

Genome-wide Analysis of Polymorphic Differences That Affect Gene Expression

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Natural genetic variation can cause significant differences in gene expression, suggesting that regulatory variation is an important source of phenotypic diversity. However, little is known regarding the mechanisms by which natural polymorphisms affect gene regulation. To begin to understand the genetics of variation in gene expression, we carried out genetic linkage analysis of genome-wide expression patterns in a cross between laboratory and wild strains of *Saccharomyces cerevisiae*. Over 1500 genes were differentially expressed between the parent strains. Expression levels of over 2000 genes were linked to one or more loci, with most expression levels showing complex inheritance patterns. The loci detected by linkage fell largely into two categories: *cis*-acting modulators of single genes and *trans*-acting modulators of many genes, with most of the linkages involving *trans*-acting factors (variations in genes affecting expression of other genes). Positional cloning and functional assays demonstrated that polymorphisms in *GPA1* and *AMN1* affect expression of genes involved in pheromone response and daughter cell separation, respectively. Segregating genetic variation was used to define 593 clusters of significantly co-regulated genes. 31 clusters were significantly enriched for targets of particular transcription factors, explaining their coordinate regulation. However, variation in expression of genes within a cluster mapped to the location of the corresponding transcription factor in only one case. More generally, we asked whether particular classes of genes were more likely to contain trans-regulatory polymorphisms. Surprisingly, transcription factors showed no enrichment, and trans-regulatory variation appears to be broadly dispersed across classes of genes with different molecular functions.