mer: TTCCGGAA Enrichment Score: 0.47196



Protein: Phd1 Seed k-mer: CATGCAT.A Enrichment Score: 0.49390





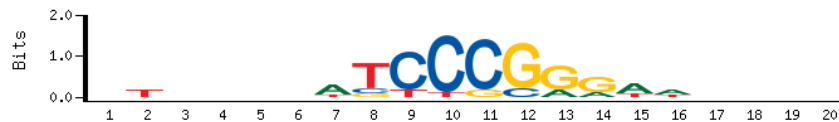
Protein: Pho2    Seed k-mer: TTAATTAA    Enrichment Score: 0.49563



Protein: Pho4    Seed k-mer: GCACGTGC    Enrichment Score: 0.49893



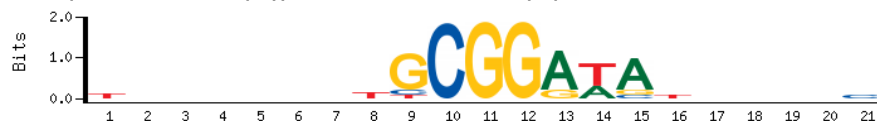
Protein: Put3    Seed k-mer: ATCCCGGG    Enrichment Score: 0.48089



Protein: Rap1    Seed k-mer: GGGTGATC    Enrichment Score: 0.48508



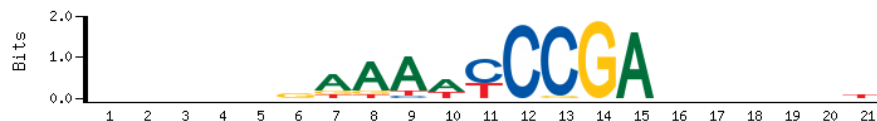
Protein: Rdr1    Seed k-mer: C..GCGGATA    Enrichment Score: 0.48670



Protein: Rds1    Seed k-mer: TCGGCCGA    Enrichment Score: 0.49746

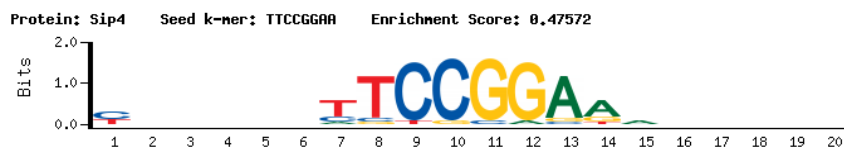
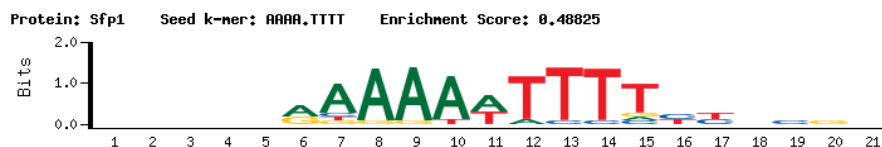
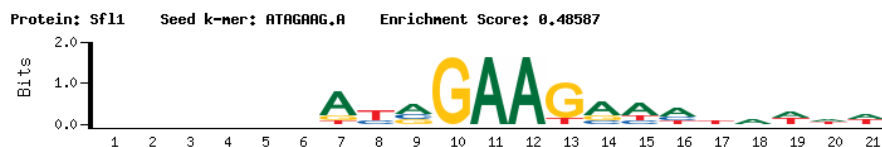
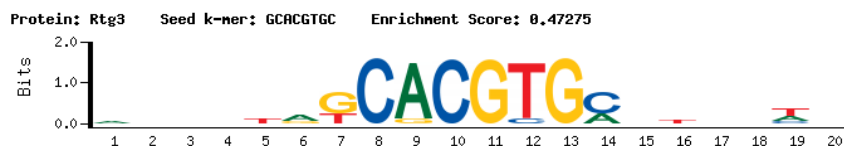
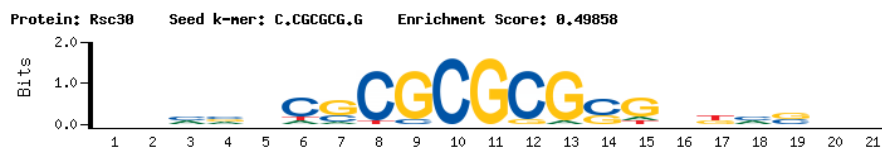
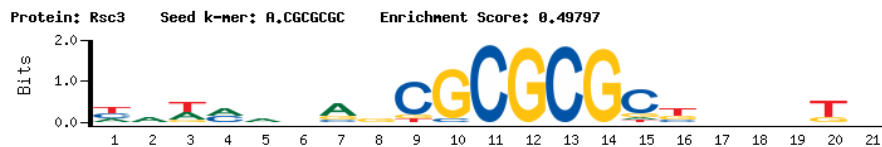
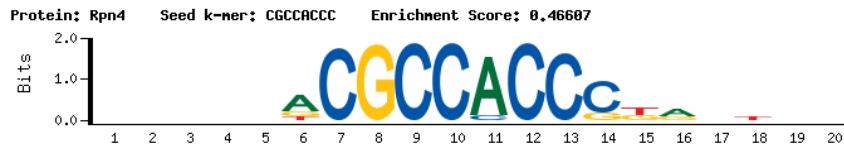
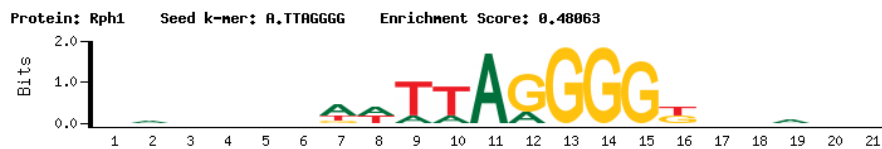


