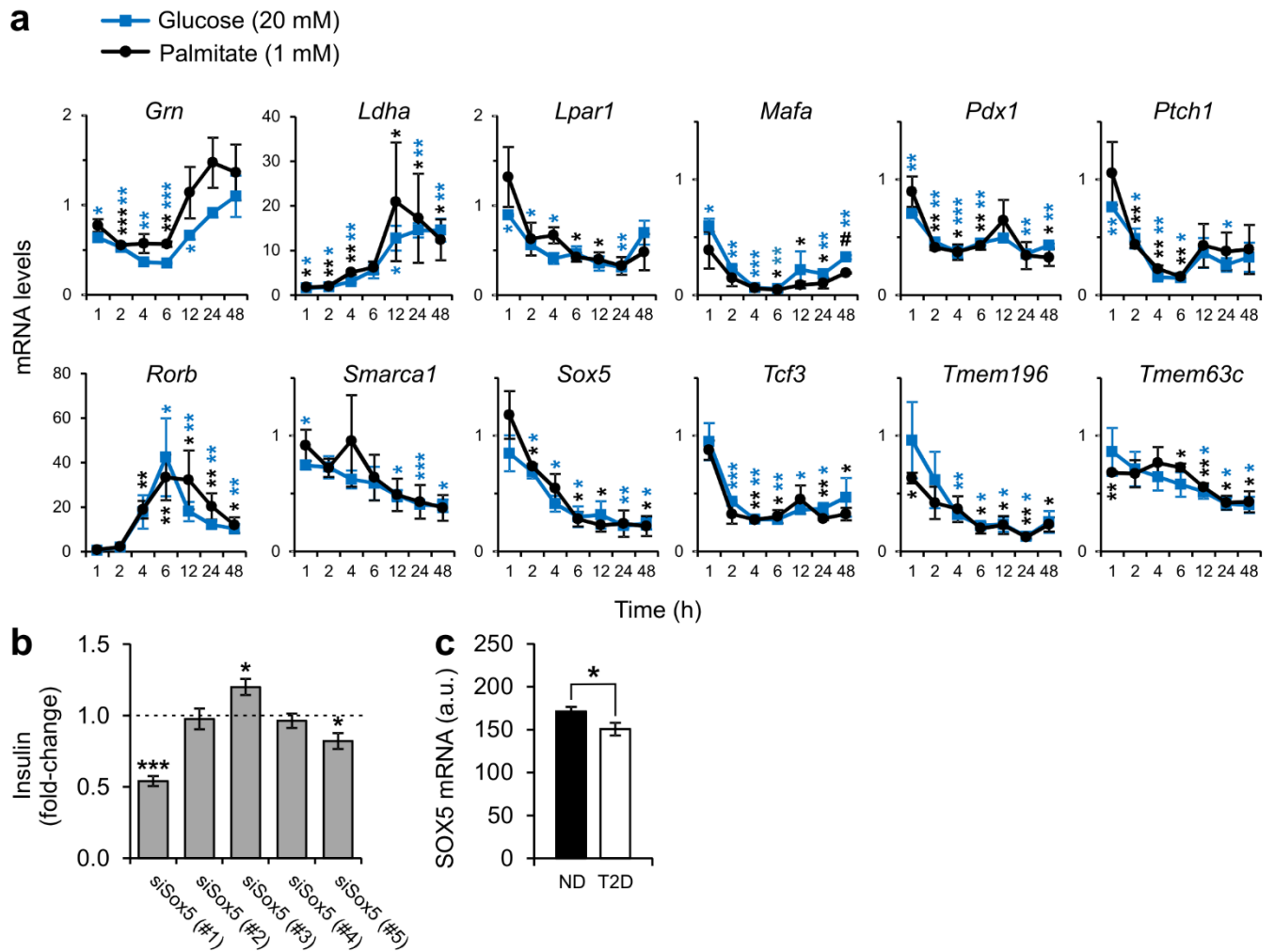




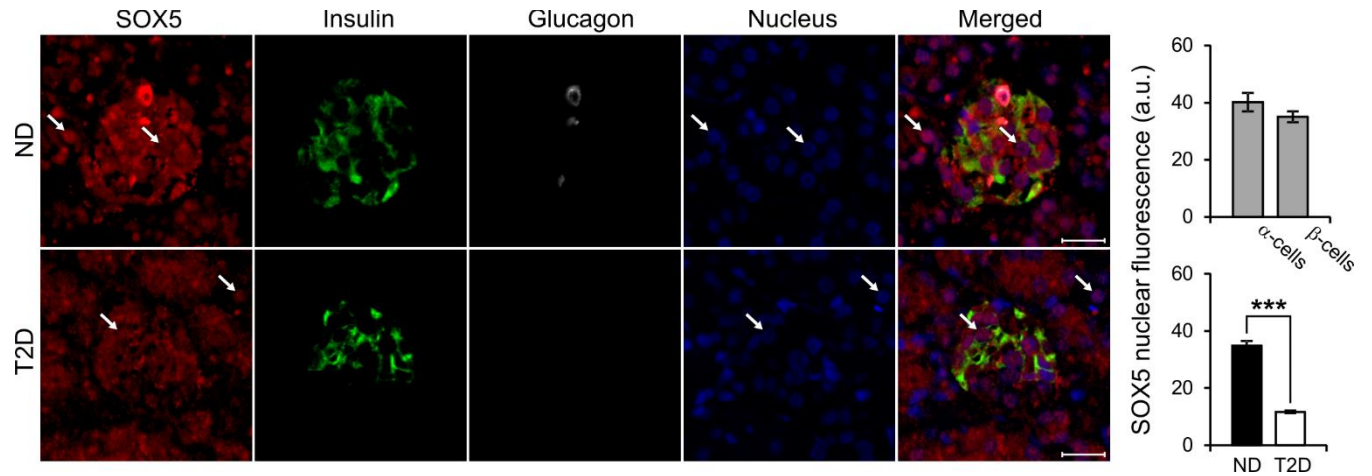
Supplementary Figure 1. Characterization of Sox5 expression

(a) The expression of putative key regulators of the T2D-associated gene module in rat pancreatic islets during 48 h incubation at 20 mM glucose (blue line) or 1 mM palmitate (black line). Expression at time point 0 was set to 1, and the graphs depict fold-change and statistical significance at time points 1, 2, 6, 8, 12, 24 and 48 h relative to the expression at time point 0 (n=3). #*Mafa* palmitate outlier removed (n=2)

(b) Fold-change of insulin secretion at 16.7 mM glucose 48 h after transfecting INS1-832/13 cells with different siRNAs targeting *Sox5*. Data are compared to cells treated with negative control siRNA (n=4 independent experiments per group). The oligonucleotides were from Life Technologies (#1), Sigma-Aldrich (#2 and #3), and Thermo Scientific (#4 and #5). Knockdown efficiency was for siRNA #1) $72 \pm 2\%$, #2) $62 \pm 4\%$, #3) $68 \pm 6\%$, #4) $58 \pm 15\%$ and for #5) $43 \pm 9\%$.

(c) *SOX5* mRNA levels measured by microarray in human islets from non-diabetic (ND; n=82) and T2D (n=41) individuals.

