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Type 2 diabetes (T2D) is a complex disease that involves multiple genes. Numerous risk loci have already been associated with T2D, although many susceptibility genes remain to be identified given heritability estimates. Systems biology approaches hold potential for discovering novel T2D genes by considering their biological context, such as tissue-specific protein interaction partners. Pancreatic islets are a key T2D tissue and many of the known genetic risk variants lead to impaired islet function, hence a better understanding of the islet-specific dysregulation in the disease-state is essential to unveil the full potential of person-specific profiles. Here we identify 3,692 overlapping pancreatic islet protein complexes (containing 10,805 genes) by integrating islet gene and protein expression data with protein interactions. We found 24 of these complexes to be significantly enriched for genes associated with diabetic phenotypes through heterogeneous evidence sources, including genetic variation, methylation, and gene expression in islets. The analysis specifically revealed ten T2D candidate genes with probable roles in islets (ANPEP, HADH, FAM105A, PDLIM4, PDLIM5, MAP2K4, PPP2R5E, SNX13, GNAS, and FRS2), of which the last six are novel in the context of T2D and the data that went into the analysis. Fifteen of the twenty-four complexes were further enriched for combined genetic associations with glycemic traits, exemplifying how perturbation of protein complexes by multiple small effects can give rise to diabetic phenotypes. The complex nature of T2D ultimately prompts an understanding of the individual patients at the network biology level. We present the foundation for such work by exposing a subset of the global interactome that is dysregulated in T2D and consequently provides a good starting point when evaluating an individual's alterations at the genome, transcriptome, or proteome level in relation to T2D in clinical settings.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology
Contributors: Pedersen, H. K., Gudmundsdottir, V., Brunak, S.
Number of pages: 16
Publication date: 2017
Peer-reviewed: Yes

Publication information
Journal: Frontiers in Genetics
Volume: 8
Article number: 43
ISSN (Print): 1664-8021
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 3.78 SJR 2.274 SNIP 1.032
Web of Science (2017): Impact factor 4.151
Web of Science (2017): Indexed yes
Scopus rating (2016): CiteScore 3.44 SJR 2.067 SNIP 0.884
Web of Science (2016): Impact factor 3.789
Scopus rating (2015): CiteScore 3.38 SJR 2.021 SNIP 0.84
Web of Science (2015): Indexed yes
Scopus rating (2014): CiteScore 3.1 SJR 1.798 SNIP 0.758
Web of Science (2014): Indexed yes
Scopus rating (2013): CiteScore 2.57 SJR 1.342 SNIP 0.596
Scopus rating (2012): CiteScore 1.55 SJR 0.736 SNIP 0.374
Scopus rating (2011): SJR 0.147 SNIP 0.023
Original language: English
Keywords: Diabetes, Data integration, Protein complexes, Tissue specificity, Pancreatic islets, Patient network biology, Genetics, QH426-470
Electronic versions:
fgene_08_00043.pdf
DOIs:
10.3389/fgene.2017.00043
Source: FindIt
Source-ID: 2358010478
Research output: Research - peer-review → Journal article – Annual report year: 2017