KSN 2017 Abstract

Title: Prioritizing treatment targets by integration of genomic variants and tissue specific gene expression pattern

Sek Won Kong

Boston Children's Hospital, USA

Transcriptional activity in diseased tissue often suggests causal pathways, pathophysiological changes related to disease activities, and treatment targets. Causal and reactive pathways perturbed in disease, however, are difficult to distinguish. To evaluate the relationship between transcriptional-activity of genes implicated in rare genetic disorders and tissue-related disease phenotypes, we integrated 6,665 tissue-wide transcriptomes with genetic disorder knowledge databases covering 3,397 diseases. Many disease genes were up regulated in affected tissues compared to unaffected ones. This was more pronounced for genes associated with autosomal dominant over recessive disorders and mainly for diseases affecting brain and muscle but not blood. Receiver operating characteristics analysis using relative expression levels within each tissue and across tissues indicated significant associations between elevated expression and phenotypes for most tissues. Associations at extreme expression levels were marked. These results suggest features useful for evaluating the likelihood of specific manifestations in genetic disorders. As such, for the diseases with strong genetic components, genetic variants can be causal associated with disease, and modify clinical courses as well as treatment targets and responses. Using whole exome sequencing (WES) data from a trio and gene expression profiles from diseased tissue biopsy, we illustrate an approach to integrating WES and functional genomic data to prioritize treatment targets.