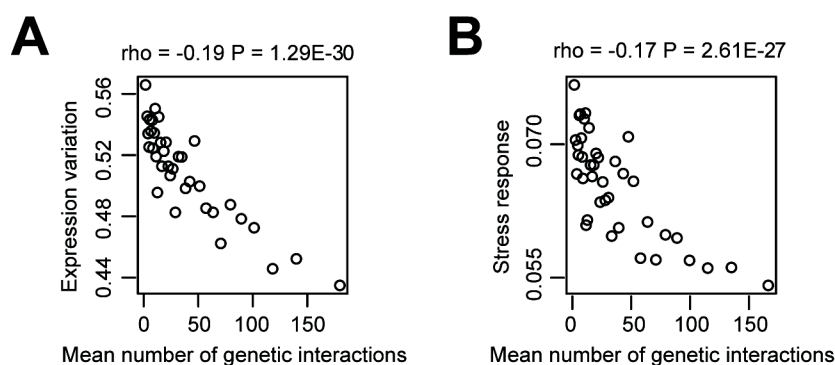


Supplementary Figures

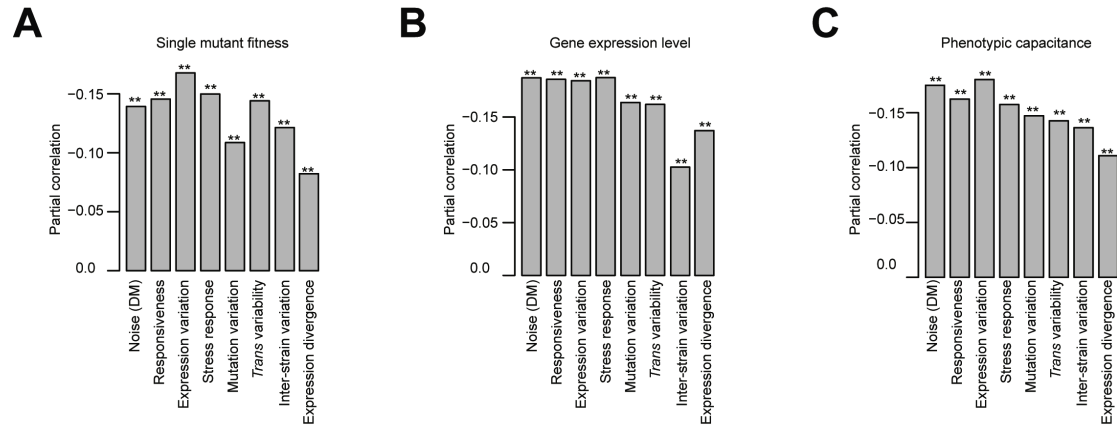


Supplementary Figure 1. The gene expression of genetic hubs is tightly regulated in yeast. Genes with more genetic interactions have lower gene expression variation at several different scales: ‘expression variation’ across environmental conditions (**A**) and ‘stress responsiveness’ across different stress conditions (**B**). All plots for quantitative variables are shown for equally sized groups of genes ($n = 100$), ranked according to the variable under consideration. Spearman’s rank correlation coefficients and P -values are shown inset.