Protein: Rds2    Seed k-mer: AAA.CCCGA    Enrichment Score: 0.48761

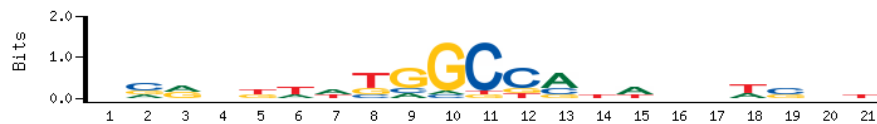


Protein: Rgt1    Seed k-mer: CGGA AAAA    Enrichment Score: 0.49445

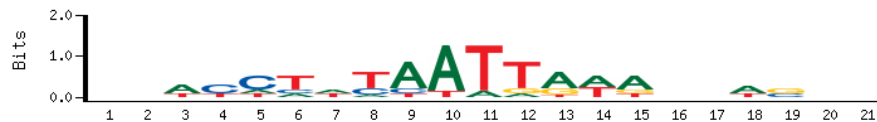




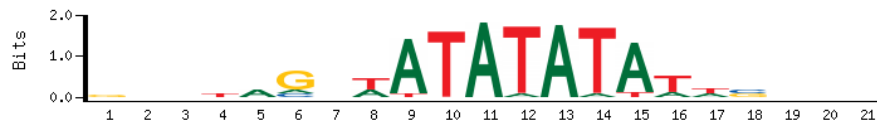
Protein: Skn7    Seed k-mer: T.TGGCCA.A    Enrichment Score: 0.49144



Protein: Snp1    Seed k-mer: T.TAATTA.A    Enrichment Score: 0.46604



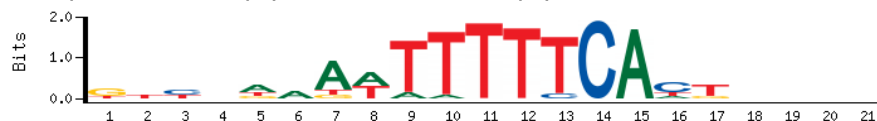
Protein: Spt15    Seed k-mer: G..ATATATA    Enrichment Score: 0.49072



Protein: Srd1    Seed k-mer: AGATCTAC    Enrichment Score: 0.49938



Protein: Stb3    Seed k-mer: A.TTTTTC A    Enrichment Score: 0.49893



Protein: Stp2    Seed k-mer: GCGCCGCA    Enrichment Score: 0.49265



Protein: Stp4    Seed k-mer: G..CGGCTGA    Enrichment Score: 0.48892



Protein: Sum1    Seed k-mer: AATTAA TT    Enrichment Score: 0.49492



Protein: Sut2    Seed k-mer: AACTCCGA    Enrichment Score: 0.49927



Protein: Tbf1    Seed k-mer: AACCTTAA    Enrichment Score: 0.49904



Protein: Tbs1    Seed k-mer: CGGATCCG    Enrichment Score: 0.49955



Protein: Tea1    Seed k-mer: CGG, A, TTAA    Enrichment Score: 0.49736



Protein: Tec1    Seed k-mer: ACATTCTC    Enrichment Score: 0.49324



Protein: Tye7    Seed k-mer: TCACGTGA    Enrichment Score: 0.49908



Protein: Une6    Seed k-mer: GCGGCTA    Enrichment Score: 0.49539



Protein: Usv1    Seed k-mer: CCCCTGAA    Enrichment Score: 0.49854



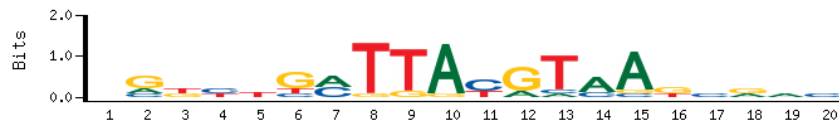
Protein: Xbp1    Seed k-mer: TCTCGAGA    Enrichment Score: 0.49131



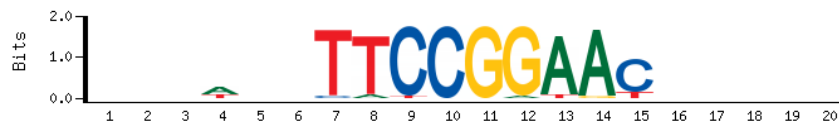
Protein: Yap1    Seed k-mer: TTACGTAA    Enrichment Score: 0.49863



Protein: Yap6    Seed k-mer: G.TTACGT.A    Enrichment Score: 0.49409



Protein: Ybr239c    Seed k-mer: TTCCGGAA    Enrichment Score: 0.49668



Protein: Ydr520c    Seed k-mer: CGGAGATA    Enrichment Score: 0.49931



Protein: Yer130c    Seed k-mer: AATAGGGG    Enrichment Score: 0.49695



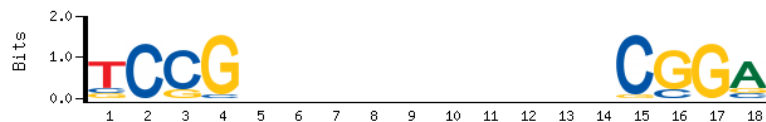
Protein: Ygr067c    Seed k-mer: GCGGGGTA    Enrichment Score: 0.49669



Protein: Ykl222c    Seed k-mer: ACGGA.ATA    Enrichment Score: 0.49102



Protein: Yll054c Seed k-mer: TCCG.....CGGA Enrichment Score: 0.47333



Protein: Ynl081w Seed k-mer: T.CCCC GCA Enrichment Score: 0.49812



Protein: Ynr063w Seed k-mer: ATCTCCGA Enrichment Score: 0.49886



Protein: Yox1 Seed k-mer: TTAATTAA Enrichment Score: 0.49972



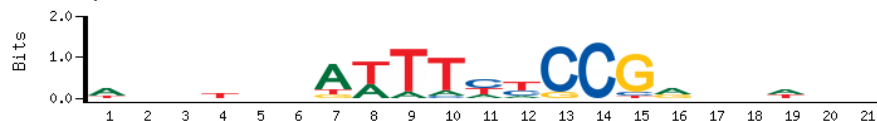
Protein: Ypr013c Seed k-mer: GTAATCA Enrichment Score: 0.49843



