Tissue-derived transcriptomes are increasingly viewed as a biological bridge between genetic risk factors for complex disease and their associated pathophysiology. Gene expression quantitative trait loci (eQTL) and large-scale genome-wide association (GWAS) facilitate a conceptual model to potentially infer genetic variants that alter nearby gene expression and account for co-localized disease risk. However, these studies in humans are consistently limited by mismatched populations and sample sizes for eQTL vs GWAS, limited tissue availability, and human population history and structure. Here, we perform a multi-tissue analysis of multiple traits related to metabolic disorders in an outbred population of laboratory mice. The combination of comprehensive clinical phenotyping with corresponding tissue gene expression from the same genetically diverse animals enables an advanced analytical strategy linking genetics, tissue-specific transcriptomes, and disease biomarkers. We infer paths of QTL that alter gene expression patterns linked to correlated metabolic traits, thereby augmenting genetic associations with pathway alterations that reveal the underlying molecular dysfunction of disease and candidate proteins for intervention.