Understanding Gene Sequence Variation in the Context of Transcription Regulation in Yeast

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The availability of expression quantitative trait loci (eQTL) data can help understanding the genetic basis of variation in gene expression. However, it has proven difficult to accurately predict functional genetic changes due to low statistical power. To address this challenge, we developed a novel computational approach for combining eQTL data with complementary regulatory network to identify modules of genes, their underlying genetic polymorphism and their shared regulatory proteins activity. The resulting eQTL model implicates novel central protein complexes that share not only a regulatory protein but also an underlying genetic variation. Our method manifests higher sensitivity than prior computational efforts.

Computationally, we tackle the important problem of automatic prediction of eQTL-target relations. The integrated approach makes it possible to capture weaker linkage signals and to avoid groups of genes that happen by chance to be linked to the same genomic interval. In terms of biological and medical discovery, using our framework on eQTL data in yeast, we implicate a novel role of eQTLs on genes comprising protein complexes, including the aerobic cellular respiration complex, affected by genetic changes in the mitochondrial inner membrane proteins Crd1/Cat5, and the Sum1p/Rfm1p/Hst1p middle sporulation repression complex, which is influenced by genetic variation residing within the Rfm1 itself.

Our discovery of previously uncharacterized modules in the well-studied segregating yeast population underscores the utility of our integrated methods in genetic analysis. Thus, our study establishes a broadly applicable, comprehensive approach to reveal eQTL-target relationships.

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