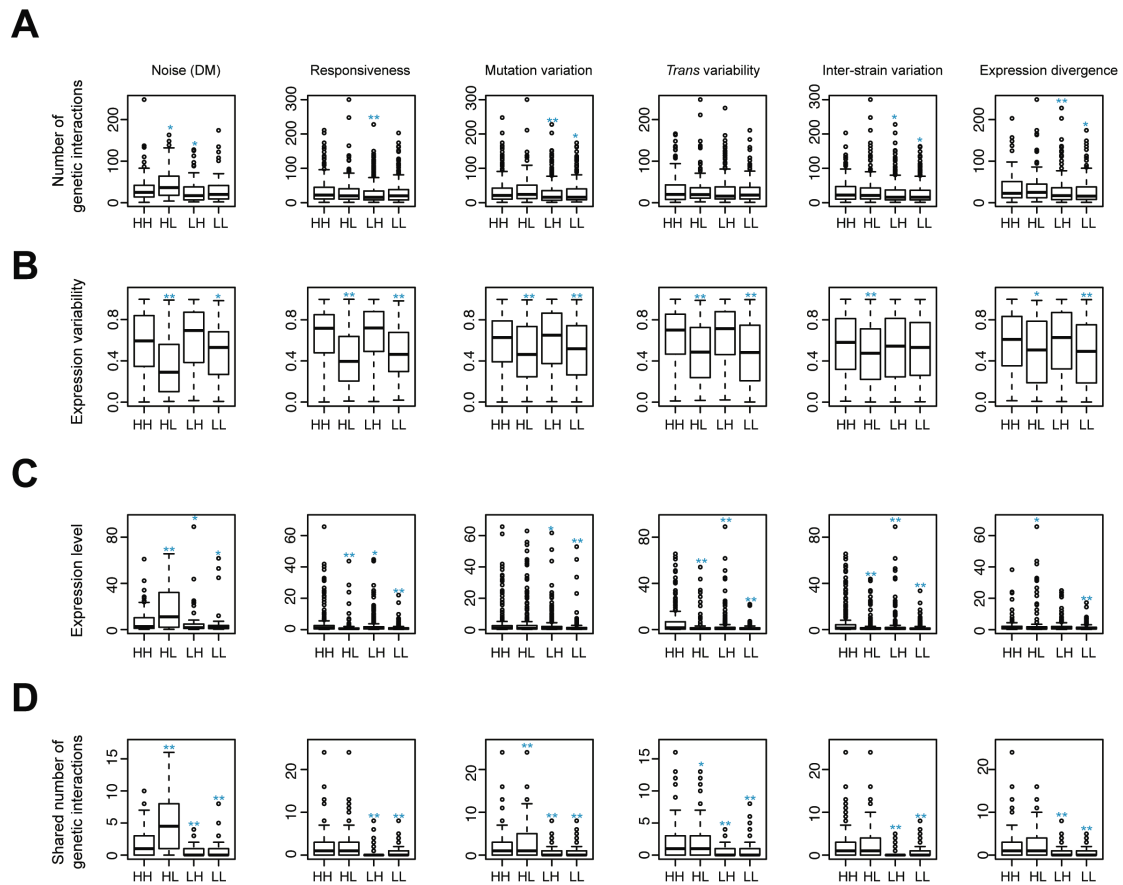
A				B		
	Gene expression variation	Correlation	P -value		Partial correlation	P -value
	Noise (DM)	-0.204	3.52E-14	-0.103	1.51E-04	
	Responsiveness	-0.145	9.18E-19	0.006	7.12E-01	
	Expression variation	-0.250	9.96E-14	-0.002	9.62E-01	
	Stress response	-0.132	4.34E-17	0.022	1.70E-01	
	Mutation variation	-0.135	4.06E-16	-0.003	8.65E-01	
	<i>Trans</i> variability	-0.123	1.89E-11	0.015	4.32E-01	
	Inter-strain variation	-0.137	1.28E-17	-0.012	4.48E-01	
	Expression divergence	-0.109	2.99E-08	-0.007	7.20E-01	

Supplementary Figure 2. (A) Correlations between degree of positive genetic interaction and variation in gene expression. (B) Partial correlations between degree of positive genetic interaction and variation in gene expression after controlling for

the linear effect of negative genetic interaction degrees. Spearman's rank correlation coefficient and P -value are shown.

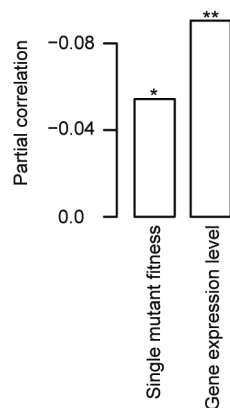


Supplementary Figure 3. Correlation between degree of negative genetic interaction and variation in gene expression controlling for the linear effect of (A) single mutant fitness, (B) gene expression level, and (C) phenotypic capacitance, using partial correlation analysis (** $P < 5.0E-4$).

