**Defective glucose homeostasis in mice inactivated selectively for Tcf7l2 in the adult beta cell with an Ins1*-*controlled Cre**

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**Background and aims:** Single nucleotide polymorphisms in the *TCF7L2* gene, including rs7903146,

are associated with an elevated risk of type 2 diabetes in man. Previous studies of the effects of *Tcf7l2*

deletion in mice have provided conflicting results. In the present report we therefore inactivated *Tcf7l2*

specifically in pancreatic beta cells to investigate the cell-autonomous role for *Tcf7l2* in these cells.

**Materials and methods:** To achieve highly selective deletion in the adult pancreatic beta cell, but not

brain or other tissues, we crossed mice bearing flox’d (exon 1) *Tcf7l2* alleles to animals in which *Cre*

recombinase was expressed from the Ins1 locus. *Tcf7l2*f/f::Ins1*Cre*+, and littermate control mice were

maintained on a C57BL/6 background and on either a normal or a high fat (60%; HFD; age 8 - 20

weeks) diet (Research Diet, New Brunswick, NJ, USA). Glucose tolerance was assessed by oral and

intraperitoneal administration (1 g/kg body weight) following a 16 h fast, and insulin secretion *in vivo*

measured after intraperitoneal injection of glucose (3 g/kg). Insulin secretion *in vitro* was measured

from groups of six islets by radioimmunoassay (Millipore). Quantitiative real-time PCR was

performed on islet cDNA on a Fast 7500 device (ABI) running 7500 software (ABI) and with

powerSYBR reagent (ABI). Changes in cytosolic calcium were assessed by Nipkow spinning disc

confocal microscopy of whole islets loaded with fluo-2. Beta and alpha cell mass were assessed by

optical projection tomography (19 μm resolution) of chemically-clarified pancreata double-stained for

insulin and glucagon.

**Results:** Compared to littermate controls, *Tcf7l2*f/f::Ins1*Cre*+ mice displayed impaired intraperitoneal

glucose tolerance by 16 weeks (increase in AUC of 13.6 ± 2.8 %, n=6 mice per genotype, p<0.05), and

impaired oral glucose tolerance (increase in AUC of 10.6 ± 1.3 %, n=6, p<0.05) from 8 weeks.

Glucose intolerance was thus apparent earlier than in mice deleted for *Tcf7l2* throughput the pancreas

(*Tcf7l2*fl/fl::Pdx1.*Cre*+ mice; observed at 20 and 12 weeks when glucose was administered by the

intraperitoneal and oral route, respectively). Islets of Langerhans isolated from *Tcf7l2*f/f::Ins1*Cre*+ mice

at 20 weeks displayed impaired glucose (p<0.05) and GLP-1-(p<0.05) stimulated insulin secretion,

and decreased insulin and GLP-1 receptor gene expression (p<0.01). Similarly, when maintained on a

HFD, *Tcf7l2*f/f::Ins1*Cre*+ mice displayed impaired glucose tolerance, and lower plasma insulin

following an intraperitoneal glucose tolerance test, than littermate controls, and impaired GLP-1

stimulated insulin secretion (p<0.01) and cytosolic calcium increases (p<0.03). 20 week-old

*Tcf7l2*f/f::Ins1*Cre*+ mice that had been maintained on HFD for 12 weeks also displayed decreased (n=4,

31.7%, p<0.05) beta cell mass, but normal alpha cell mass, compared to littermate controls.

**Conclusion:** These findings provide further support for the view that type 2 diabetes-associated

*TCF7L2* variants may exert their effects, at least in part, through cell autonomous actions on the beta

cell. These include impairments in Ca2+ signalling, and expansion in response to insulin resistance.

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