Integrative network analysis highlights biological processes underlying GLP-1 stimulated insulin secretion: A DIRECT study - DTU Orbit (09/10/2018)

Glucagon-like peptide 1 (GLP-1) stimulated insulin secretion has a considerable heritable component as estimated from twin studies, yet few genetic variants influencing this phenotype have been identified. We performed the first genome-wide association study (GWAS) of GLP-1 stimulated insulin secretion in non-diabetic individuals from the Netherlands Twin register (n = 126). This GWAS was enhanced using a tissue-specific protein-protein interaction network approach. We identified a beta-cell protein-protein interaction module that was significantly enriched for low gene scores based on the GWAS P-values and found support at the network level in an independent cohort from Tübingen, Germany (n = 100). Additionally, a polygenic risk score based on SNPs prioritized from the network was associated (P <0.05) with glucose-stimulated insulin secretion phenotypes in up to 5,318 individuals in MAGIC cohorts. The network contains both known and novel genes in the context of insulin secretion and is enriched for members of the focal adhesion, extracellular-matrix receptor interaction, actin cytoskeleton regulation, Rap1 and PI3K-Akt signaling pathways. Adipose tissue is, like the beta-cell, one of the target tissues of GLP-1 and we thus hypothesized that similar networks might be functional in both tissues. In order to verify peripheral effects of GLP-1 stimulation, we compared the transcriptome profiling of ob/ob mice treated with liraglutide, a clinically used GLP-1 receptor agonist, versus baseline controls. Some of the upstream regulators of differentially expressed genes in the white adipose tissue of ob/ob mice were also detected in the human beta-cell network of genes associated with GLP-1 stimulated insulin secretion. The findings provide biological insight into the mechanisms through which the effects of GLP-1 may be modulated and highlight a potential role of the beta-cell expressed genes RYR2, GDI2, KIAA0232, COL4A1 and COL4A2 in GLP-1 stimulated insulin secretion.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Disease Intelligence and Molecular Evolution, Vrije Universiteit Amsterdam, Sanofi Aventis Deutschland GmbH, University of Copenhagen, NIHR Oxford Biomedical Research Centre, University of Oxford, University of Dundee, Eberhard-Karls-Universität Tübingen, VU University Medical Centre, Leiden University Medical Center, Imperial College London
Number of pages: 12
Publication date: 2018
Main Research Area: Technical/natural sciences

Publication information
Journal: P L o S One
Volume: 13
Issue number: 1
Article number: e0189886
ISSN (Print): 1932-6203
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 3.01 SJR 1.164 SNIP 1.111
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.772 SNIP 1.153 CiteScore 3.94