Abstract ID:- 78

Abstract Topic:- Complex traits and polygenic disorders

Abstract Title:- Integrative genomics approach to investigate the role of Transcription Factors in Complex Diseases.

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Aims:-Expression of genes in tissue is a highly regulated process starting from the selection of a gene to express in response to stimuli till its translation, there exist a lot of regulatory factors in those processes. Transcription factors (TF) play a key role in targeting genes given a specific environment; all the targets of a TF in tissue might not be expressed after TF activation; only a subset of genes is regulated in a specific sequence. The criteria that determine specific set of target genes include cis regulators, trans regulators, chromatic accessibility, histone modification, cofactors and post transcriptional level. SNPs in the GWAS might alter one of the above-described regulatory processes, there might be a change in the affinity of TF binding on DNA sequence due to SNP in the cis-eQTL directly controlling expression of the neighboring gene as well as trans eQTL regulating distal genes via TF. So, we integrate various data sources to identify key targets of a TF within a disease relevant tissue, and also the SNPs that are controlling the targets of a TF directly or indirectly.

Methods:- Enrichment analysis is performed on GWAS SNPs to understand which TFs are enriched in the diseased individuals compared to controls. Subsequently we accounted for disease relevance of tissues by incorporating data sources from DIAGRAM constortium, GTEX data, and some regulatory annotations like H3K27ac and ChIP-seq data from ENCODE. This enabled us to understand the importance of TFs in a tissue as well as SNPs that directly or indirectly regulate the expression and activation of TFs. We also developed pipelines to identify cis- and trans- eQTL SNPs regulating TF activation and expression and also associated biological processes that are perturbed within a tissue by alteration of a TF. We applied these pipelines to a model complex trait, i.e., T2D, focusing on some important disease-relevant TF-s extracted from the literature such as SREBP1, KLF14 and PPARG.

Results:- We found potential tissues where these TF-s have a causal role in T2D. We also found GWAS-derived associated SNP-s that act as cis- or trans-regulators of the TF. For example, we found rs4925138 which is a cis-eQTL for SREBP1 in skeletal muscle is also a significant trans-eQTL for enhancer-defined targets of SREBP1 in the same tissue. Another SNP rs1784223 present on chr11 was found to be a significant trans-eQTL for SREBP1 targets in skeletal muscle tissue thus indicating that it is a potential trans-regulator of SREBP1.

Conclusions:- Integrating various data sources and creating pipelines to investigate the etiology and molecular basis of complex diseases.

Keywords:- cis-eQTL, trans-eQTL