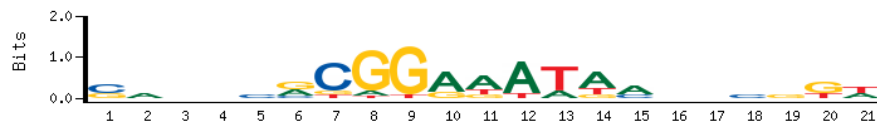
Protein: Ypr015c Seed k-mer: CGTAATC Enrichment Score: 0.49783



Protein: Ypr196w Seed k-mer: ATTTC.CCG Enrichment Score: 0.47442

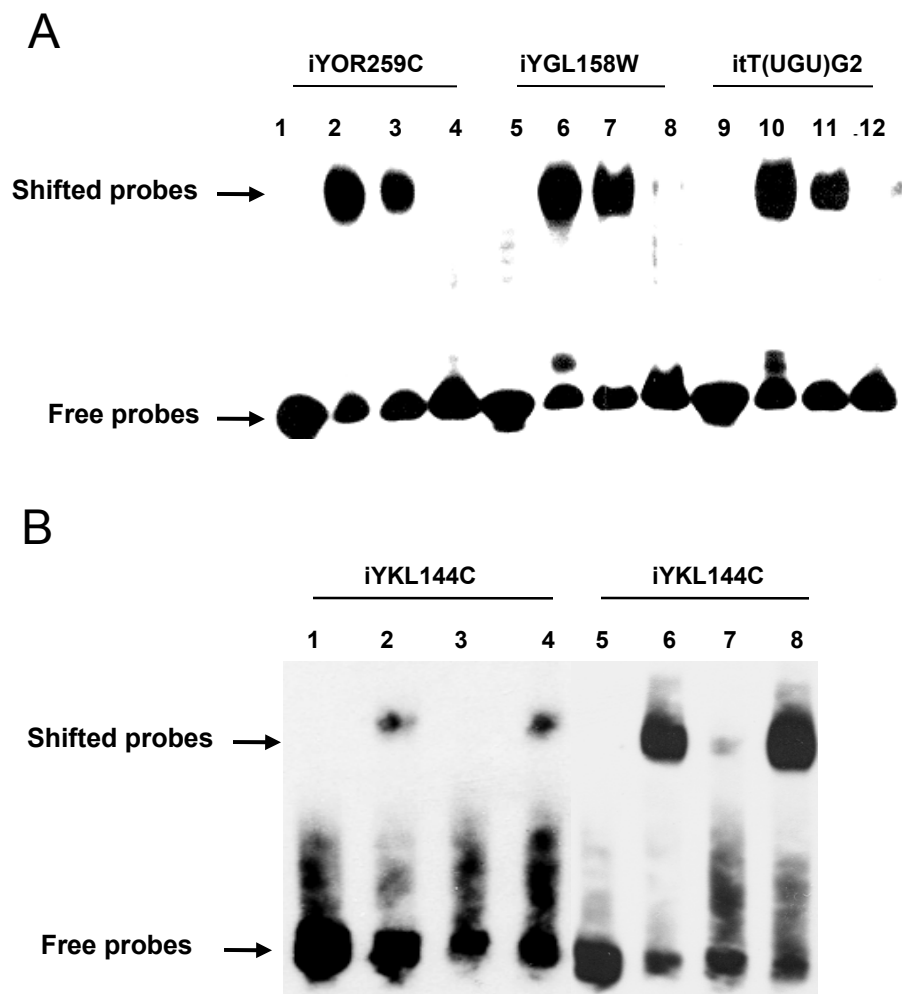


Protein: Yrm1 Seed k-mer: CGGA.ATAA Enrichment Score: 0.46831



Protein: Yrr1      Seed k-mer: CGGAATAA      Enrichment Score: 0.49899





**Figure S5. EMSAs for Yer130c, Pbf1, and Pbf2. (A)** Yer130c can bind the STRE motif *in vitro*. Lanes 1, 5 and 9 are labeled positive probes containing the STRE motif (AGGGG) in the native sequence context of the indicated intergenic regions, without Yer130c protein in the reaction; lanes 2, 6 and 10 are the same as 1, 5, and 9 but with Yer130c protein added; lanes 3, 7 and 11 are the same as lanes 2, 6 and 10 except with 10-fold excess of unlabeled negative probe (nonspecific competitor) that doesn't contain the STRE motif; lanes 4, 8 and 12 are the same as lanes 2, 6 and 10 except with 10-fold excess of unlabeled positive probe (specific competitor) that contains STRE motif. **(B)** Pbf1 and Pbf2 can bind the PAC motif *in vitro*. Reactions in lanes 2-4 were performed using Pbf1 protein while those in lanes 6-8 were performed using Pbf2 protein. Lanes 1 and 5 are labeled positive probes containing the PAC motif (GCGATGAG) in the intergenic region of *RPC25* (iYKL144C), which encodes a subunit of RNA polymerase III, without Pbf1 or Pbf2 proteins in the reactions; lanes 2 and 6 contain both labeled positive probe and proteins (Pbf1 or Pbf2, respectively); lanes 3 and 7 contain labeled positive probe, proteins and 10-fold excess of unlabeled positive probe (specific competitor); lanes 4 and 8 contain labeled positive probe, proteins and 10-fold excess of unlabeled negative probe (nonspecific competitor) that contains a mutated version of the PAC motif (GCCATCAC).

