Functional Analysis of Single Nucleotide Polymorphisms Associated with Type 2 Diabetes
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Abstract

Type 2 diabetes (T2D), a metabolic disorder characterized by insulin resistance and relative insulin deficiency, is a life-long, common, complex disease of major public health importance. To date, there have been 86 published studies that have reported 639 associations between single nucleotide polymorphisms (SNPs) and T2D in the GWAS Catalog database, and others studies in literature. However, the majority (~93%) of the SNPs emerging from these studies are located within noncoding sequence, complicating their functional evaluation. Recently, several lines of evidence have suggested the involvement of a proportion of such variants in transcriptional regulatory mechanisms, including modulation of promoter and enhancer elements and enrichment within expression quantitative trait loci (eQTL). In this study, we downloaded T2D-associated SNPs from GWASdb, a derived database that included the data from GWAS Catalog. We then annotated them with transcription factor (TF) motif, promoter/enhancer, and eQTL information followed by the construction of a TF-target network module, in order to better detect the underlying mechanism of genetic variants involving in T2D. We found that T2D associated SNPs were significantly enriched with functional information. In addition, we found that functional annotations could significantly improve the power of detecting causal variants and understanding their pathogenesis. Using the data collected from the Gene-Tissue Expression Project (GTEx), we could further find the target genes for those eQTL SNPs. When cross-referencing with the Drug Bank database, we were able to discover certain drugs that might regulate the expression of these genes and fight against T2D.

Keywords

Genetic variants; type 2 diabetes; association; functional roles; Genome-wide Association Studies

Cover Page Footnote

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ABSTRACT

Type 2 diabetes (T2D), a metabolic disorder characterized by insulin resistance and relative insulin deficiency, is a life-long, common, complex disease of major public health importance. To date, there have been 86 published studies that have reported 639 associations between single nucleotide polymorphisms (SNPs) and T2D in the GWAS Catalog database, and others studies in literature. However, the majority (~93%) of the SNPs emerging from these studies are located within noncoding sequence, complicating their functional evaluation. Recently, several lines of evidence have suggested the involvement of a proportion of such variants in transcriptional regulatory mechanisms, including modulation of promoter and enhancer elements and enrichment within expression quantitative trait loci (eQTL). In this study, we downloaded T2D-associated SNPs from GWASdb, a derived database that included the data from GWAS Catalog. We then annotated them with transcription factor (TF) motif, promoter/enhancer, and eQTL information followed by the construction of a TF-target network module, in order to better detect the underlying mechanism of genetic variants involving in T2D. We found that T2D associated SNPs were significantly enriched with functional information. In addition, we found that functional annotations could significantly improve the power of detecting causal variants and understanding their pathogenesis. Using the data collected from the Gene-Tissue Expression Project (GTEx), we could further find the target genes for those eQTL SNPs. When cross-referencing with the Drug Bank database, we were able to discover certain drugs that might regulate the expression of these genes and fight against T2D.

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