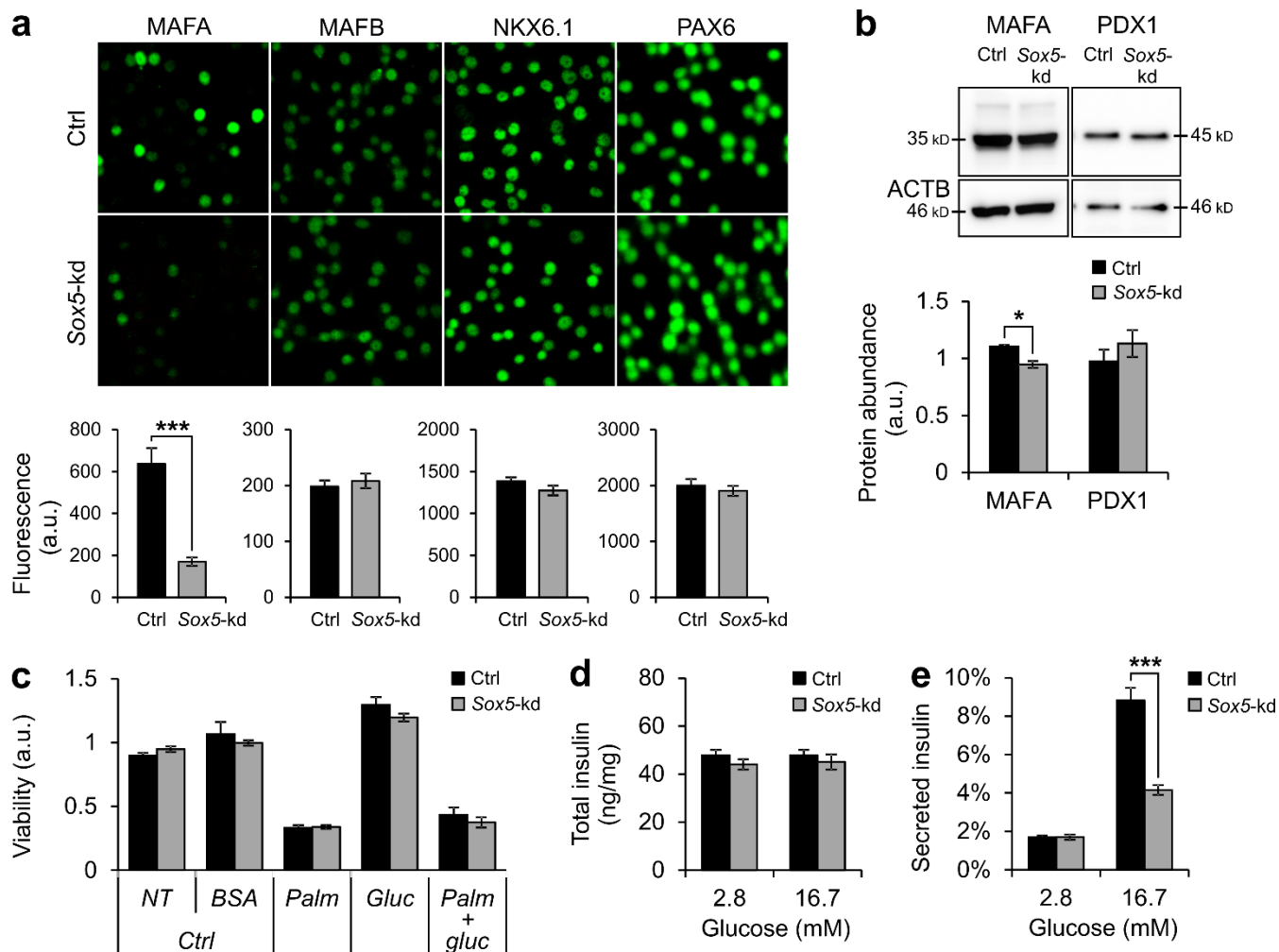
Data are mean $\pm$ SEM * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ using Student's t-test.



Supplementary Figure 2. Sox5 protein expression in human islets

Representative image of Sox5 protein expression in human pancreas paraffin sections from a non-diabetic and a T2D donor. Examples of nuclear SOX5 staining in β -cells and in exocrine tissue are indicated with white arrows. Scale bar=20 μ m. The bar graphs show nuclear SOX5 expression in α -cells (42 cells) and β -cells (56 cells) from a non-diabetic donor and nuclear SOX5 expression in β -cells from a non-diabetic donor (ND; 116 cells) and a T2D donor (113 cells).

Data are mean $\pm$ SEM ***p<0.001 using Student's t-test.



Supplementary Figure 3. Effects of Sox5 knockdown in INS1-832/13 cells

(a) Immunostaining of Sox5-kd and control INS-1 832/13 cells with anti-MafA, anti-MafB, anti-Nkx6.1 and anti-Pax6 antibodies. The bar graphs show the average fluorescence intensity for each antibody (n= 25 cells).

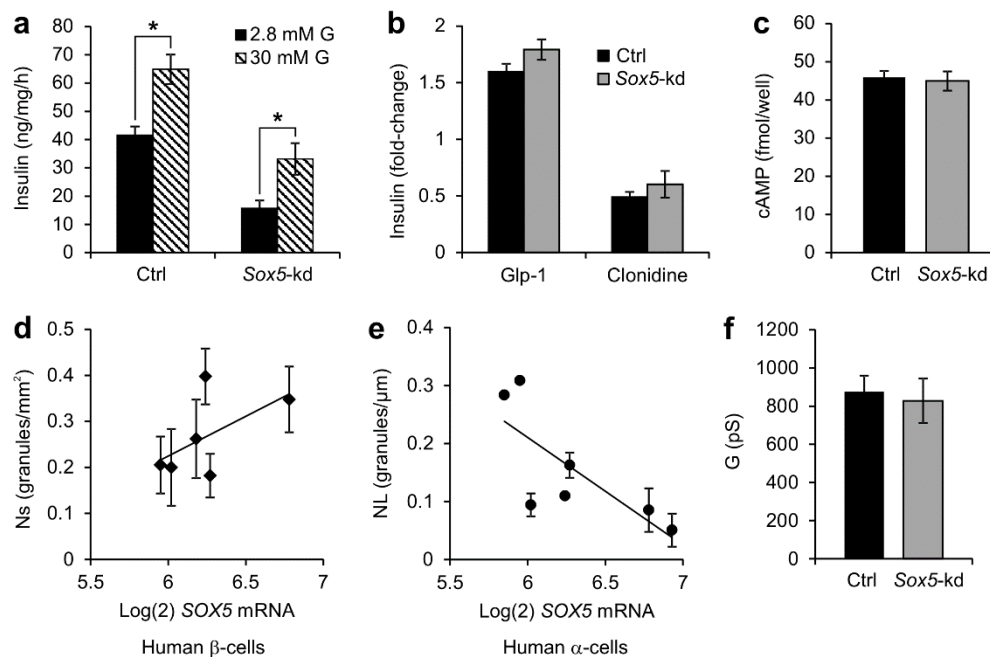
(b) Representative immunoblot of total protein from Sox5-kd and control INS-1 832/13 cells. Polyclonal antibodies against MafA and Pdx1 and monoclonal antibody against β -actin (ACTB) were used as indicated. The graph shows average levels of MafA and Pdx1 normalized for β -actin (n=3 for MafA and n=6 for Pdx1).

(c) Cell viability in Sox5-kd and ctrl INS-1 832/13 cells treated with 0.5 mM palmitate and/or 20 mM glucose for 48 h (n=3). BSA-treated cells (1% BSA, same concentration as in the palmitate solution) and non-treated (NT) cells were used as controls. Viability was measured with the Aqueous One Solution Cell Proliferation Assay Reagent (Promega).

(d) Total insulin content in INS-1 832/13 cells normalized to total protein content after 1 h incubation at 2.8 or 16.7 mM glucose (n=6).

(e) Secreted insulin normalized to insulin content after 1 h stimulation with 2.8 or 16.7 mM glucose. Data from same samples as in **(f)** (n=6).

Data are mean $\pm$ SEM *p<0.05; ***p<0.001 using Student's t-test.



Supplementary Figure 4. Effects of Sox5 knockdown on insulin secretion pathways and characterization of SOX5 expression in human islets

The experiments were performed in INS-1 832/13 cells if not stated otherwise. Sox5-kd cells were transfected with Sox5 siRNA 48 h before the experiment, and control cells were transfected with negative control siRNA.

(a) The amplifying pathway of insulin secretion was assessed using 250 mM diazoxide to open the K_{ATP} channels and 30 mM K^+ to depolarize the cells at 2.8 or 30 mM glucose. Data show insulin secretion after 1 h incubation at the different conditions in Sox5-kd and control cells (n=3).

(b) Insulin secretion in Sox5-kd and control cells incubated at 16.7 mM glucose in the presence or absence of 100 nM Glp-1 or 1 mM clonidine as indicated. Data denote fold-change of insulin secretion relative to levels at 16.7 mM glucose (n=3).