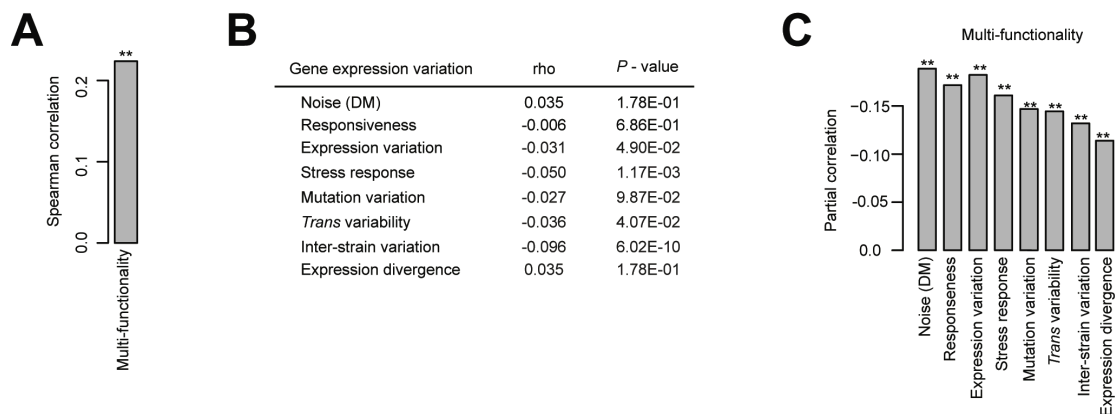


Supplementary Figure 4. Characteristics of the duplicates of variable and non-variable genes. Each duplicate is classified into four types: HH; duplicate of highly variable (variations are above the median value) highly connected genes (genes with degree at least 25), HL; duplicates of lowly variable (variations are below the median value) highly connected genes, LH; duplicates of highly variable non-highly connected genes and LL; duplicates of lowly variable non-highly connected genes. (A) Duplicates of both variable and non-variable highly connected genes are more likely to have many genetic interaction partners than duplicates of both variable and non-variable non-highly connected genes. (B) Duplicates of highly (or lowly) variable both highly connected and non-highly connected genes are likely to be highly (or lowly) variable both highly connected and non-highly connected genes. (C) Duplicates of both variable and non-variable genetic interaction hubs tend to be more highly expressed than duplicates of both variable and non-variable highly connected

genes. **(D)** Both variable and non-variable highly connected genes and their duplicates tend to share more genetic interaction partners than both variable and non-variable non-highly connected genes and their duplicates. *P*-values are calculated using the Mann-Whitney *U* test (***P* < 5.0E-3, **P* < 5.0E-2).

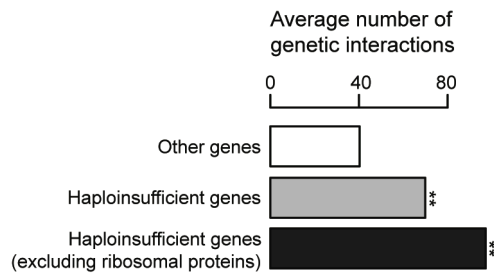


Supplementary Figure 5. Correlation between degree of negative genetic interaction and expression divergence between human and chimpanzee controlling for the linear effect of single mutant fitness or gene expression level (***P* < 5.0E-3, **P* < 5.0E-2).

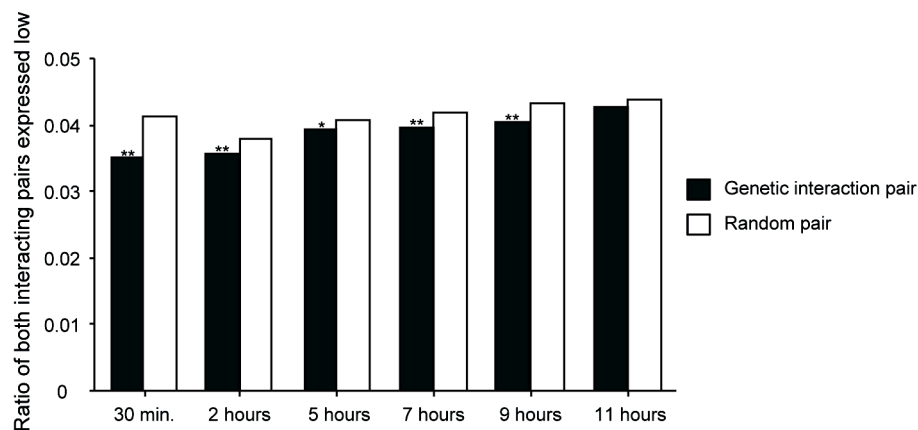


Supplementary Figure 6. Genetic interaction hubs have low expression variation when controlling for multi-functionality. **(A)** Correlation between genetic interaction

