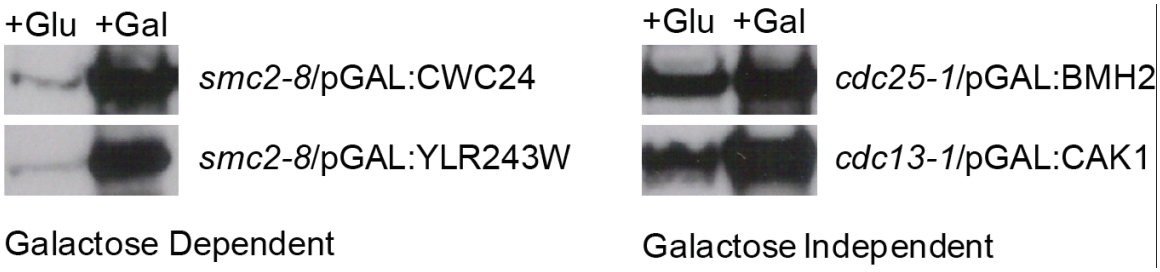
Supplementary Figure S1

Example MORF protein expression in presence or absence of galactose.

Galactose dependency of dosage suppression determined by Western blotting: *ts* mutant strains harboring CWC24, YLR243W, BMH2 and CAK1 MORFs grown in presence of glucose and galactose separately and proteins extracted, equal amount of proteins blotted to PVDF membrane and probed with anti-HA antibody. CWC24 and YLR243W are galactose dependent; BMH2 and CAK1 are galactose independent.



Supplementary Figure S2

Dosage suppressor network of 53 *ts* lethal mutations. 660 interactions were discovered through the general screen and several focused screens. Nodes are either essential gene mutations or their suppressors, and the directed edges (color and thickness weighted by edge-betweenness centrality) are dosage suppressor interactions. Many suppressors are likely specific to the experimental conditions adopted here, and at least a subset may be allele specific. Alternate experimental methods may reveal additional suppressors.