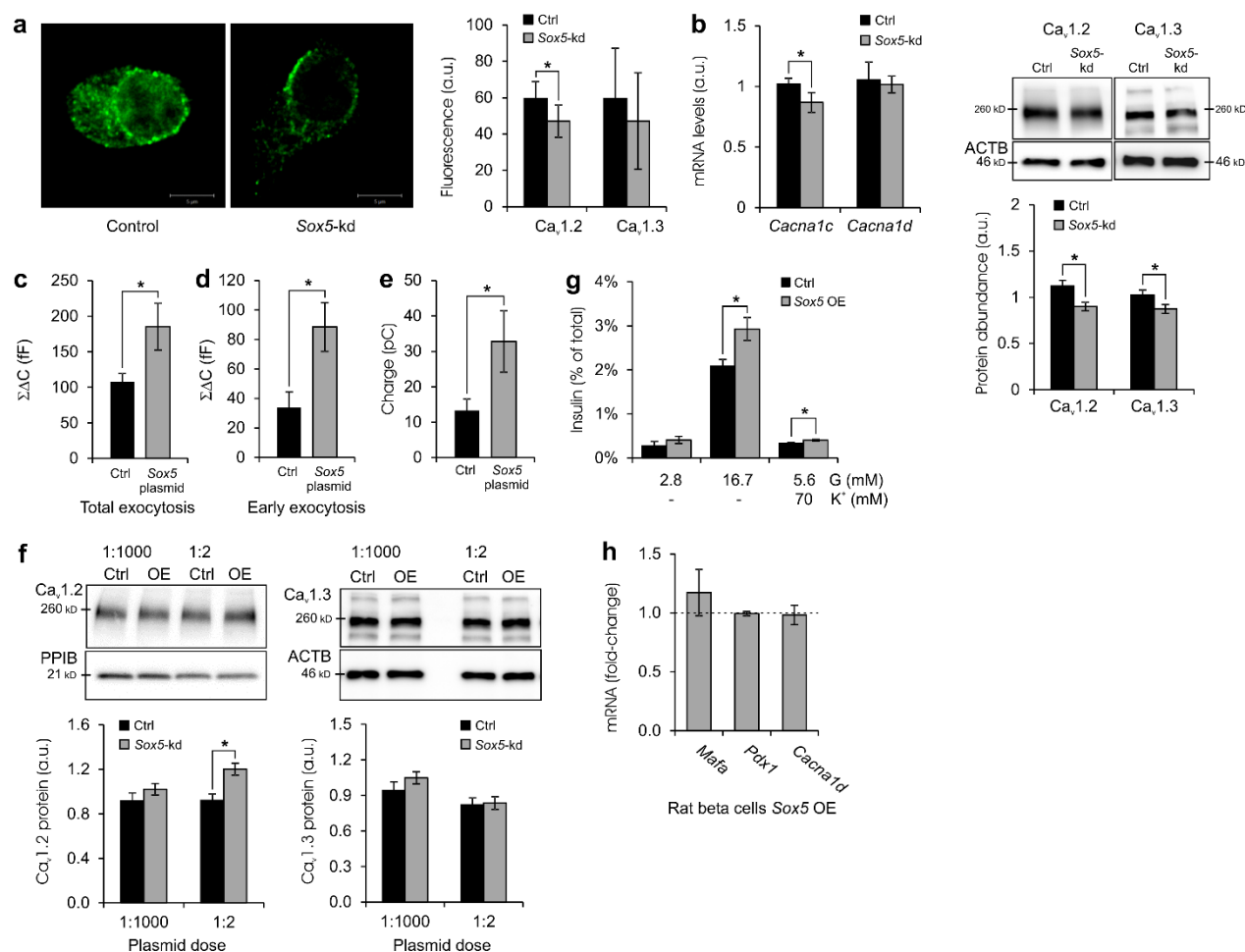
(c) Intracellular cAMP levels measured with the cAMP Biotrak Enzyme Immunoassay (EIA) System (GE Healthcare Life Sciences) after 1 h incubation at 16.7 mM glucose (n=3).

(d) Log2-transformed SOX5 mRNA levels plotted against the number of docked granules as surface density (Ns; granules mm⁻²) in human β -cells (n=5-9 cells per donor from 6 donors with T2D). A granule was defined as docked when the center of the granule was located within 150 nm from the plasma membrane.

(e) Log2-transformed SOX5 mRNA levels plotted against the number of docked glucagon granules measured as NL (granules μ m⁻¹) in human α -cells (n=1-13 cells per donor from 7 donors with T2D). No error bars are shown when less than 3 cells were analyzed per donor. A granule was defined as docked when the center of the granule was located within 150 nm from the plasma membrane.

(f) Whole-cell membrane conductance at 2.8 mM glucose in Sox5-kd and control cells (n=25-32 cells per group).

Data are mean $\pm$ SEM *p<0.05 using Student's t-test.



Supplementary Figure 5. Effects of knockdown and overexpression of Sox5 on calcium channels and exocytosis

(a) Representative image of immunostaining of $Ca_v1.2$ in *Sox5*-kd cells and control (ctrl) INS-1 832/13 cells. Bar graphs show average expression determined by immunostaining for $Ca_v1.2$ and $Ca_v1.3$ in *Sox5*-kd cells and control cells (n=3 with 28 cells per condition in each experiment). Scale bar=5 μ m.

(b) The bar graph to the left shows the mRNA levels of *Cacna1c* ($Ca_v1.2$) and *Cacna1d* ($Ca_v1.3$) in *Sox5*-kd and control INS-1 832/13 cells (n=4). To the right are representative immunoblots of total protein from *Sox5*-kd and control INS-1 832/13 cells. Polyclonal antibodies against $Ca_v1.2$, $Ca_v1.3$ and monoclonal antibody against β -actin (ACTB) were used as indicated. The graph shows average levels of $Ca_v1.2$ and $Ca_v1.3$ normalized to beta-actin in *Sox5*-kd and control cells (n=5-6).

(c) Total capacitance increase ($\Sigma\Delta C$) ('total exocytosis') evoked by a train of ten 500 ms depolarizations from -70 to 0 mV applied to control INS-1 832/13 cells (n=17) and cells overexpressing *Sox5* (n=14 cells).