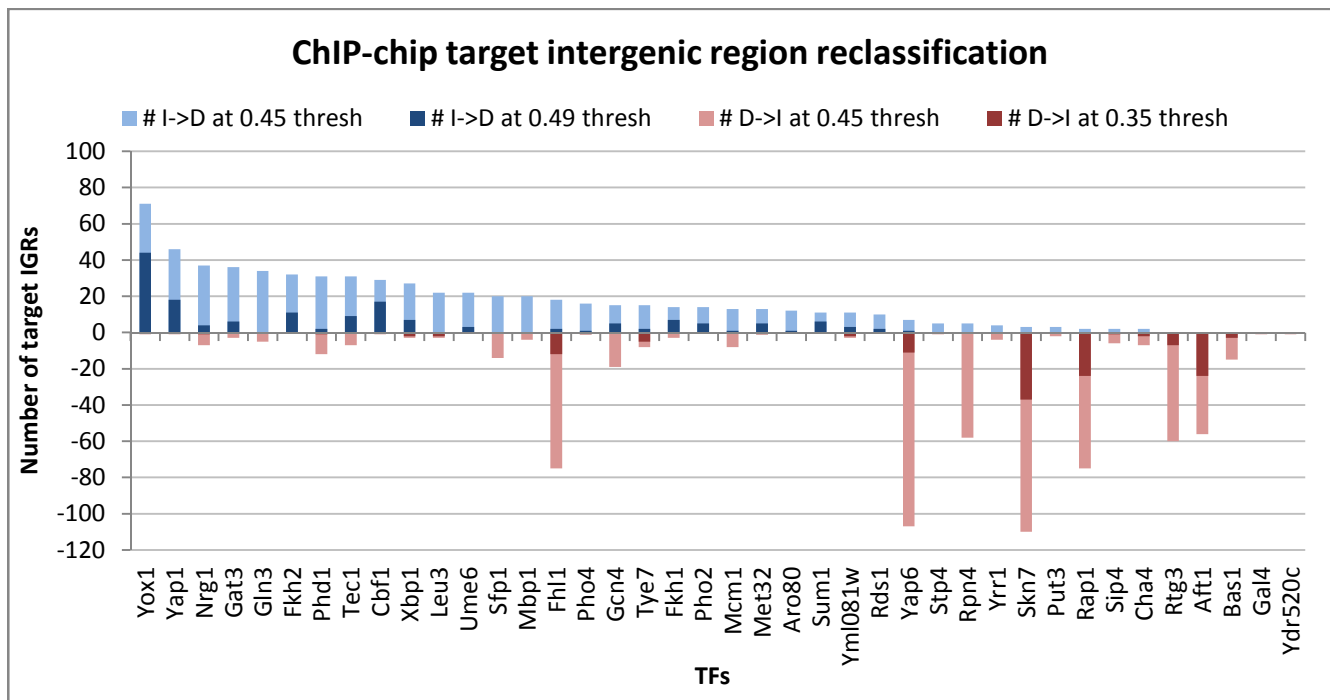


| TF   | PBM   |               | ChIP-chip |               | AUC % diff | PBM motif | ChIP-chip motif |
|------|-------|---------------|-----------|---------------|------------|-----------|-----------------|
|      | AUC   | <i>p</i> -val | AUC       | <i>p</i> -val |            |           |                 |
| Ume6 | 0.911 | <1E-12        | 0.895     | <1E-12        | 1.8        |           |                 |
| Cbf1 | 0.903 | <1E-12        | 0.832     | <1E-12        | 8.6        |           |                 |
| Rap1 | 0.881 | <1E-12        | 0.948     | <1E-12        | -7.1       |           |                 |
| Gcn4 | 0.862 | <1E-12        | 0.895     | <1E-12        | -3.6       |           |                 |
| Mcm1 | 0.856 | <1E-12        | 0.867     | <1E-12        | -1.2       |           |                 |
| Mbp1 | 0.842 | <1E-12        | 0.750     | <1E-12        | 12.2       |           |                 |
| Nrg1 | 0.831 | <1E-12        | 0.793     | <1E-12        | 4.8        |           |                 |
| Phd1 | 0.825 | <1E-12        | 0.796     | <1E-12        | 3.6        |           |                 |
| Mig1 | 0.820 | 6.1E-07       | N/A       | N/A           | N/A        |           | N/A             |
| Fkh2 | 0.818 | <1E-12        | 0.818     | <1E-12        | 0.1        |           |                 |
| Fkh1 | 0.807 | <1E-12        | 0.743     | <1E-12        | 8.6        |           |                 |
| Yap1 | 0.806 | <1E-12        | 0.621     | 5.8E-04       | 29.9       |           |                 |
| Tye7 | 0.779 | <1E-12        | 0.641     | 8.5E-06       | 21.6       |           |                 |
| Yap6 | 0.746 | <1E-12        | 0.776     | <1E-12        | -3.9       |           |                 |
| Bas1 | 0.738 | 6.9E-08       | 0.659     | 3.0E-04       | 12.0       |           |                 |
| Gln3 | 0.718 | 8.5E-11       | 0.716     | 1.1E-10       | 0.4        |           |                 |
| Pho2 | 0.714 | 2.0E-04       | 0.685     | 0.001         | 4.2        |           |                 |
| Tec1 | 0.702 | 3.6E-08       | 0.688     | 5.6E-09       | 1.9        |           |                 |
| Fhl1 | 0.692 | <1E-12        | 0.835     | <1E-12        | -17.2      |           |                 |
| Sum1 | 0.691 | 3.2E-07       | 0.858     | <1E-12        | -19.5      |           |                 |

