The Construction of a Tool that Predicts the Pathways from the Genome to Phenotype

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The power of systems biology as a concept for decoding the relationship between genome and phenotype is becoming evident. We are continuing development of the Hybrid Rat Diversity Panel, an informative population in which to apply the systems biology approach. This panel will comprise 96 inbred rat strains, all of which will have deep sequencing of their genome, RNASeq and exon array information on gene expression in four organs, and phenotype information. The analysis of these data allows for selection of proper markers for high resolution mapping of gene expression and additional traits to the genome. The gene expression phenotype is mapped as QTLs for modules derived through weighted gene co-expression network analysis (WGCNA), and represented by their eigengenes. Our approach requires that the eigengene values across strains correlate with the phenotype of interest and that the module eigengene QTL overlaps the QTL for the phenotype, i.e., gene expression within the module is controlled from the same area of the genome as the phenotype. Even though we are approximately half way through the transcriptome data collection, we have applied this approach to several complex traits to produce a solid proof of concept. We de novo uncovered a long non-coding RNA that is a hub gene for a module predisposing various levels of alcohol consumption; we found that liver, as well as brain, contributes to levels of alcohol consumption; we identified brown fat modules that contribute to “metabolic syndrome” phenotypes; we demonstrated that the approach identifies the expected enzymes responsible for alcohol metabolism, but also links the alcohol dehydrogenases to immune system function. Furthermore, we deleted (CRISPR/Cas9) the hub gene associated with alcohol drinking level, resulting in a change in phenotype and in expression s of transcripts within and outside the module. Supported by NIAAA/NIH (R24AA013162) and the Banbury Fund.