New algorithms that statistically associate features of genomic data to predict phenotypic outcome are becoming increasingly important in precision medicine, synthetic biology, and microbial ecology. One of the first critical steps is the detection of patterns in the data which group together features across measured molecules that are similar over a subset of conditions. Many such algorithms are based on a biclustering procedure wherein sets of molecular features such as genetic sequence, molecular abundance or molecular interactions co-occur in certain patterns across a set of conditions or outcomes. While current approaches have proven useful it has also become clear that they suffer from limitations that reduce their predictive power: inability to identify overlapping patterns, discovery of biclusters that are too small or too large, and low coverage of the available signal in datasets. Moreover, it has proven difficult to compare the strengths and weakness of different algorithms to one another because of a lack of gold-standard data sets and criteria for evaluation. We developed a new method, Massive Associative K-biclustering (MAK), addressing the key limitations in other biclustering approaches. In a formal evaluation against new simulated data sets with more realistic properties MAK improves recovery of biclusters exhibiting common behavior across conditions, with the highest F1 scores, a measure of a tests accuracy, and lowest false positive rates, the probability of falsely rejecting the null hypothesis, compared to established methods. We show how MAK can be applied to a popular data set from Saccharomyces cerevisiae to uncover new properties not captured by other methods. MAK biclusters showed increased statistical enrichments for known regulatory associations and gene functions, including for nearly 30