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From regulatory SNPs to pathways: multi-omics insights into the biological mechanisms underlying type 2 diabetes (TD2M) and metformin response

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Motivation and Aim: The experience with GWAS analysis has revealed the success of studies in connecting genotype and phenotype but certain limitations when informing on the functional consequences of *SNPs* on genes. Therefore, the multi-omics studies aimed at identifying functionally significant genetic variants are gaining popularity. In this work, we focus on identifying regulatory SNPs (rSNPs) potentially involved in the development of type 2 diabetes mellitus (T2DM) and response to antihyperglycemic therapy.
Methods and Algorithms: Paired data on gene expression profiles (RNA-seq) and active chromatin marks H3K4me3 and H3K27ac (ChIP-seq) data were received for peripheral blood mononuclear cells (PBMCs) of nine healthy donors and analyzed to identify rSNPs associated with both allele-asymmetric binding and expression events [1]. GWAS catalog and Genotype-Tissue Expression (GTEx) project were used to explore the resulting rSNP list. We implemented RNA-seq datasets GSE221521 and GSE153315 to identify differentially expressed genes between T2DM and normal samples and between metformin responders and non-responders using R software. We then constructed protein-protein interaction networks using the STRING database, analyzed the networks by Cytoscape software, explored gene ontology and key pathway analysis and predicted *hub* genes targeted by identified rSNPs.
Results: We identified 14 796 rSNPs in the promoters of more than 5000 genes of human PBMCs and from this number 4280 rSNPs were associated with both GWAS-derived phenotypic traits and GTEx-reported eQTLs. 4612 DEGs were identified between T2DM patients with diabetic retinopathy and controls from GSE221521. The promoters of 1284 DEGs harbored rSNPs from our list. We found 31 hub genes in the PPI network in type 2 diabetes, including the genes involved in inflammation, obesity, insulin resistance, and signaling pathways related to the control of glucose levels (AMPK- and FoxO- signaling pathways by KEGG). In total, 496 DEGs were found between metformin responders and non-responders from GSE153315 and the promoters of 131 DEGs harbored identified rSNPs. Many of these were shown to be involved in the T2DM pathogenesis. The most significant group of DEGs targeted by rSNPs in metformin monotherapy response was a group of genes encoding known transcriptional regulators (including FOXP1, POU2F2, YY-1, KLF6, NFIX, and GMEB1 transcription factors).
Conclusion: We conclude that the list of human rSNPs identified from PBMCs add to the functional interpretation of GWAS-association signals. Our results also suggest the

candidate causal rSNPs for T2DM as well as for the beneficial effects of metformin and the rSNP-targeted genes are enriched in the pathways related to glucose metabolism and inflammation.

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References

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