HelmholtzZentrum münchen
German Research Center for Environmental Health

Scientific Highlight September 2019

Institute for Pancreatic Islet Research, Paul Langerhans Institute Dresden
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Highlight / Publication:
Laser capture microdissection of human pancreatic islets reveals novel eQTLs associated with type 2 diabetes. Khamis A, Canouil M, Siddiq A, Crouch H, Falchi M, Bulow MV, Ehehalt F, Marselli L, Distler M, Richter D, Weitz J, Bokvist K, Xenarios I, Thorens B, Schulte AM, Ibberson M, Bonnefond A, Marchetti P, **Solimena M**, Froguel P. Mol Metab. 2019 Jun;24:98-107. doi: 10.1016/j.molmet.2019.03.004. Epub 2019 Mar 18.

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Keywords:
Type 2 diabetes; eQTLs; Genetics; Islets; Laser capture microdissection

Central statement of the highlight in one sentence:
The authors provide a catalogue of eQTLs from the largest to date sample size from two separate cohorts of non-diabetic and T2D subjects and which includes the first in-depth combined genetic and expression analysis of human islets isolated by LCM.

Text of the highlight:
Genome wide association studies (GWAS) for type 2 diabetes (T2D) have identified genetic loci that often localise in non-coding regions of the genome, suggesting gene regulation effects. We combined genetic and transcriptomic analysis from human islets obtained from brain-dead organ donors or surgical patients to detect expression quantitative trait loci (eQTLs) and shed light into the regulatory mechanisms of these genes.
Pancreatic islets were isolated either by laser capture microdissection (LCM) from surgical specimens of 103 metabolically phenotyped pancreatectomized patients (PPP) or by collagenase digestion of pancreas from 100 brain-dead organ donors (OD). Genotyping (> 8.7 million single nucleotide polymorphisms) and expression (> 47,000 transcripts and splice variants) analyses were combined to generate cis-eQTLs.
After applying genome-wide false discovery rate significance thresholds, we identified 1,173 and 1,021 eQTLs in samples of OD and PPP, respectively. Among the strongest eQTLs shared between OD and PPP were CHURC1 and PSPH. We identified eQTLs in linkage-disequilibrium with GWAS loci T2D and associated traits, including TTLL6, MLX and KIF9 loci, which do not implicate the nearest gene. We found in the PPP datasets 11 eQTL genes, which were differentially expressed in T2D and two genes (CYP4V2 and TSEN2) associated with HbA1c but none in the OD samples.
eQTL analysis of LCM islets from PPP led us to identify novel genes which had not been previously linked to islet biology and T2D. The understanding gained from eQTL approaches, especially using surgical samples of living patients, provides a more accurate 3-dimensional presentation than those from genetic studies alone.

Taking account of the HMGU mission:
Deciphering the causal variants and making inferences from GWAS to physiology is still a challenge. With regard to diabetes, only a few studies have investigated eQTLs in pancreatic islet samples. Here we show the most comprehensive cis-eQTL analysis in relevant islet samples in two distinct cohorts, including samples from 100 OD and for the first time 103 PPP (e.g. from living surgical patients). To our knowledge, this is also the largest eQTL study using islet samples to date. A deeper knowledge of the transcriptome of PPPs will foster the understanding on the natural history of type-2 diabetes.

The internal HMGU co-operation partners with whom the highlight was compiled, if appropriate:
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