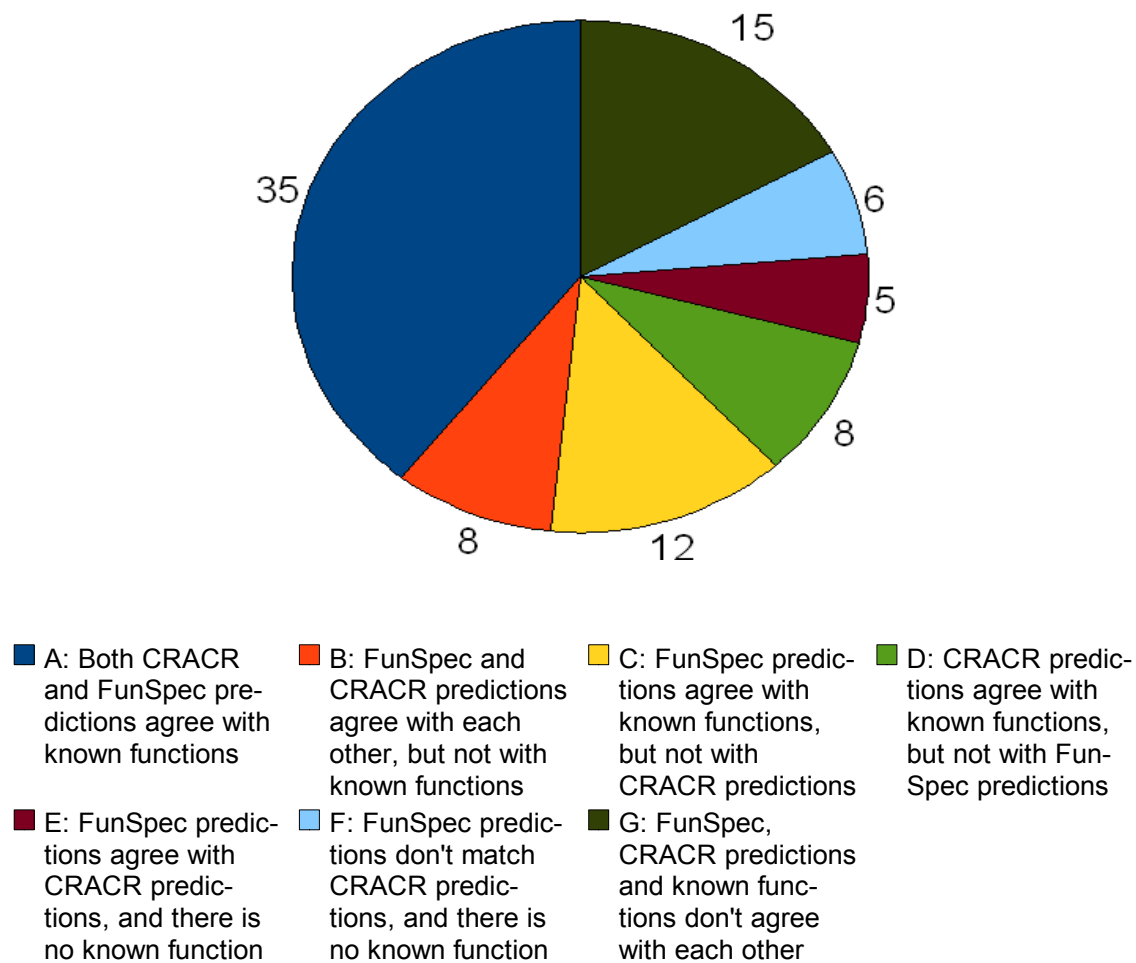
**Figure S6.** Enrichment of PBM-predicted or ChIP-chip motif-predicted target intergenic regions among intergenic regions bound in ChIP-chip at  $p < 0.001$ . The AUC statistic and associated  $p$ -value are calculated as described in the Supplementary Experimental Procedures.

|         |       |         |       |         |       |  |     |
|---------|-------|---------|-------|---------|-------|--|-----|
| Skn7    | 0.689 | <1E-12  | 0.827 | <1E-12  | -16.7 |  |     |
| Xbp1    | 0.684 | 4.8E-08 | 0.681 | 1.2E-10 | 0.4   |  |     |
| Gat3    | 0.674 | 6.1E-06 | 0.817 | 1.8E-15 | -17.6 |  |     |
| Pho4    | 0.671 | 2.2E-06 | 0.588 | 3.4E-10 | 14.2  |  |     |
| Stp4    | 0.665 | 1.5E-04 | 0.552 | N/A     | 20.6  |  |     |
| Rpn4    | 0.663 | 1.0E-05 | 0.898 | <1E-12  | -26.1 |  |     |
| Aft1    | 0.657 | 2.8E-11 | 0.702 | 1.3E-10 | -6.4  |  |     |
| Sfp1    | 0.654 | 0.014   | 0.826 | 5.5E-07 | -20.7 |  |     |
| Leu3    | 0.648 | 3.2E-05 | 0.614 | <1E-12  | 5.6   |  |     |
| Rph1    | 0.626 | 0.011   | N/A   | N/A     | N/A   |  | N/A |
| Rtg3    | 0.624 | 4.0E-04 | 0.641 | 5.2E-06 | -2.7  |  |     |
| Smp1    | 0.621 | 6.0E-05 | N/A   | N/A     | N/A   |  | N/A |
| Mga1    | 0.614 | 1.9E-03 | N/A   | N/A     | N/A   |  | N/A |
| Aro80   | 0.593 | 0.030   | 0.527 | N/A     | 12.4  |  |     |
| Ydr520c | 0.591 | 0.128   | 0.650 | <1E-12  | -9.0  |  |     |
| Met32   | 0.582 | 0.015   | 0.574 | 0.00    | 1.4   |  |     |
| Mig3    | 0.580 | 0.030   | N/A   | N/A     | N/A   |  | N/A |
| Sip4    | 0.578 | 0.071   | 0.646 | 1.9E-11 | -10.5 |  |     |
| Yox1    | 0.576 | 0.010   | 0.542 | N/A     | 6.3   |  |     |
| Gal4    | 0.568 | 0.044   | 0.606 | <1E-12  | -6.3  |  |     |
| Rds1    | 0.568 | 0.084   | 0.622 | <1E-12  | -8.6  |  |     |
| Cup9    | 0.567 | 0.077   | N/A   | N/A     | N/A   |  | N/A |
| Oaf1    | 0.544 | 0.139   | N/A   | N/A     | N/A   |  | N/A |

|         |       |       |       |         |       |  |     |
|---------|-------|-------|-------|---------|-------|--|-----|
| Srd1    | 0.540 | 0.326 | N/A   | N/A     | N/A   |  | N/A |
| Gat1    | 0.539 | 0.137 | N/A   | N/A     | N/A   |  | N/A |
| Gzf3    | 0.521 | 0.344 | N/A   | N/A     | N/A   |  | N/A |
| Put3    | 0.508 | 0.460 | 0.679 | 6.1E-07 | -25.2 |  |     |
| Mig2    | 0.501 | 0.486 | N/A   | N/A     | N/A   |  | N/A |
| Ndt80   | 0.459 | 0.736 | N/A   | N/A     | N/A   |  | N/A |
| Pdr1    | 0.449 | 0.954 | N/A   | N/A     | N/A   |  | N/A |
| Yrr1    | 0.444 | 0.850 | 0.508 | 0.39    | -12.6 |  |     |
| Yer130c | 0.443 | 0.778 | N/A   | N/A     | N/A   |  | N/A |
| Cha4    | 0.434 | 0.856 | 0.561 | 0.183   | -22.6 |  |     |
| Hal9    | 0.422 | 0.994 | N/A   | N/A     | N/A   |  | N/A |
| Yml081w | 0.369 | 1     | 0.547 | <1E-12  | -32.6 |  |     |
| Ypr196w | 0.360 | 0.944 | N/A   | N/A     | N/A   |  | N/A |
| Stp2    | 0.276 | 0.999 | N/A   | N/A     | N/A   |  | N/A |