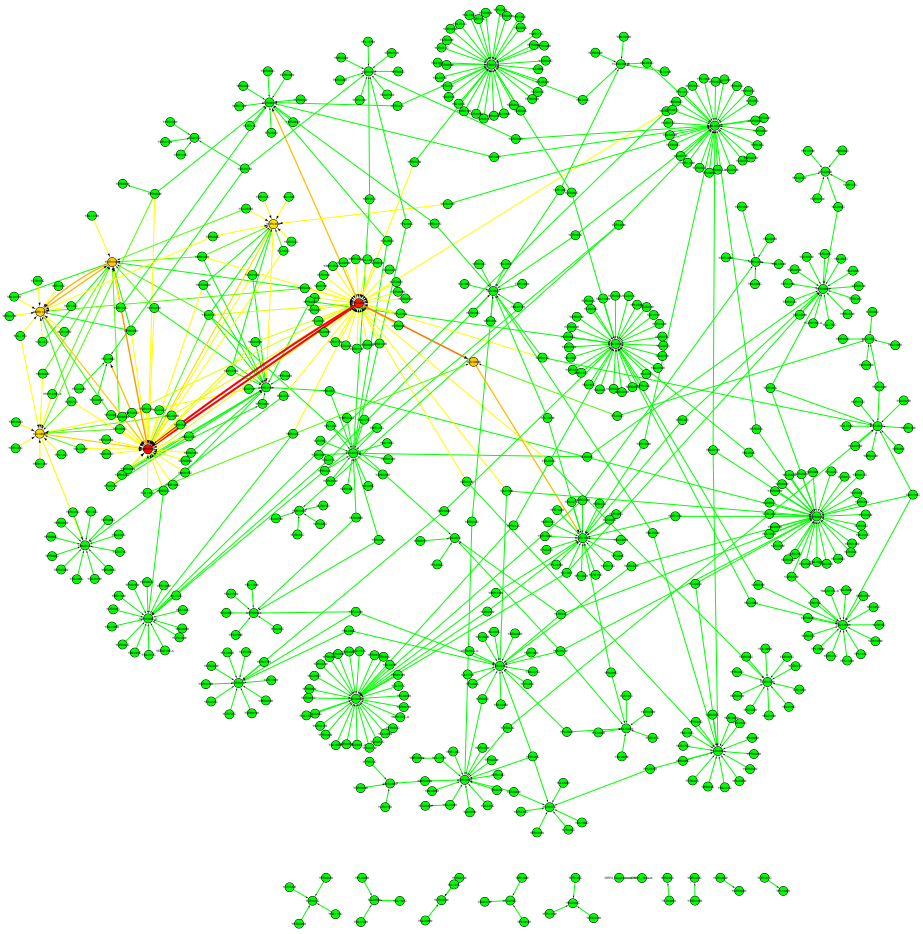


Figure S3

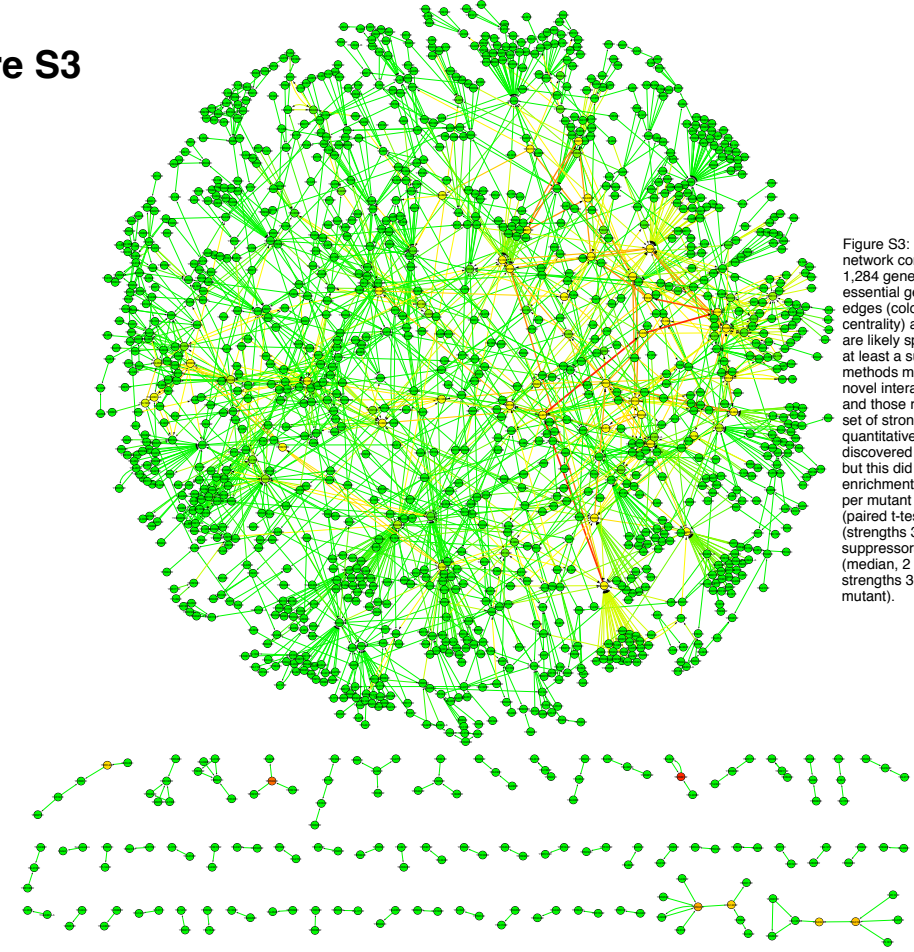
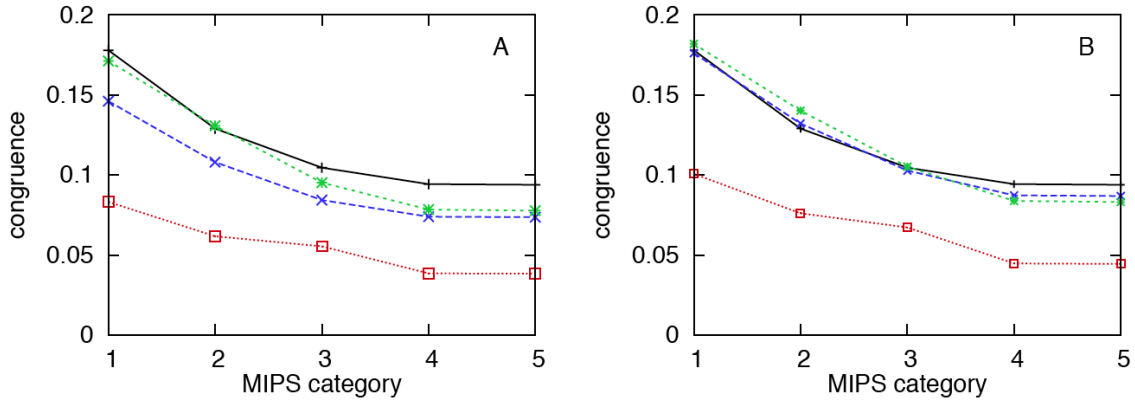