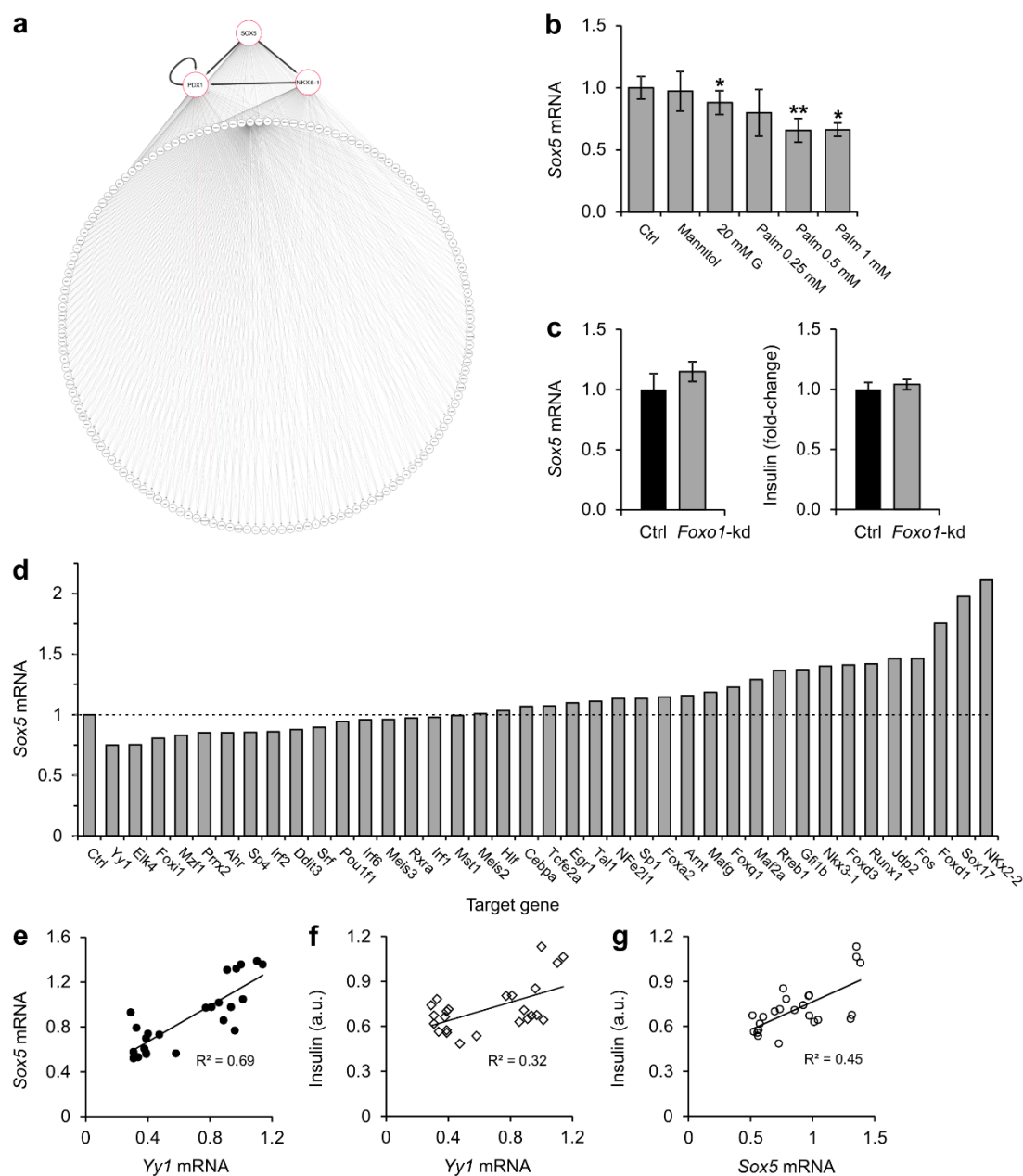
(d) Capacitance increase ($\Sigma\Delta C$) in response to the first two depolarizations of the train ('early exocytosis'). Data are from the same cells as in (c).

(e) The integrated Ca^{2+} -current (charge) in the same cells as in (c)

(f) Representative immunoblots show $\text{Ca}_v1.2$ and $\text{Ca}_v1.3$ protein levels in control and Sox5-overexpressing cells (OE). The bars denote average protein levels of $\text{Ca}_v1.2$ and $\text{Ca}_v1.3$ normalized to cyclophilin B (PPIB) or beta-actin (ACTB) (n=5).

(g) mRNA expression of three genes in the β -cell fraction of sorted dispersed cells from Wistar rat islets after Sox5 overexpression (OE) with lentivirus relative to islets transduced with control virus (n=3).

(h) Insulin secretion (as percent of total insulin content) from batch-incubated Wistar rat islets after Sox5 overexpression with lentivirus relative to islets transduced with control virus. Insulin secretion was performed 72 h after transduction. Islets were incubated for 1 h with glucose (G) and for 15 min with K^+ as indicated (n=11 tubes per condition from 2 independent experiments). Data are mean $\pm$ SEM *p<0.05 using Student's t-test.



Supplementary Figure 6. Characterization of the regulation of Sox5

(a) The figure depicts a regulatory network generated by connecting *SOX5*, *PDX1* and *NKX6.1* to open chromatin genes with motifs (in their promoter regions) for these three transcription factors. *SOX5*, *PDX1* and *NKX6.1* were significantly enriched for putative binding sites to the 168 open chromatin genes. Sox5 has predicted binding sites to 133 of the genes. Sox5 also has predicted binding sites to the promoter regions of *PDX1* and *NKX6.1*, and is thereby connected with 150 of the 168 genes in this regulatory network model.

(b) Sox5 mRNA levels in INS-1 832/13 cells after 48 h incubation with 20 mM glucose (G), 20 mM mannitol and 0.25, 0.5 or 1 mM palmitate (palm). Data are normalized to the expression in non-treated cells (n=3).

(c) *Sox5* mRNA levels (left) and insulin secretion in response to 1 h stimulation at 16.7 mM glucose (right) in INS-1 832/13 cells treated with siRNA against *Foxo1* (*Foxo1*-kd) or negative control siRNA (Ctrl). Data are normalized to control (n=7).

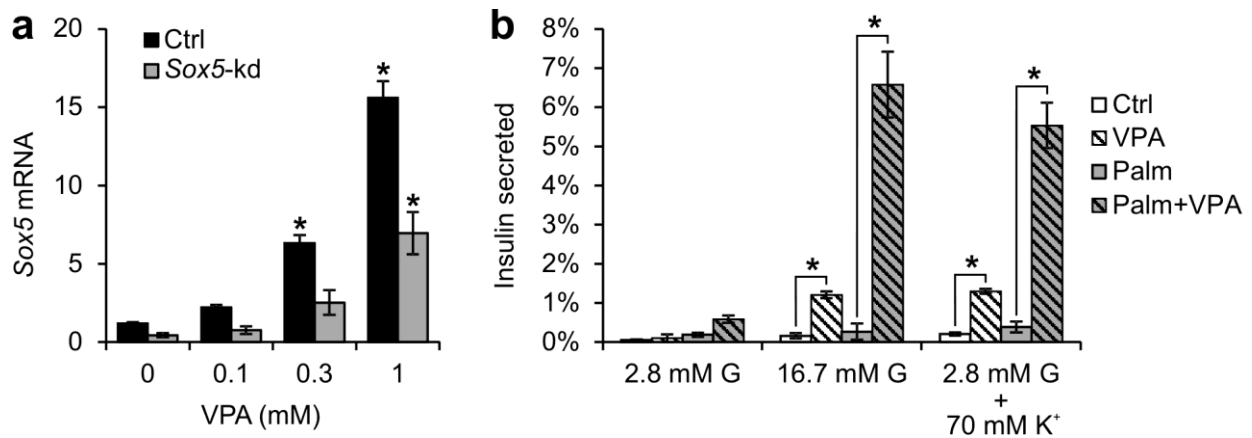
(d) *Sox5* mRNA levels after transfection with siRNA targeting each of the 39 putative regulators of *Sox5* expression. Data are from triplicate measurements in one experiment.

(e) *Yy1* mRNA levels plotted against *Sox5* mRNA levels in *Yy1*-kd cells and control cells treated with 0, 0.25, 0.5 or 1 mM palmitate (graph shows pooled data from the different conditions; n=3).

(f) *Yy1* mRNA levels plotted against insulin secretion at 16.7 mM glucose. Data are from the same experiments as in **(e)**.

(g) *Sox5* mRNA levels plotted against insulin secretion at 16.7 mM glucose. Data as in **(e)**.

Data are mean $\pm$ SEM *p<0.05; **p<0.01 using Student's t-test.

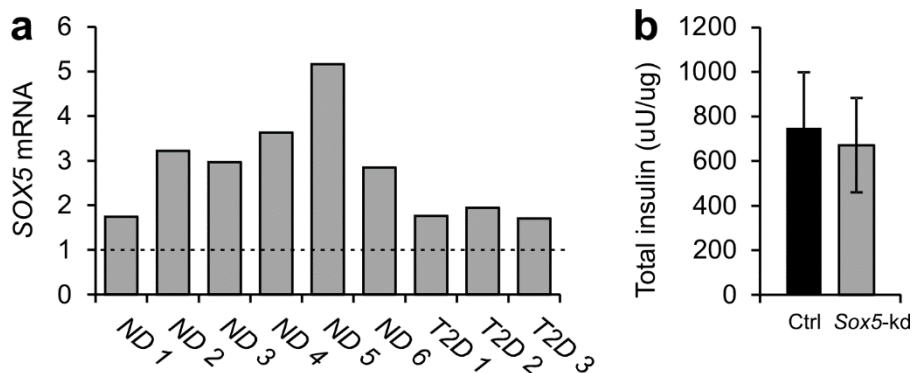


Supplementary Figure 7. Effect of valproic acid on Sox5 expression and insulin secretion

(a) Sox5 mRNA levels in Sox5-kd and control cells (Ctrl) in response to valproic acid (VPA) at the doses indicated. Sox5 levels in the presence of VPA relative to non-VPA-treated cells were used for statistical comparisons (n=4).

