Gene Polymorphism-Centered Approaches to Integrative Biomedical Informatics Applied to the Analysis and Treatment of Disease

[1,2]Jegga, AG, [1]Gowrisankar, S, [1]Muthukrishnan, A, [1]Sychay, G, [1]Chen, J, [1]Gudivada, R, [1]Sue Kong, [1]Deshmukh, MA and [1,2]Aronow, BJ

[1]Biomedical Informatics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]Pediatrics, University of Cincinnati, Cincinnati, OH

A variety of genetic markers and genomic pattern-signatures may provide predictions and insights into the molecular basis of diseases, individual susceptibilities, likelihood of severity, optimal therapeutic approach, new therapeutic avenues, and clinical outcome. Since most common diseases have been shown to be influenced by inherited genetic variations, mapping variations across the human genome for many individuals will have a tremendous impact on our approach to medicine. New developments in genotyping techniques and bioinformatics--enabling detection of single-nucleotide and other polymorphisms--may lead to extensive changes our understanding of human biology. We have adopted an integrative approach to the analysis of potential polymorphism impact by developing a set of interconnected systems (PolyDoms: http://polydoms.cchmc.org; PatholoGene: http://abstrainer.cchmc.org, GenomeTrafac: http://genometrafac.cchmc.org/), to allow for linkage of genetic polymorphisms to biological processes and pathways operative in diseases, and that influence response to therapy. To approach this, we have divided genomic medicine into two separate networks: gene networks and disease networks. Diseases can be related to each other on the basis of shared etiology, pathophysiology, clinical signs and symptoms, or cellular phenotypes. Genes and genomic elements can be related to each other by mining pathway, interactions, and functional genomics. Literature mining allowed a first-pass establishment of over 7000 disease-gene relationships. For a new disease or a syndrome of unknown etiology, disorders sharing similar clinical features could be used as a first step to hypothesize gene network connections, and these can prioritize genes that can serve as candidate modifiers for subsequent association studies, particularly after prioritization of potentially harmful polymorphisms within the hypothesized genes. Mapping between clinical features and genes networks may allow for significant reduction of gene polymorphism search space. Achieving this goal fundamentally requires integrating clinical informatics databases with genomics databases, improved disease classification and individual patient descriptions, complete access to biomedical literature and population and genome-scale datasets. The results