Figure S3: Dosage suppressor interaction network in yeast. This network contains 454 ts lethal mutations that are suppressed by 1,284 genes, representing 2,286 interactions. Nodes are either essential gene mutations or their suppressors, and the directed edges (color and thickness weighted by edge-betweenness centrality) are dosage suppressor interactions. Many suppressors are likely specific to the experimental conditions adopted here, and at least a subset may be allele specific. Alternate experimental methods may reveal additional suppressors. The data contain 660 novel interactions reported here, added to those listed in BioGrid and those reported by Magtanong et al. (33). To test whether the set of stronger suppressors (of strengths 3-5) are qualitatively or quantitatively different from the whole dataset of suppressors discovered in this work, we eliminated suppressors of strengths <3, but this did not change the general conclusions derived by GO enrichment analysis, and the frequency distribution of suppressors per mutant of the whole dataset is statistically indistinguishable (paired t-test P=1.00) from that of the reduced set of suppressors (strengths 3-5 only) (Supplementary Table S15). For the full set of suppressors, the mean was 3.7±6.3 suppressors per mutant (median, 2 suppressors per mutant). For the set of suppressors of strengths 3-5 only, the mean was 3.8±9.6 per mutant (median, 1 per mutant).

Supplementary Fig. S4A: Functional congruence between ts-mutants and their suppressors. Red (dotted): congruence between mutants and their suppressors for the pairs described in this work, as a function of the MIPS category. Congruence decreases with increasing category because function becomes more and more specialized. Blue (long-dashed): congruence from pairs reported in the BioGRID database. Green (short-dashed): pairs reported in Magtanong *et al*. (2011). Black: congruence between proteins that share an edge in the curated PPI for comparison.

Supplementary Fig. S4B: Functional congruence among co-suppressors of the same ts-mutant. Red (dotted): congruence between suppressors of a mutant for the pairs described in this work, as a function of the MIPS category. Blue (long-dashed): congruence from pairs reported in the BioGRID database. Green (short-dashed): pairs reported in Magtanong *et al.*, (2011). Black: congruence between proteins that share an edge in the curated PPI (same as in Fig. S4A).