(b) Insulin secretion (as percent of total insulin) in islets from C57BL/6 male mice cultured with 1 mM VPA at 5 mM glucose with or without 1 mM palmitate for 72 h before measurements. Insulin secretion was measured after 1-h incubation with 2.8 and 16.7 mM glucose and after 15 min incubation with [2.8 mM glucose + 70 mM K⁺] (n=3).

Data are mean $\pm$ SEM *p<0.05 using Student's t-test.



Supplementary Figure 8. SOX5 overexpression in human islets

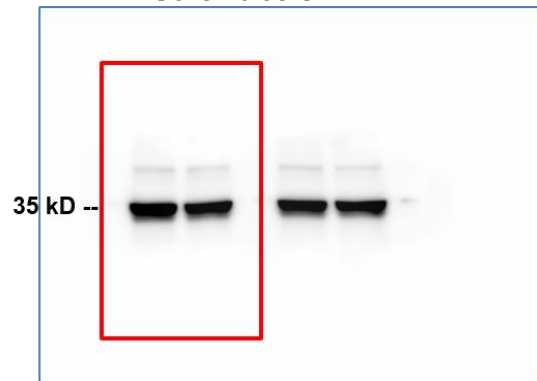
(a) SOX5 overexpression in human islets after lentiviral transduction relative to islets transduced with control virus. Islets are from 6 non-diabetic donors (ND) and 3 diabetic donors (T2D).

(b) Insulin content of human islets with SOX5 overexpression after lentiviral transduction relative to islets transduced with control virus (n=9 donors).

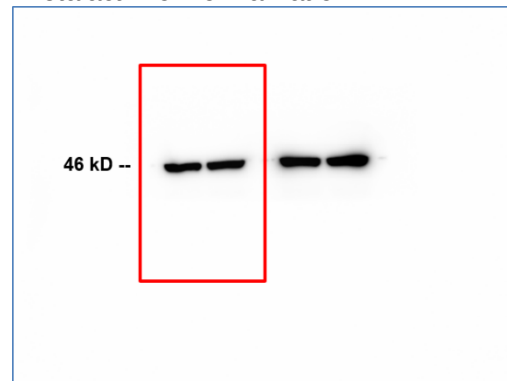
Data are mean $\pm$ SEM

a

MAFA in Sox5-kd cells

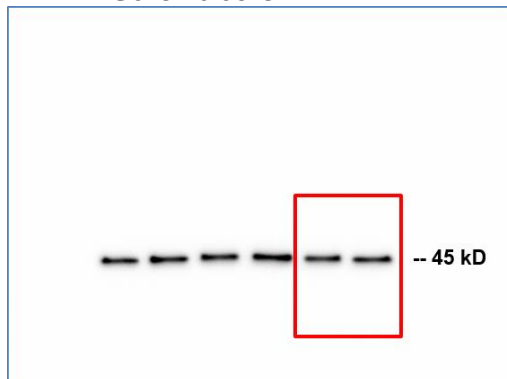


Beta actin for normalization



b

PDX1 in Sox5-kd cells

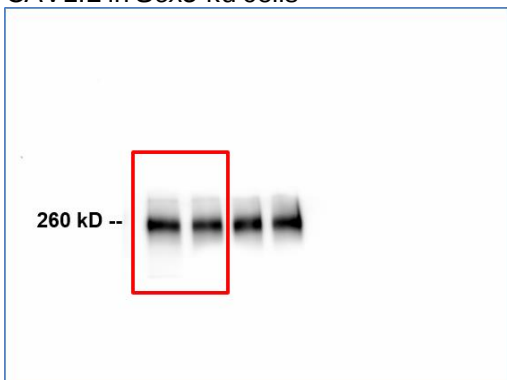


Beta actin for normalization

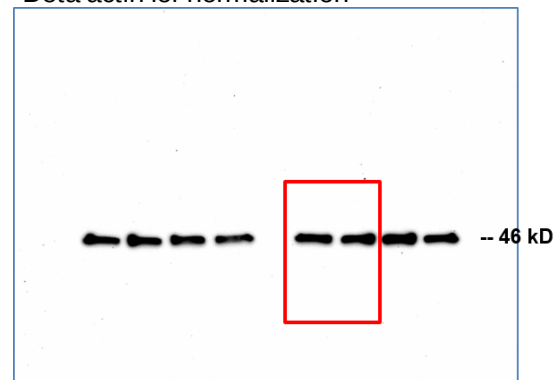


c

CAV1.2 in Sox5-kd cells

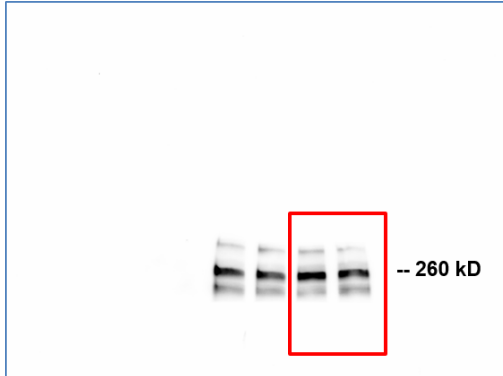


Beta actin for normalization

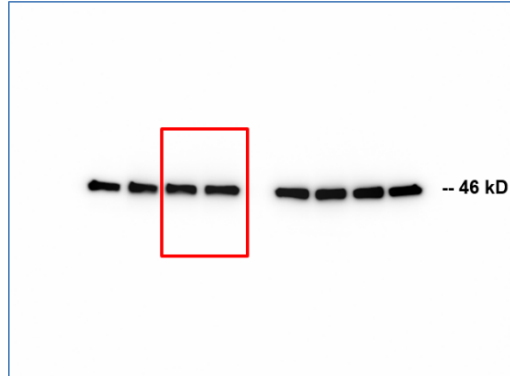


d

CAV1.3 in Sox5-kd cells



Beta actin for normalization

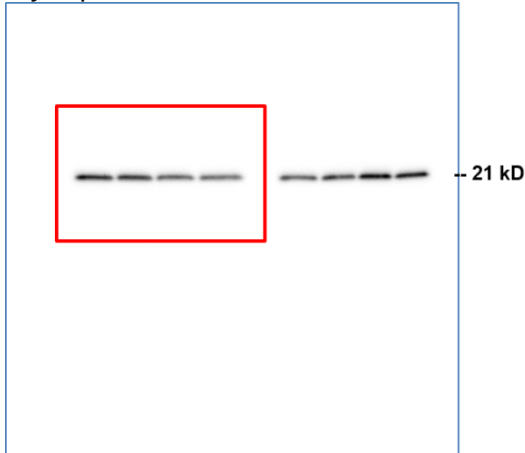


e

CAV1.2 in Sox5-overexpressing cells

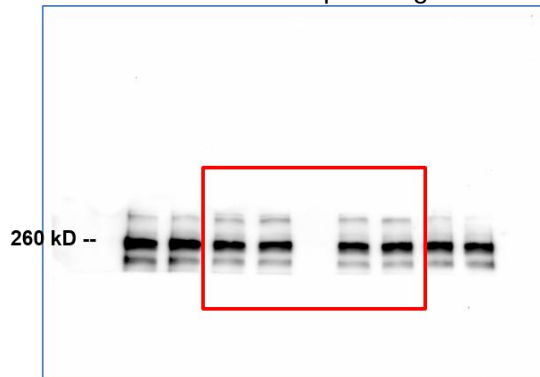


Cyclophilin B for normalization



f

CAV1.3 in Sox5-overexpressing cells



Beta actin for normalization



Supplementary Figure 9. Full pictures of protein blots displayed in Supplemental Figures
Protein blots from which the red boxes correspond, with similar band order, to Supplemental Figure 3b (a-b), Supplemental Figure 5b (c-d), and Supplemental Figure 5f (e-f).
(a) MAFA (left) and beta actin for normalization (right) in control and INS-1 832/13 cells with Sox5-kd.