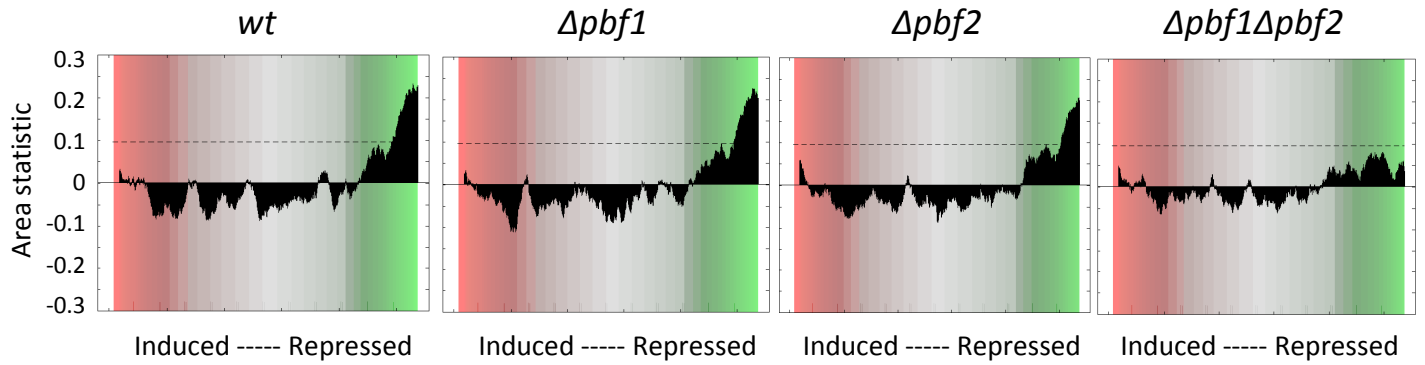


**Figure S7.** Re-classification of ChIP-chip target intergenic regions (IGRs) according to both conservative and permissive E score thresholds. Light blue bars indicate the number of ChIP-chip "indirect" target IGRs that would be reclassified as "direct" targets according to the presence of a TF specific k-mer with an E Score > 0.45 from PBM data. Dark blue bars show this same reannotation at a more stringent minimum E Score (0.49). Light red bars indicate the number of ChIP-chip "direct" IGR targets that would be reclassified as "indirect" targets because they have no k-mers with an E Score > 0.45 from PBM data. Dark red bars impose a more stringent requirement (no kmers E score > 0.35) for reannotating an IGR from "direct" to "indirect."

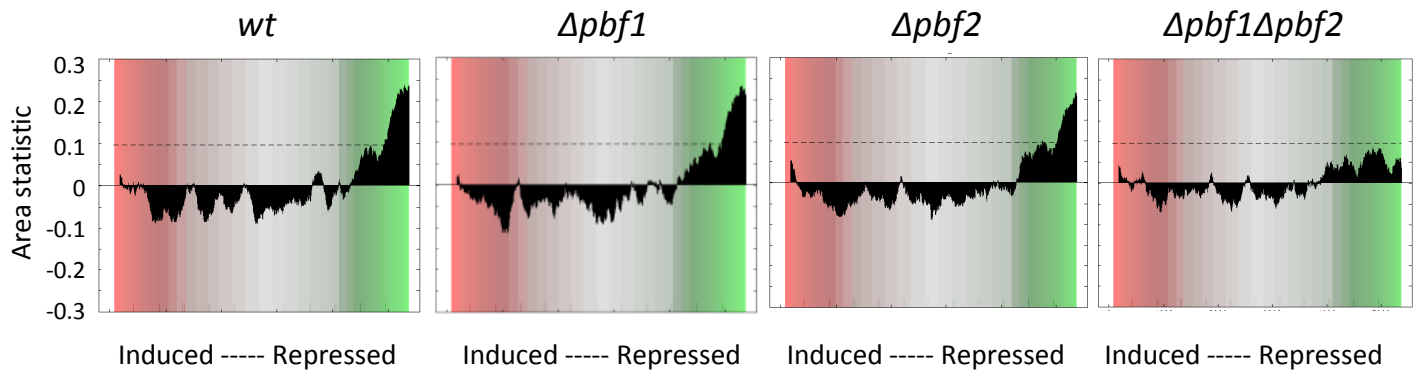


**Fig. S8. PBM-derived function predictions are consistent with prior function information.** Function predictions for each TF were derived from PBM 8-mer binding data using CRACR and target genes' over-represented functional categories ("FunSpec"). The annotations were then compared with SGD function annotation and literature descriptions, if available.

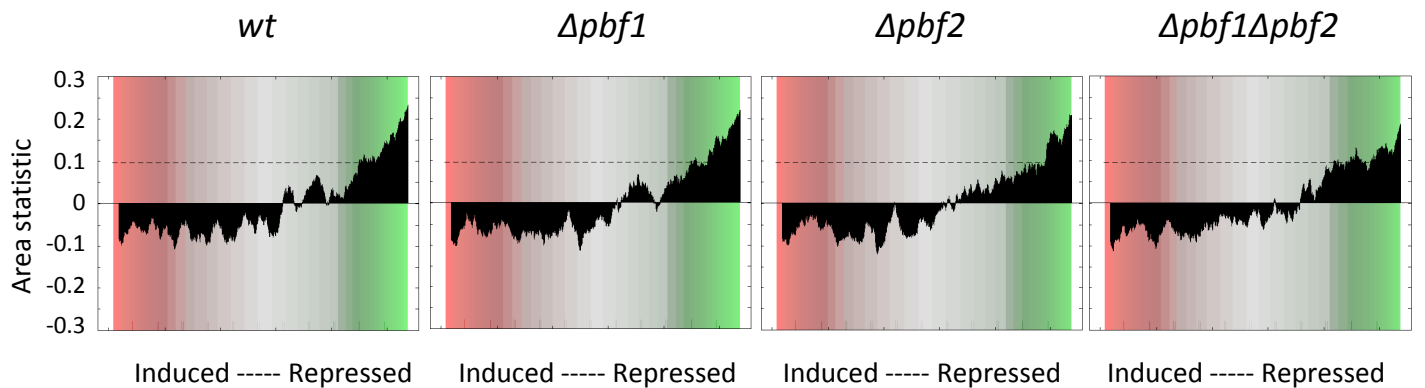
Pbf1 PBM-derived target enrichment in heat shock 20 min @ 37°C expression data in:



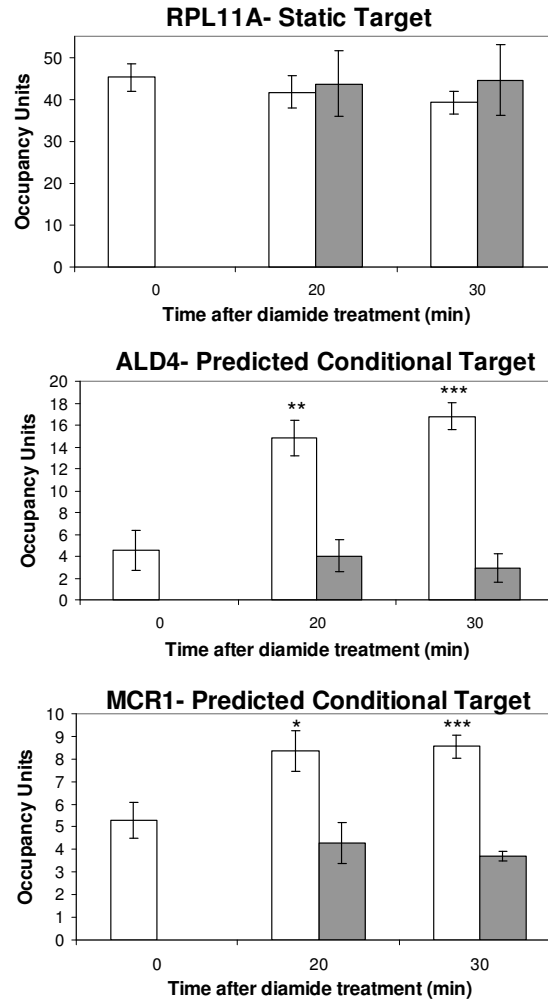
Pbf2 PBM-derived target enrichment in heat shock 20 min @ 37°C expression data in:



Stb3 PBM-derived target enrichment in heat shock 20 min @ 37°C expression data in:



**Figure S9.** Predicted target genes of Pbf1 and Pbf2 are significantly repressed (CRACR  $p < 10^{-12}$ ) at 20 min heat shock in wild type,  $\Delta pbf1$ , and  $\Delta pbf2$  strains, but not in the  $\Delta pbf1\Delta pbf2$  double deletion strain, in gene expression profiling of triplicate biological replicate cultures. In contrast, predicted target genes of Stb3 are significantly repressed (CRACR  $p < 10^{-12}$ ) at 20 min heat shock in all 4 strains.



**Figure S10. Rap1 associates with promoters of its target genes in a CRACR-predicted condition-specific manner.** Using CRACR we predicted that a distinct set of binding sites are occupied and up-regulated by Rap1 in certain conditions, such as after diamide treatment. We performed ChIP-qPCR to validate these CRACR predictions and observed that Rap1 shows constant binding at a characterized static target (*RPL11A*) (Buck and Lieb, *Nat Genet* (2006) 38:1446) but increased binding after diamide treatment at CRACR-predicted conditional targets (*ALD4*, *MCR1*). ChIP-qPCR results for Rap1 after treatment of culture with 1.5 mM diamide. White bars indicate treated samples, light gray bars indicate untreated samples. Error bars represent 1 s.e.m. of 4 biological replicates. Significance (\*  $p < 0.05$ , \*\*  $p < 0.005$ , \*\*\*  $p < 0.001$ ) was calculated by Student's t-test.





| Cluster | Function                                    | Representative motifs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Selected k-mer correlations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                |
|---------|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| C1      | Chromatin remodeling                        | Rsc3:<br>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Rsc3/Rsc30: 0.956                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |
| C2      | Carbohydrate metabolism, response to stress | Mig1:<br><br>Ygr067c:<br><br>Nrg1:<br><br>Rph1:<br><br>Yer130c:<br>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Mig1/Mig2: 0.870<br>Mig2/Mig3: 0.823<br>Mig1/Yml081w: 0.718<br>Mig1/Ygr067c: 0.636<br>Nrg1/Usv1: 0.475<br>Rph1/Yer130c: 0.425<br>Mig1/Yer130c: 0.263<br>Mig1/Rph1: 0.248<br>Nrg1/Yer130c: 0.236<br>Mig1/Nrg1: 0.185                                                                                                                                                                                                                                                                                                                                                                        | Usv1/Yml081w: 0.167<br>Nrg1/Ygr067c: 0.158<br>Mig1/Usv1: 0.143<br>Mig2/Rph1: 0.0924<br>Mig3/Nrg1: 0.078                                                                        |
| C3      | Stress response, drug response              | Sip4:<br><br>Rds1:<br><br>Ecm22:<br><br>Hal9:<br><br>Tbs1:<br><br>Yrr1:<br><br>Oaf1:<br><br>Ynr063w:<br><br>Rds2:<br><br>Cep3:<br><br>Ybr239c:<br><br>Ume6:<br><br>Stp2:<br><br>Rgt1:<br> | Hal9/Rdr1: 0.834<br>Gsm1/Ecm22: 0.83<br>Rdr1/Cha4: 0.82<br>Hal9/Asg1: 0.82<br>Asg1/Aro80: 0.812<br>Gsm1/Put3: 0.809<br>Hal9/Yll054c: 0.803<br>Put3/Rds2: 0.774<br>Hal9/Ykl222c: 0.764<br>Yll054c/Tbs1: 0.764<br>Leu3/Gsm1: 0.757<br>Rds1/Cha4: 0.721<br>Hal9/Ybr239c: 0.667<br>Cep3/Aro80: 0.623<br>Sip4/Ecm22: 0.592<br>Ynr063w/Ybr239c: 0.532<br>Oaf1/Rds2: 0.518<br>Yrr1/Ynr063w: 0.495<br>Stp4/Stp2: 0.3906<br>Ume6/Stp2: 0.3808<br>Tbs1/Oaf1: 0.275<br>Rds1/Ynr063w: 0.181<br>Rds1/Yrr1: 0.035<br>Ume6/Ynr063w: 0.0324<br>Stp4/Rds2: 0.0288<br>Stp4/Rgt1: 0.0212<br>Stp2/Put3: 0.0198 | Ume6/Ybr239c: 0.0126<br>Ume6/Oaf1: 0.012<br>Stp2/Rds2: 0.011<br>Stp2/Oaf1: 0.0088<br>Ume6/Yrr1: -0.0259<br>Stp2/Ybr239c: -0.0378<br>Stp2/Ynr063w: -0.082<br>Stp2/Yrr1: -0.1402 |