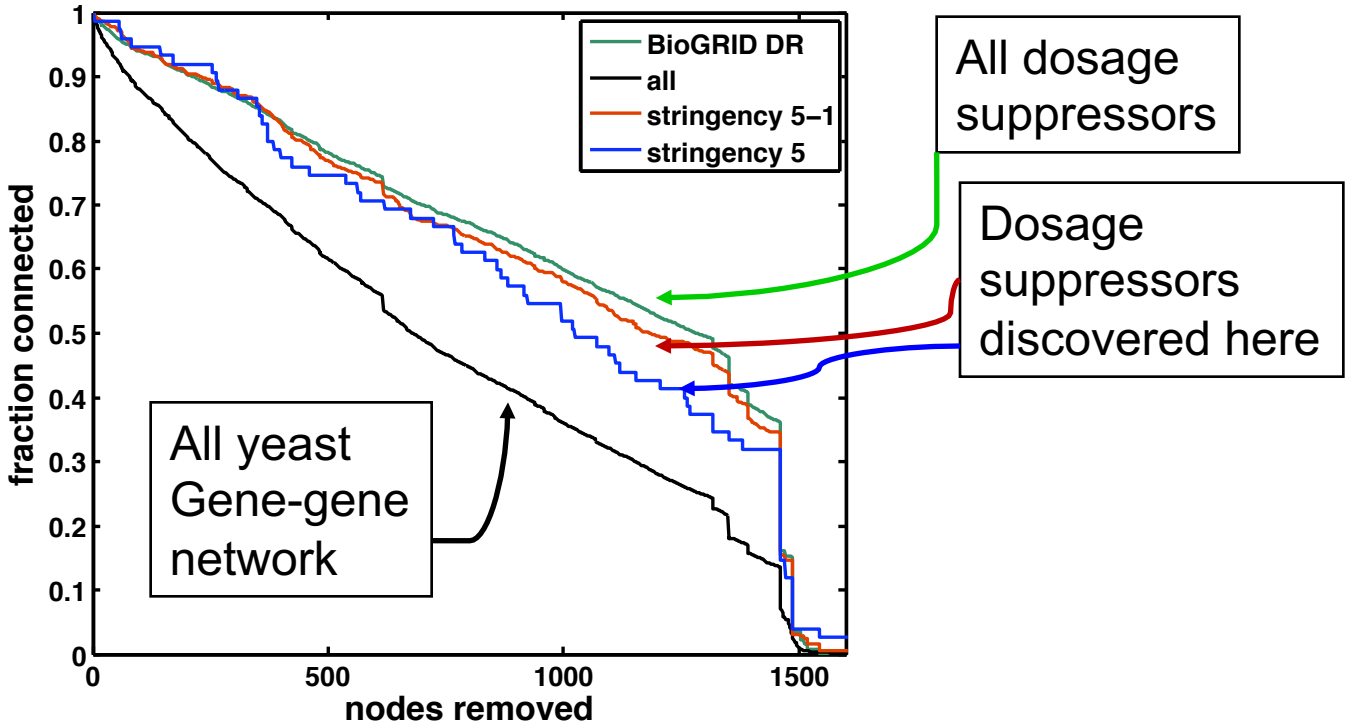
Supplementary Figure S5: Fraction of node pairs connected Within the PPI network upon removal of genes with descending BC

(BC = Betweenness Centrality)

Remove nodes with highest BC successively and compute fraction of DS nodes connected

$$B'_i = \sum_{\text{all pairs}} b_i$$

$$B_i = \frac{2B'_i}{(n-1)(n-2)}$$



P=2.3 × 10^{-72} that DS nodes are within interacting protein clusters

Conclusion: The dosage-suppressor interaction network has an underlying modularity

Supplementary Figure S6

Examples of dosage suppressors of RNA Pol II mutants.