degree and multi-functionality (measuring the number of annotated gene ontology terms in Costanzo *et al.*, 2010). Spearman's rank correlation coefficient and P -value was calculated. **(B)** Correlations between multi-functionality and gene expression variation. Spearman's rank correlation coefficient and P -value are shown. **(C)** Correlations of genetic interaction degree and variations in gene expression controlling for the linear effect of multi-functionality, using partial correlation analysis (** $P < 5.0E-4$).

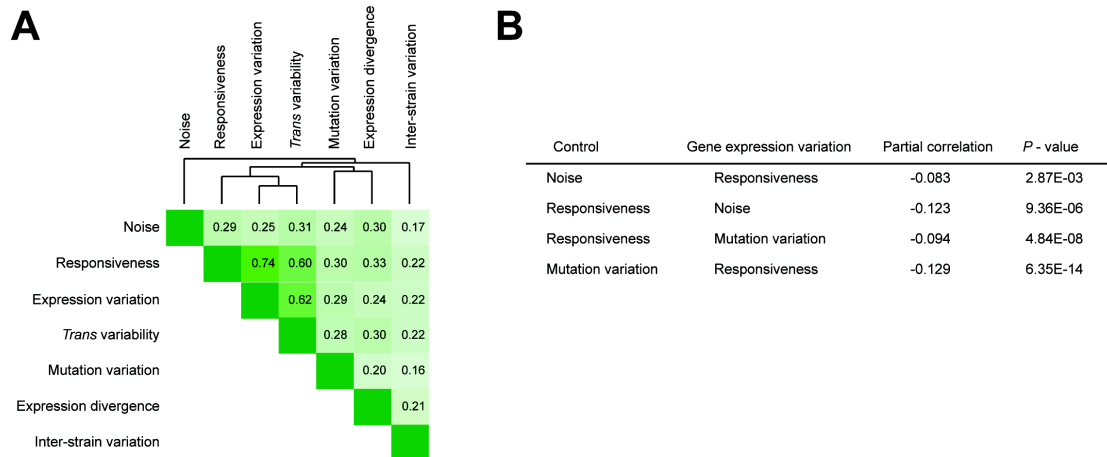


Supplementary Figure 7. Haploinsufficient genes are two times more likely to have genetic interaction partners as other genes. P -value is calculated using the Mann-Whitney U test (** $P < 5.0E-4$).