- (b)** PDX1 (left) and beta actin for normalization (right) in control and INS-1 832/13 cells with Sox5-kd.
- (c)** CAV1.2 (left) and beta actin for normalization (right) in control and INS-1 832/13 cells with Sox5-kd.
- (d)** CAV1.3 (left) and beta actin for normalization (right) in control and INS-1 832/13 cells with Sox5-kd.
- (e)** CAV1.2 (left) and cyclophilin B for normalization (right) in control and INS-1 832/13 cells overexpressing Sox5.
- (f)** CAV1.3 (left) and beta actin for normalization (right) in control and INS-1 832/13 cells overexpressing Sox5.

Supplementary Table 1. Characteristics of human islet donors

	All (n=64)	Non-diabetic (n=45)	T2D (n=19)
Age (years)	57 ± 10	56 ± 11	59 ± 9
Sex (female / male)	33 / 31	23 / 22	10 / 9
BMI (kg m ⁻²)	26.2 ± 3.8	25.2 ± 2.9	28.7 ± 4.6
Purity (%)	66±18	69±17	61±20
Number of donors from which HbA1c was available	52	34	18
Number of donors from which insulin secretion measurements were conducted	48	32	16

Data are presented as mean ± s.d.

Supplementary Table 2. Analysis of network properties

β	R^2	mean k	max k
1	0.00904	4820	7990
2	0.351	1290	3160
3	0.630	448	1660
4	0.750	185	1020
5	0.811	86.9	685
6	0.834	45.0	488
7	0.851	25.2	363
8	0.876	15.1	279
9	0.868	9.50	220
10	0.878	6.26	177
11	0.887	4.28	144
12	0.902	3.03	119

Values of β from 1 to 12 were used to generate the adjacency matrix $a_{i,j} = |\text{cor}(x_i, x_j)|^\beta$, where x_i represents the expression vector for gene i across the 64 samples. The degree k denotes the connectivity of a gene. A linear relation between the logarithm of k and the logarithm of the degree distribution $p(k)$ implies that the network has scale-free topology. R^2 denotes the scale-free fit index. To obtain a network with approximately scale-free topology ($R^2 > 0.8$) and yet high connectivity, $\beta=5$ was used for subsequent analyses.

Supplementary Table 3. Association of module eigengenes with phenotype traits

Module	No of genes	T2D (n=64)		HbA1c (n=52)		GSIS (n=48)		KSIS (n=26)	
		p-value	beta	p-value	beta	p-value	beta	p-value	beta
1	4328	0.58	0.04	0.77	-0.049	0.22	-0.17	0.33	-0.12
2	3148	0.013	-0.32	0.0025	-0.39	0.0059	0.37	0.048	0.41
3	1474	0.53	-0.032	0.94	-0.035	0.73	-0.13	0.27	-0.31
4	1223	0.52	0.06	0.93	0.043	0.64	0.039	0.94	-0.13
5	1116	0.52	0.079	0.16	0.25	0.34	-0.14	0.79	-0.019
6	815	0.011	0.3	0.031	0.32	0.1	-0.24	0.32	-0.4
7	806	0.39	0.071	0.57	-0.036	0.12	-0.2	0.25	-0.22
8	714	0.16	0.22	0.087	0.21	0.46	-0.2	0.32	-0.092
9	702	0.014	-0.3	0.0097	-0.33	0.0087	0.33	0.11	0.38
10	649	0.4	-0.11	0.35	-0.15	0.2	0.21	0.24	0.18
11	598	0.034	-0.25	0.0088	-0.34	0.0031	0.36	0.089	0.38
12	424	0.037	-0.26	0.026	-0.25	0.018	0.33	0.058	0.38
13	380	0.56	0.15	0.54	0.17	0.65	-0.1	0.64	-0.14
14	358	0.00055	0.39	0.0041	0.38	0.033	-0.25	0.22	-0.43
15	347	0.18	-0.088	0.33	-0.063	0.61	0.087	0.99	-0.12
16	209	0.48	0.038	0.16	0.1	0.69	-0.014	0.92	0.033
17	203	0.07	-0.23	0.24	-0.099	0.063	0.22	0.1	0.4
18	198	0.67	0.12	0.69	0.069	0.69	-0.032	0.83	-0.054
19	196	0.0064	0.32	0.002	0.41	0.0061	-0.35	0.19	-0.34
20	196	0.43	0.14	0.89	0.087	0.27	0.19	0.086	0.18
21	188	0.53	-0.088	0.6	-0.097	0.1	0.21	0.34	0.21
22	159	0.12	-0.19	0.48	-0.019	0.3	0.16	0.35	0.28
23	152	0.17	0.19	0.13	0.29	0.97	-0.072	0.073	0.061
24	151	0.13	-0.18	0.23	-0.18	0.4	0.17	0.62	0.05
25	143	0.77	0.094	0.27	0.19	0.35	-0.13	0.24	-0.28
26	140	0.024	0.23	0.06	0.21	0.15	-0.12	0.33	-0.27
27	125	0.056	-0.21	0.42	-0.12	0.48	0.05	0.46	0.23
28	120	0.043	-0.26	0.31	-0.15	0.36	0.081	0.68	0.087
29	115	0.89	0.025	0.96	0.032	0.075	0.2	0.19	0.23
30	112	0.7	0.00093	0.5	-0.079	0.44	0.19	0.077	0.21
31	95	0.04	0.27	0.13	0.26	0.82	-0.1	0.97	-0.043
32	70	0.75	0.071	0.26	0.23	0.38	-0.099	0.62	-0.067
33	65	0.31	0.094	0.011	0.21	0.41	-0.051	0.83	0.0038
34	64	0.57	0.11	0.2	0.21	0.87	-0.06	0.97	-0.071
35	64	0.013	-0.31	0.024	-0.3	0.011	0.29	0.36	0.33
36	64	0.31	-0.14	0.59	-0.081	0.44	0.075	0.38	0.29
37	58	0.38	-0.16	0.65	-0.048	0.4	0.13	0.39	0.27
38	51	0.15	-0.13	0.037	-0.18	0.0043	0.31	0.089	0.33
39	50	0.43	-0.079	0.55	-0.2	0.34	-0.17	0.11	-0.34

40	50	0.56	0.11	0.54	0.18	0.32	0.15	0.22	0.29
41	44	0.69	-0.0083	0.75	0.011	0.22	0.16	0.95	-0.013
42	43	0.1	0.22	0.66	0.14	0.17	0.024	0.96	0.084
43	40	0.3	-0.12	0.47	-0.19	0.2	-0.24	0.077	-0.44
44	38	0.42	0.068	0.89	0.037	0.75	0.046	0.47	0.13
45	35	0.59	0.044	0.86	-0.02	0.91	-0.055	0.95	0.13
46	32	0.52	-0.04	0.11	-0.087	0.7	0.014	0.99	-0.17
47	31	0.18	0.16	0.41	0.23	0.97	0.034	0.15	0.24
48	30	0.2	0.095	0.15	0.076	0.65	-0.14	0.95	0.022
49	26	0.53	-0.027	0.72	0.14	0.03	0.25	0.43	0.29
50	24	0.8	0.012	0.8	-0.065	0.056	-0.24	0.91	-0.034
51	24	0.71	0.012	0.66	-0.022	0.9	0.041	0.92	-0.12
52	21	0.54	-0.092	0.12	-0.36	0.99	-0.045	0.056	-0.35
53	20	0.083	-0.18	0.0093	-0.3	0.019	0.3	0.17	0.2
54	17	0.55	0.064	0.48	0.17	0.16	0.094	0.92	-0.068
55	17	0.82	0.0065	0.55	0.2	0.076	0.21	0.24	0.2
56	16	0.38	0.13	0.64	0.16	0.19	0.18	0.28	0.24

The module eigengene denotes the 1st principal component of the expression matrix of the module genes across the 64 samples. For each module eigengene we analyzed the association with T2D status, HbA1c, glucose-stimulated insulin secretion (GSIS) and K⁺-stimulated insulin secretion (KSIS). The T2D-associated module is indicated in boldface. P-values shown in the table are not corrected for multiple testing.

