

ABSTRACT

The genetics and mechanisms underlying most human traits and diseases can be very complex, where the number of true gene associations can number in the many hundreds. Thus, when trying to better understand a trait/disease, researchers are faced with two main challenges; missing knowledge of which genes are truly related to the trait/disease, and understanding how those genes work together through molecular pathways. These knowledge gaps make it hard to translate large scale genetic information into actionable hypotheses. The overarching goal of the research presented in this dissertation is to develop methods that address these challenges in order to gain a better understanding of the etiology of complex traits and diseases. We worked towards this goal by developing general-purpose computational frameworks that leverage vast publicly-available datasets — genome-scale gene networks, gene functional annotations, thousands of gene expression signatures, and experimentally-derived gene-phenotype associations in humans and model organisms — to resolve large gene lists associated with highly polygenic disease into relevant genes, pathways, and critical interactions. Together, these findings reveal nuanced understanding of disease mechanisms. Overall, this research helps get away from treating each disease as a single well-defined condition, and instead find mechanism-based disease subtypes and use these insights to find novel diagnostic and treatment avenues.