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Novel approaches to identify genes for type 2 diabetes in human islets: combination of SNP information, islets gene expression and in vitro measurements

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Type 2 diabetes (T2D) is one of the fastest increasing diseases worldwide, with an estimated prevalence of 280 million affected patients in 2011. This epidemic has been ascribed to an interaction between common genetic variants and environmental factors. Genome-wide association studies (GWAS) have identified 70 common genetic variants associated with T2D or glucose/insulin levels, but they explain only 15% of the heritability. These T2D-variants seem to influence insulin secretion rather than action. In most cases the causal variant is not known, nor is it known how the identified variants may influence islet function in man. Thus, novel approaches to identify susceptibility genesfor T2D is needed.

Herein, using human pancreatic islets we described two novel approaches to identify susceptibility genes for T2D. On the first approach, we have systematically characterized donated human islets by performing cDNA microarray and GWAS in addition to measuring insulin response to glucose and glycemic control (HbA1c) from the same individuals. We combined data from human islet gene expression, genetics, and function to build a global map of genes associated with islet dysfunction in T2D. We identified CHL1, LRFN2, RASGRP1, PPM1k and GRP120 as novel genes that affect islets function in man and might contribute to T2D.

Secondly,we introduced a novel approach by correlating islet gene expression with insulin secretion and HbA1c levels in islets from 78 organ donors. The expression of 649 genes ($P < 0.05$) was correlated with insulin secretion and HbA1c. Of them, five genes (GLR1A, PPP1R1A, PLCDXD3, FAM105A and ENO2) correlated positively with insulin secretion/negatively with HbA1c and one gene (GNG5) correlated negatively with insulin secretion/positively with HbA1c were followed up by siRNA silencing in an INS-1 cell line and SNP analysis for associated with T2D in the DIAGRAM+ database or could influence gene expression in cis expression quantitative trait loci (eQTLs).

In conclusion, several genes were identified and experimentally validated as potential players in the pathogenesis of islet dysfunction in T2D. We also provide a list of potential genes involved in protection from and susceptibility to T2D based upon correlation between their expression in human pancreatic islets and insulin secretion and glycemia (HbA1c). This gene list should serve as a resource for future studies exploring their potential role in β-cell failure and the pathogenesis of hyperglycemia and T2D.

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