Supplementary Table 4. Module genes with islet-selective open chromatin

Gene symbol	Fold-change in T2D	Connectivity (k_{in})
<i>ABCC9</i>	-1.13	225
<i>ABHD10</i>	-1.19	345
<i>ACVR1C</i>	-1.28	293
<i>ADAMTS2</i>	-1.13	128
<i>AGBL4</i>	-1.10	92
<i>ANKS1B</i>	-1.04	137
<i>ATRNL1</i>	-1.27	330
<i>BARX2</i>	1.12	150
<i>BMP5</i>	-1.24	172
<i>C1orf158</i>	1.01	15
<i>C1orf168</i>	-1.01	90
<i>C3orf14</i>	-1.11	222
<i>C9orf150</i>	1.03	77
<i>CACNA1H</i>	-1.11	92
<i>CACNA2D1</i>	-1.23	364
<i>CACNB2</i>	-1.14	278
<i>CADM1</i>	-1.14	380
<i>CADPS</i>	-1.21	316
<i>CERKL</i>	-1.13	403
<i>CHODL</i>	-1.10	61
<i>CNTN1</i>	-1.19	498
<i>CNTN4</i>	-1.33	245
<i>CPE</i>	-1.16	474
<i>D4S234E</i>	-1.26	314
<i>DACH1</i>	-1.16	459
<i>DCX</i>	-1.13	200
<i>DGKB</i>	-1.05	51
<i>DIRAS2</i>	-1.15	118
<i>DSCAM</i>	-1.01	45
<i>DZIP3</i>	-1.21	364
<i>ELAVL4</i>	-1.29	420
<i>ELP4</i>	-1.20	213
<i>EML5</i>	-1.17	155
<i>ENAM</i>	-1.11	174
<i>FAM123C</i>	-1.06	85
<i>FAM135A</i>	-1.15	50
<i>FAM135B</i>	-1.06	247
<i>FAM148A</i>	-1.14	20
<i>FAM19A4</i>	-1.17	81
<i>FAM84A</i>	-1.03	27

<i>FBXW7</i>	-1.07	105
<i>FGF14</i>	-1.19	475
<i>FLJ25770</i>	-1.17	148
<i>FOXC1</i>	1.03	69
<i>FOXP2</i>	-1.06	180
<i>G6PC2</i>	-1.31	263
<i>GABRA1</i>	-1.19	19
<i>GABRB3</i>	-1.13	431
<i>GABRG2</i>	-1.25	209
<i>GAD2</i>	-1.19	283
<i>GDAP1</i>	-1.17	338
<i>GLP1R</i>	-1.35	262
<i>GNAI1</i>	-1.10	394
<i>GPM6A</i>	-1.30	99
<i>GPR27</i>	-1.05	76
<i>GRIA2</i>	-1.24	288
<i>GRIA4</i>	-1.30	152
<i>GRIK2</i>	-1.10	286
<i>HMGCLL1</i>	-1.22	377
<i>HS6ST3</i>	-1.18	330
<i>IAPP</i>	-1.38	68
<i>IGSF11</i>	-1.14	246
<i>ISL1</i>	-1.19	223
<i>JAKMIP2</i>	-1.14	382
<i>KBTBD7</i>	-1.19	241
<i>KCNB2</i>	-1.21	327
<i>KCNK16</i>	-1.23	226
<i>KCNMA1</i>	-1.18	415
<i>KIAA0774</i>	-1.19	249
<i>KIAA1257</i>	-1.04	83
<i>KIAA1383</i>	-1.03	37
<i>KIAA1486</i>	-1.07	56
<i>KIAA1804</i>	1.08	102
<i>KL</i>	-1.13	360
<i>KLHL1</i>	-1.18	43
<i>LIG4</i>	-1.08	140
<i>LIMCH1</i>	-1.11	255
<i>LRRTM3</i>	-1.33	249
<i>LSAMP</i>	1.01	62
<i>MAGI2</i>	-1.16	335
<i>MAP9</i>	-1.04	171
<i>MAPK10</i>	-1.15	367
<i>MCTP2</i>	-1.11	41

<i>MEIS2</i>	-1.22	309
<i>MEIS3</i>	-1.02	28
<i>MMP16</i>	-1.02	57
<i>MS4A8B</i>	-1.17	89
<i>MYO3A</i>	-1.16	269
<i>NALCN</i>	-1.19	443
<i>NBEA</i>	-1.19	272
<i>NECAB2</i>	-1.01	89
<i>NEGR1</i>	1.02	156
<i>NEUROD1</i>	-1.22	382
<i>NKX6-1</i>	-1.27	283
<i>NMNAT3</i>	-1.05	118
<i>NOL4</i>	-1.24	482
<i>NR3C2</i>	-1.11	94
<i>NRXN1</i>	-1.15	473
<i>ODZ3</i>	-1.08	256
<i>OXGR1</i>	-1.10	161
<i>PAM</i>	-1.19	411
<i>PAPPA2</i>	-1.10	88
<i>PAX6</i>	-1.20	337
<i>PCDH17</i>	-1.13	349
<i>PCDH20</i>	-1.12	74
<i>PCDHAC1</i>	-1.06	269
<i>PCLO</i>	-1.22	300
<i>PCP4</i>	-1.21	81
<i>PDK4</i>	-1.04	131
<i>PDX1</i>	-1.21	129
<i>PDZRN3</i>	-1.09	295
<i>PGR</i>	-1.12	355
<i>PRKACB</i>	-1.14	345
<i>PRUNE2</i>	-1.08	43
<i>PVRL3</i>	-1.21	277
<i>RAB3C</i>	-1.17	311
<i>RALYL</i>	-1.08	70
<i>RASEF</i>	1.27	373
<i>RGS17</i>	-1.16	108
<i>RGS4</i>	-1.10	202
<i>RIMBP2</i>	-1.23	360
<i>RIMS2</i>	-1.18	342
<i>RNF150</i>	-1.08	245
<i>RNF180</i>	-1.12	250
<i>ROBO2</i>	-1.35	300
<i>ROR1</i>	-1.07	111

<i>RORB</i>	-1.12	222
<i>RTN1</i>	-1.15	426
<i>SCG2</i>	-1.17	372
<i>SCGB2A1</i>	-1.07	42
<i>SDK1</i>	-1.02	143
<i>SERPINI2</i>	1.08	72
<i>SGCB</i>	-1.08	216
<i>SGCZ</i>	-1.03	58
<i>SIM1</i>	-1.16	279
<i>SLC17A6</i>	-1.26	176
<i>SLC18A2</i>	-1.21	61
<i>SLC30A8</i>	-1.20	259
<i>SLC35F4</i>	-1.12	90
<i>SLC5A1</i>	-1.07	62
<i>SLC5A8</i>	-1.03	39
<i>SLC7A2</i>	-1.08	195
<i>SLCO1A2</i>	-1.22	80
<i>SNAP91</i>	-1.24	455
<i>SOX6</i>	-1.14	125
<i>SPATA7</i>	-1.12	100
<i>SPTB</i>	-1.10	260
<i>ST18</i>	-1.27	345
<i>ST6GALNAC5</i>	-1.23	286
<i>ST8SIA3</i>	-1.12	395
<i>STXBP5L</i>	-1.25	380
<i>SULT4A1</i>	-1.14	131
<i>SYT14</i>	-1.27	431
<i>SYT4</i>	-1.24	459
<i>TMEM132B</i>	-1.19	58
<i>TMEM132D</i>	-1.09	242
<i>TMEM196</i>	-1.21	516
<i>TMEM61</i>	-1.07	161
<i>TMEM63C</i>	-1.24	490
<i>TRPM3</i>	-1.24	338
<i>TSC22D1</i>	-1.05	106
<i>TSHZ3</i>	-1.10	84
<i>TSPYL5</i>	-1.11	276
<i>TTC8</i>	-1.16	450
<i>UNC5D</i>	-1.17	47
<i>ZNF223</i>	-1.09	80
<i>ZNF585B</i>	-1.10	217
<i>ZSCAN18</i>	-1.06	99

Fold-change denotes mRNA expression in T2D donors vs. non-diabetic donors.