**Figure S12.** Motifs and 8-mer binding profile correlations for potential co-regulatory TFs from CRACR-predicted condition specificities. Representative motifs and k-mer correlations shown.

| Cluster | Function                       | Representative motifs             | Selected k-mer correlations                                                                                                                                                                                            |
|---------|--------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| C4      | Cell cycle, sporulation        | Yox1:<br>Nhp6a:<br>Smp1:          | Smp1/Yox1: 0.511      Pho2/Nhp6a: 0.330<br>Smp1/Pho2: 0.507      Pho2/Nhp6b: 0.572<br>Smp1/Nhp6a: 0.352      Nhp6a/Nhp6b: 0.945<br>Smp1/Nhp6b: 0.390      Yox1/Nhp6a: 0.632<br>Yox1/Pho2: 0.826      Yox1/Nhp6b: 0.651 |
| C5      | Cell Cycle, Mating             | Fkh1:                             | Fkh1/Fkh2: 0.8612                                                                                                                                                                                                      |
| C6      |                                | Sut2:<br>Ydr520c:<br>Srd1:        | Sut2/Ydr520c: 0.3447<br>Srd1/Ydr520c: 0.2755<br>Sut2/Srd1: 0.2053                                                                                                                                                      |
| C7      | Cell fate/cell cycle           | Mga1:<br>Mcm1:                    | Mga1/Mcm1: 0.1788                                                                                                                                                                                                      |
| C8      | Transport (carb. etc)          | Lys14:<br>Sfl1:<br>Ypr196w:       | Lys14/Sfl1: 0.376<br>Ypr196w/Lys14: 0.367<br>Sfl1/Ypr196w: -0.008                                                                                                                                                      |
| C9      | AA metabolism                  | Gcn4:<br>Bas1:                    | Bas1/Gcn4: 0.151                                                                                                                                                                                                       |
| C10     | AA and phosphate metabolism    | Met32:<br>Tye7:<br>Cbf1:<br>Pho4: | Met32/Tye7: 0.038<br>Tye7/Cbf1: 0.6348<br>Met32/Cbf1: 0.005<br>Met32/Pho4: 0.090<br>Cbf1/Pho4: 0.629                                                                                                                   |
| C11     | Nitrogen and sulfur metabolism | Gln3:<br>Gat1:                    | Gzf3/Gln3: 0.874<br>Gzf3/Gat1: 0.951<br>Gln3/Gat1: 0.901                                                                                                                                                               |

| Cluster | Function                                               | Representative motifs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Selected k-mer correlations                                                                                                                                                                                                                                                  |                                                                                                                                                                     |
|---------|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| C12     | AA metabolism, cell wall, diverse functions            | Ypr013c: <br>Tbf1: <br>Gat3: <br>Gat4: <br>Aft1: <br>Skn7:                                                                                               | Gat3/Gat4: 0.636<br>Aft1/Skn7: 0.458<br>Ypr013c/Gat4: 0.285<br>Ypr013c/Aft1: 0.096<br>Gat3/Aft1: 0.033<br>Tbf1/Aft1: 0.031<br>Tbf1/Skn7: 0.012<br>Gat3/Skn7: 0.003                                                                                                           | Ypr013c/Skn7: -0.008<br>Ypr013c/Tbf1: -0.005<br>Tbf1/Gat3: -0.0323<br>Gat4/Skn7: -0.0468<br>Tbf1/Gat4: -0.0805                                                      |
| C13     | Protein biosynthesis response to stress, drug response | Sum1: <br>Yap6: <br>Sfp1: <br>Rpn4: <br>Rtg3: <br>Yrm1: <br>Pdr1:  | Sum1/Sfp1: 0.6448<br>Yrm1/Pdr1: 0.5748<br>Sfp1/Yrm1: 0.5449<br>Yap6/Sfp1: 0.524<br>Yap6/Yrm1: 0.5194<br>Yap6/Pdr1: 0.5108<br>Sfp1/Pdr1: 0.5086<br>Yap6/Rtg3: 0.4994<br>Rtg3/Yrm1: 0.4766<br>Sum1/Yrm1: 0.4739<br>Sum1/Pdr1: 0.4729<br>Sfp1/Rpn4: 0.4581<br>Rpn4/Yrm1: 0.4545 | Rtg3/Pdr1: 0.4396<br>Sum1/Yap6: 0.4355<br>Sfp1/Rtg3: 0.4235<br>Sum1/Rtg3: 0.4208<br>Sum1/Rpn4: 0.417<br>Yap6/Rpn4: 0.3644<br>Rpn4/Pdr1: 0.3062<br>Rpn4/Rtg3: 0.3027 |
| C14     | rRNA processing, ribosome                              | Pbf2: <br>Stb3:                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Pbf1/Pbf2: 0.928<br>Pbf2/Stb3: -0.040<br>Pbf1/Stb3: -0.048                                                                                                                                                                                                                   |                                                                                                                                                                     |