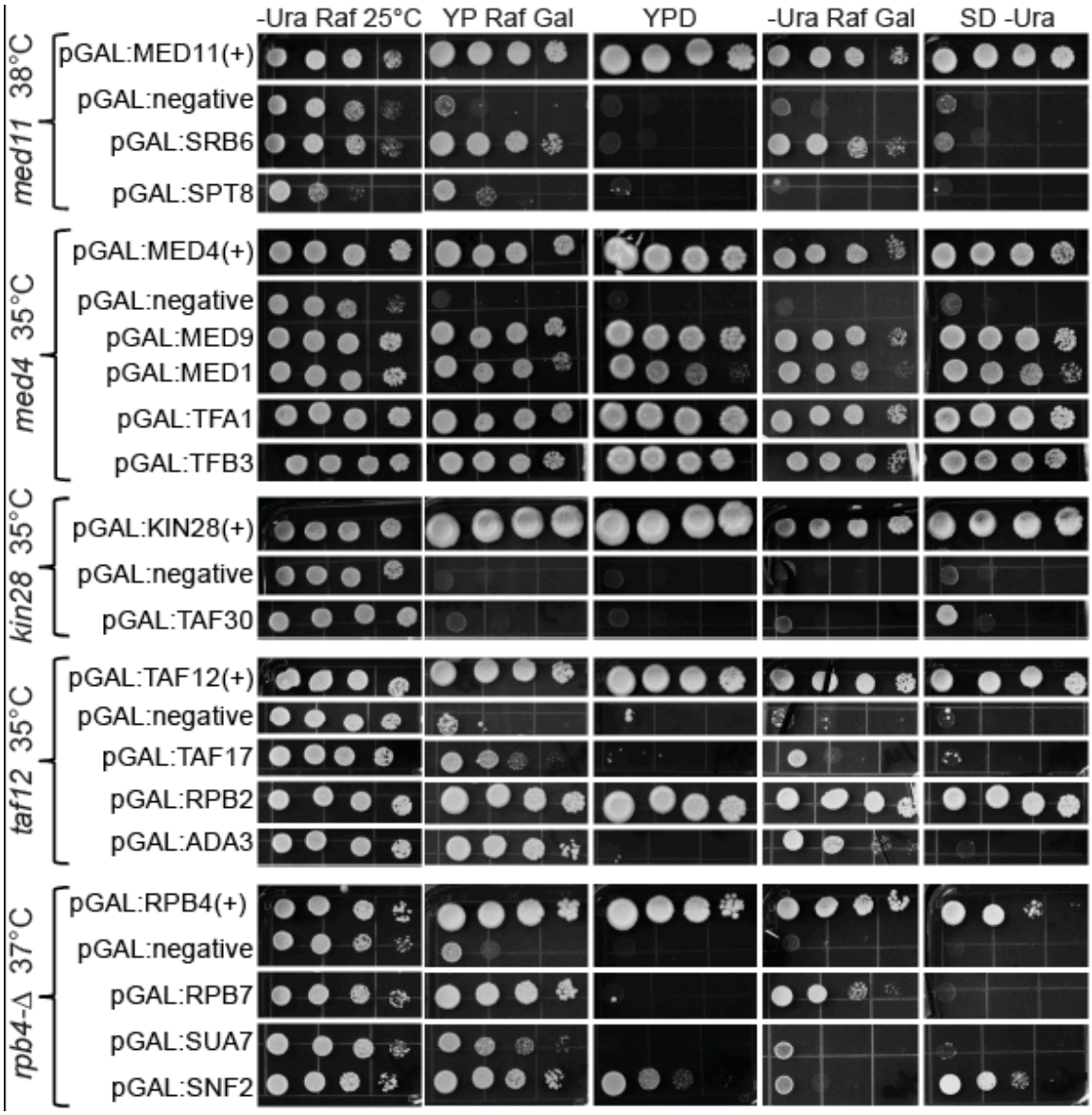
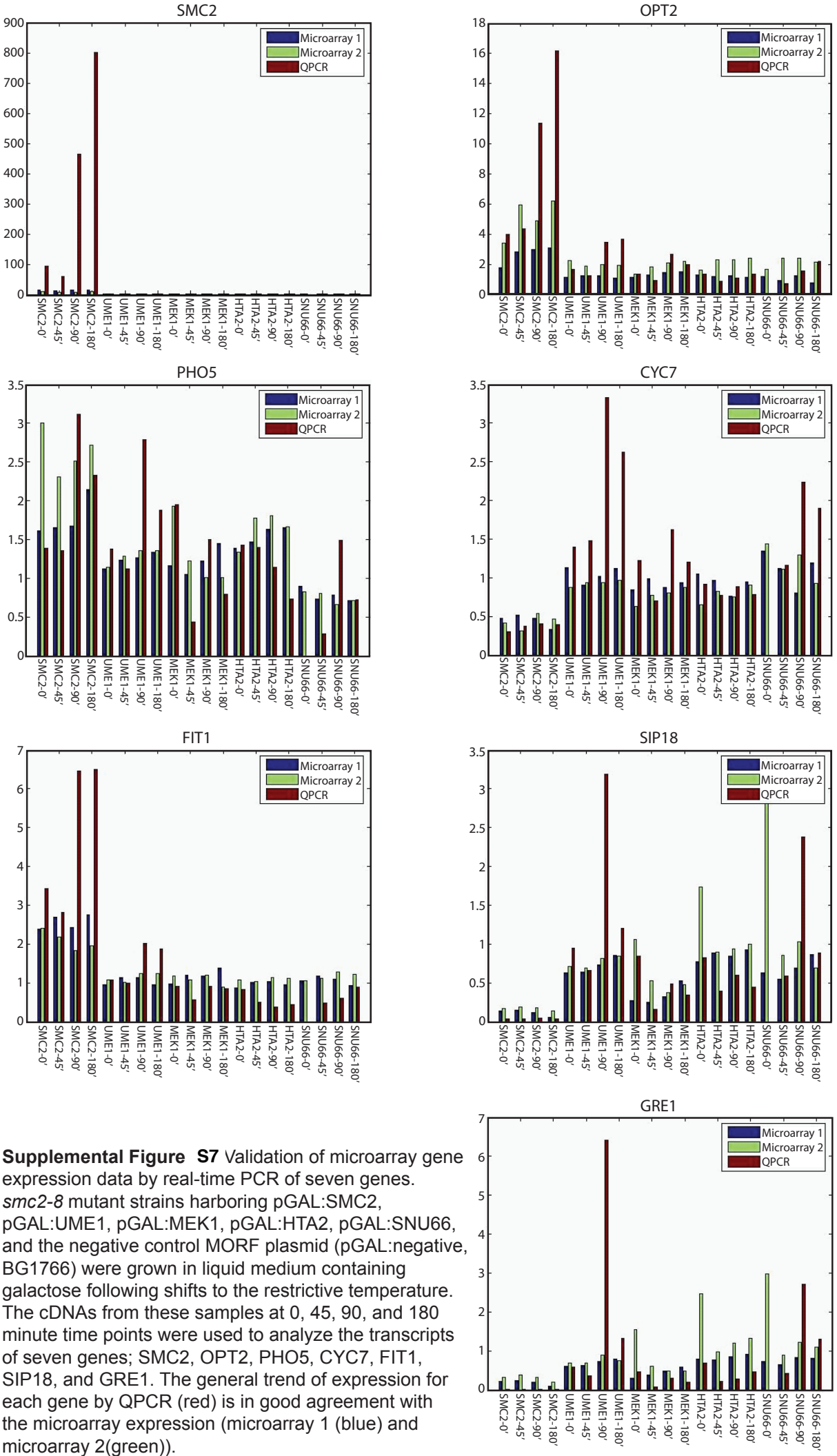


Figure S7



Supplemental Figure S7 Validation of microarray gene expression data by real-time PCR of seven genes. *smc2-8* mutant strains harboring pGAL:SMC2, pGAL:UME1, pGAL:MEK1, pGAL:HTA2, pGAL:SNU66, and the negative control MORF plasmid (pGAL:negative, BG1766) were grown in liquid medium containing galactose following shifts to the restrictive temperature. The cDNAs from these samples at 0, 45, 90, and 180 minute time points were used to analyze the transcripts of seven genes; SMC2, OPT2, PHO5, CYC7, FIT1, SIP18, and GRE1. The general trend of expression for each gene by QPCR (red) is in good agreement with the microarray expression (microarray 1 (blue) and microarray 2(green)).