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Transcription factors (TFs) regulate the expression of genes through sequence-specific interactions with DNA-binding sites. However, despite recent progress in identifying in vivo TF binding sites by microarray readout of chromatin immunoprecipitation (ChIP-chip), nearly half of all known yeast TFs are of unknown DNA-binding specificities, and many additional predicted TFs remain uncharacterized. To address these gaps in our knowledge of yeast TFs and their cis regulatory sequences, we have determined high-resolution binding profiles for 89 known and predicted yeast TFs, over more than 2.3 million gapped and ungapped 8-bp sequences ("k-mers"). We report 50 new or significantly different direct DNA-binding site motifs for yeast DNA-binding proteins and motifs for eight proteins for which only a consensus sequence was previously known; in total, this corresponds to over a 50% increase in the number of yeast DNA-binding proteins with experimentally determined DNA-binding specificities. Among other novel regulators, we discovered proteins that bind the PAC (Polymerase A and C) motif (GATGAG) and regulate ribosomal RNA (rRNA) transcription and processing, core cellular processes that are constituent to ribosome biogenesis. In contrast to earlier data types, these comprehensive k-mer binding data permit us to consider the regulatory potential of genomic sequence at the individual word level. These k-mer data allowed us to reannotate in vivo TF binding targets as direct or indirect and to examine TFs' potential effects on gene expression in approximately 1,700 environmental and cellular conditions. These approaches could be adapted to identify TFs and cis regulatory elements in higher eukaryotes.

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