## Use of a novel Down syndrome genetic screen identifies a regulator of pancreatic β-cell function linked to type 2 diabetes

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Type 2 diabetes (T2D) is a complex metabolic disease associated with obesity, insulin resistance and hypoinsulinemia due to pancreatic β-cell dysfunction. Reduced mitochondrial function is thought to be central to β-cell dysfunction. Mitochondrial dysfunction and reduced insulin secretion are also observed in β-cells of humans with the most common human genetic disorder, Down syndrome (DS, Trisomy 21). To identify regions of chromosome 21 that may be associated with perturbed glucose homeostasis we profiled the glycaemic status of different DS mouse models. This approach identified a single region of chromosome 21 associated with glycemic control. To identify if any genes in this region associate with changes in human T2D β-cells, we cross-referenced them against genes identified in a large gene expression analysis of human T2D β-cells. This approach produced a single gene, RCAN1, as a candidate gene linking hyperglycemia and functional changes in T2D β-cells. Further investigations demonstrated RCAN1 methylation is reduced in human T2D islets at multiple sites, correlating with increased expression. RCAN1 protein expression was also increased in db/db mouse islets and in human and mouse islets exposed to high glucose. Mice overexpressing RCAN1 had reduced *in vivo* GSIS and their β-cells displayed multiple aspects of mitochondrial dysfunction including reduced ATP production. This lack of β-cell ATP had functional consequences by negatively affecting both glucose-stimulated membrane depolarisation and ATP-dependent insulin granule fusion. Both *in vivo* and *in vitro* analysis also demonstrates that high RCAN1 levels reduced β-cell numbers and proliferation, and that deletion of RCAN1 enables increased β-cell proliferation. Our unique RCAN1 may be a worthwhile target of further investigation with potential relevance to both type 1 and type 2 diabetes.