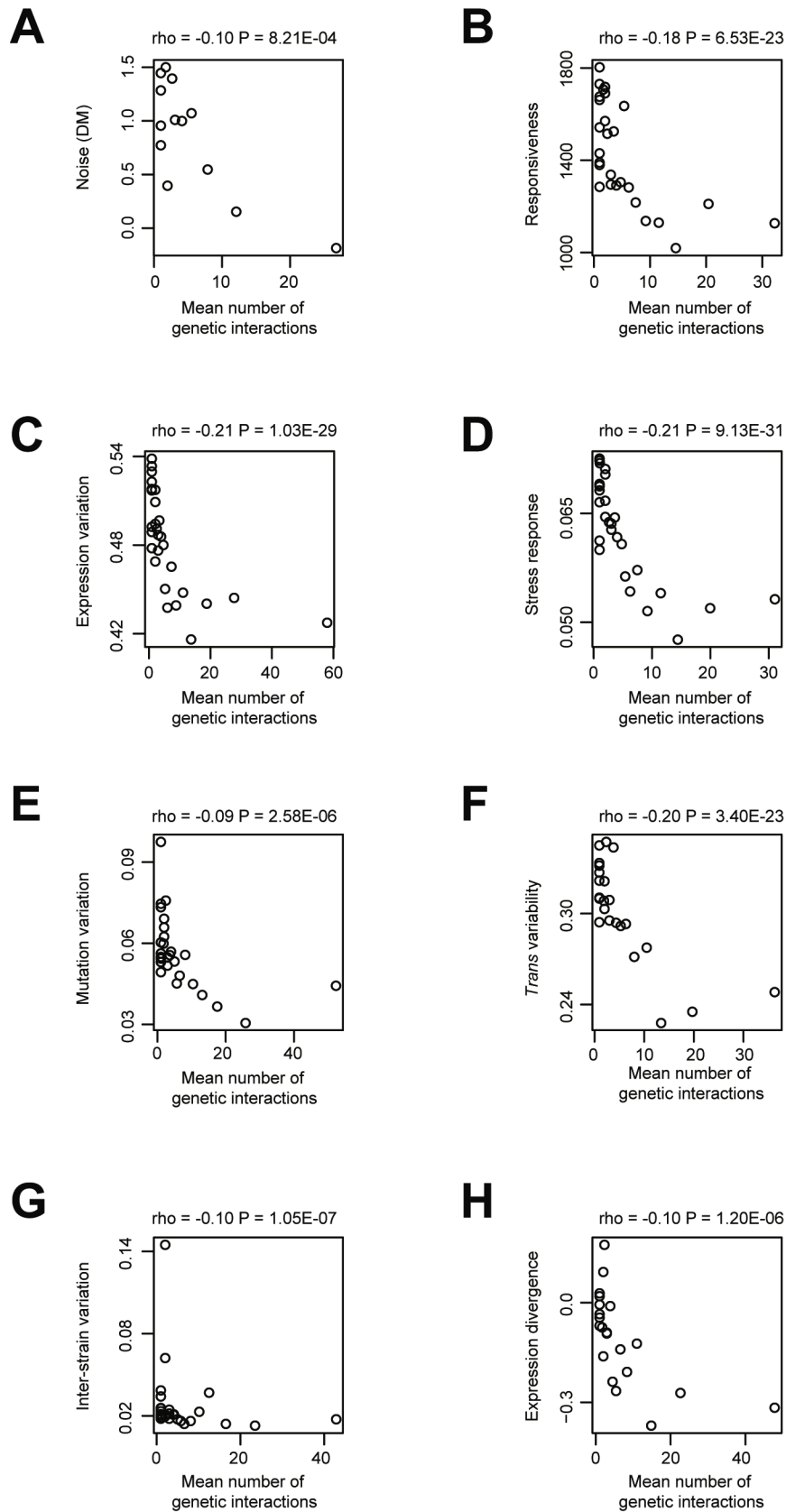


Supplementary Figure 8. Genetic interaction pairs are less likely to be simultaneously lowly expressed across different conditions (gene expression level is

less than bottom 10%; gene expression for a sporulation time series from Chu S *et al*, 1998) compared to random pairs. *P*-value is calculated using the Fisher's exact test (** $P < 5.0E-4$, * $P < 5.0E-2$).



Supplementary Figure 9. Correlations among different measures of gene expression variation. **(A)** Correlations between variations in gene expression at different scales. As the matrix is symmetrical, only the lower diagonal is shown. Color saturation indicates the Pearson correlation. **(B)** Correlations of genetic interaction degree and variation in gene expression controlling for the linear effect of one measure of expression variation, using partial correlation analysis.



Supplementary Figure 10. Genetic interaction hubs from BioGRID after removing interactions from the Costanzo *et al* (2010) and Tong *et al* (2004) have low gene

expression variation across individuals ('noise', **A**), reduced expression variation across different environmental conditions ('responsiveness', **B**; 'expression variation', **C**; 'stress response', **D**), low sensitivity to genetic change ('mutation variation', **E**; '*trans* variability', **F**), diverges slowly during evolution ('inter-strain variation', **G**; 'expression divergence', **H**). All plots for quantitative variables are shown for equally sized groups of genes ($n = 100$), ranked according to the variable under consideration. Spearman's rank correlation coefficients and P -values are shown inset.