Supplementary Table 5. Characteristics of human islet donors in replication set

	All (n=59)	Non-diabetic (n=37)	T2D (n=22)
Age (years)	61 ± 10	64 ± 7	60 ± 12
Sex (female / male)	23 / 36	17 / 20	6 / 16
BMI (kg m ⁻²)	26.8 ± 3.8	26.4 ± 3.7	27.4 ± 3.9
Purity (%)	72 ± 18	72 ± 17	72 ± 21
Number of donors from which HbA1c was available	57	35	22

Data are presented as mean ± s.d. No insulin secretion data were available from the replication set.

Supplementary Table 6. Analysis of network properties in replication set

b	R ²	mean <i>k</i>	max <i>k</i>
1	0.089	2030	3233
2	0.192	653	1510
3	0.459	266	838
4	0.601	126	516
5	0.682	66	340
6	0.730	38	235
7	0.756	23	169
8	0.800	14	126
9	0.803	9	96
10	0.767	6	74
11	0.817	4	58
12	0.834	3	47

Values of *b* from 1 to 12 were used to generate the adjacency matrix $a_{i,j} = |\text{cor}(x_i, x_j)|^b$, where x_i represents the expression vector for gene *i* across the 59 samples in the replication set. The degree *k* denotes the connectivity of a gene. A linear relation between the logarithm of *k* and the logarithm of the degree distribution $p(k)$ implies that the network has scale-free topology. R^2 denotes the scale-free fit index. To obtain a network with approximately scale-free topology ($R^2 > 0.8$) and yet high connectivity, *b*=8 was used for subsequent analyses.

Supplementary Table 7. Module genes with islet-selective open chromatin in replication set

Gene Symbol	Fold- change in T2D
<i>ABCC9</i>	-1.13
<i>ABHD10</i>	-1.10
<i>ACVR1C</i>	-1.28
<i>AGBL4</i>	-1.08
<i>ANKS1B</i>	-1.06
<i>ATRNL1</i>	-1.10
<i>BARX2</i>	1.04
<i>BMP5</i>	-1.01
<i>C1orf158</i>	-1.08
<i>C1orf168</i>	1.00
<i>C3orf14</i>	-1.13
<i>CACNA1H</i>	-1.02
<i>CACNA2D1</i>	-1.09
<i>CACNB2</i>	-1.03
<i>CADM1</i>	-1.03
<i>CADPS</i>	-1.15
<i>CERKL</i>	-1.08
<i>CHODL</i>	-1.12
<i>CNTN1</i>	-1.13
<i>CNTN4</i>	-1.27
<i>CPE</i>	-1.05
<i>DACH1</i>	-1.06
<i>DCX</i>	-1.13
<i>DGKB</i>	1.06
<i>DIRAS2</i>	-1.14
<i>DSCAM</i>	-1.04
<i>DZIP3</i>	-1.11
<i>ELAVL4</i>	-1.07
<i>ELP4</i>	-1.10
<i>EML5</i>	-1.07
<i>ENAM</i>	-1.10
<i>FAM123C</i>	-1.01
<i>FAM135A</i>	-1.10
<i>FAM135B</i>	1.04
<i>FAM19A4</i>	-1.11
<i>FAM84A</i>	-1.16
<i>FBXW7</i>	-1.07
<i>FGF14</i>	-1.06
<i>FOXC1</i>	1.08

<i>FOXP2</i>	-1.06
<i>G6PC2</i>	-1.16
<i>GABRA1</i>	-1.31
<i>GABRB3</i>	-1.14
<i>GABRG2</i>	-1.38
<i>GAD2</i>	-1.04
<i>GDAP1</i>	-1.13
<i>GLP1R</i>	-1.15
<i>GNAI1</i>	-1.01
<i>GPM6A</i>	-1.11
<i>GRIA2</i>	-1.11
<i>GRIA4</i>	-1.05
<i>GRIK2</i>	-1.21
<i>HMGCLL1</i>	-1.12
<i>HS6ST3</i>	-1.15
<i>IAPP</i>	-1.13
<i>IGSF11</i>	-1.05
<i>ISL1</i>	-1.24
<i>JAKMIP2</i>	1.03
<i>KBTD7</i>	-1.22
<i>KCNB2</i>	-1.15
<i>KCNK16</i>	-1.11
<i>KCNMA1</i>	-1.11
<i>KIAA1383</i>	-1.01
<i>KL</i>	-1.16
<i>KLHL1</i>	-1.30
<i>LIG4</i>	-1.05
<i>LIMCH1</i>	-1.03
<i>LRRTM3</i>	-1.20
<i>LSAMP</i>	1.08
<i>MAGI2</i>	-1.14
<i>MAP9</i>	-1.04
<i>MAPK10</i>	-1.07
<i>MCTP2</i>	-1.09
<i>MEIS2</i>	-1.12
<i>MEIS3</i>	-1.02
<i>MMP16</i>	-1.21
<i>MS4A8B</i>	-1.22
<i>MYO3A</i>	-1.03
<i>NALCN</i>	-1.05
<i>NBEA</i>	-1.11
<i>NECAB2</i>	1.04
<i>NEGR1</i>	1.00

<i>NEUROD1</i>	-1.16
<i>NKX6-1</i>	-1.05
<i>NMNAT3</i>	-1.14
<i>NOL4</i>	-1.16
<i>NR3C2</i>	-1.00
<i>NRXN1</i>	-1.10
<i>ODZ3</i>	-1.07
<i>OXGR1</i>	-1.03
<i>PAM</i>	-1.06
<i>PAPPA2</i>	1.07
<i>PAX6</i>	-1.13
<i>PCDH17</i>	-1.07
<i>PCDH20</i>	-1.35
<i>PCDHAC1</i>	-1.02
<i>PCLO</i>	-1.06
<i>PCP4</i>	-1.16
<i>PDX1</i>	-1.22
<i>PDZRN3</i>	-1.07
<i>PGR</i>	-1.10
<i>PRKACB</i>	-1.10
<i>PRUNE2</i>	-1.06
<i>PVRL3</i>	-1.05
<i>RAB3C</i>	-1.22
<i>RALYL</i>	-1.18
<i>RIMBP2</i>	-1.16
<i>RIMS2</i>	-1.10
<i>RNF150</i>	-1.05
<i>RNF180</i>	-1.02
<i>ROBO2</i>	-1.16
<i>ROR1</i>	1.01
<i>RORB</i>	-1.12
<i>RTN1</i>	-1.11
<i>SCG2</i>	-1.04
<i>SCGB2A1</i>	1.05
<i>SDK1</i>	-1.04
<i>SGCB</i>	-1.07
<i>SGCZ</i>	-1.08
<i>SIM1</i>	-1.12
<i>SLC17A6</i>	1.01
<i>SLC18A2</i>	1.13
<i>SLC30A8</i>	-1.14
<i>SLC35F4</i>	-1.21
<i>SLC5A1</i>	-1.08

<i>SLC7A2</i>	-1.13
<i>SLCO1A2</i>	1.01
<i>SOX6</i>	-1.11
<i>SPATA7</i>	-1.10
<i>SPTB</i>	1.01
<i>ST18</i>	-1.19
<i>ST6GALNAC5</i>	-1.17
<i>ST8SIA3</i>	-1.02
<i>STXBP5L</i>	-1.16
<i>SULT4A1</i>	-1.00
<i>SYT14</i>	-1.15
<i>SYT4</i>	-1.11
<i>TMEM132B</i>	-1.13
<i>TMEM132D</i>	-1.11
<i>TMEM196</i>	-1.10
<i>TMEM61</i>	-1.07
<i>TMEM63C</i>	-1.11
<i>TRPM3</i>	-1.14
<i>TSC22D1</i>	-1.05
<i>TSHZ3</i>	-1.04
<i>TSPYL5</i>	-1.14
<i>TTC8</i>	-1.07
<i>UNC5D</i>	-1.15
<i>ZNF585B</i>	-1.06
<i>ZSCAN18</i>	-1.06

Fold-change denotes mRNA expression in T2D donors vs. non-diabetic donors.

Supplementary Table 8. SNPs associated with module eigengenes

SNP id	Nearest gene	Associated trait	P value
rs4406574	<i>SMARCA1</i>	Eigengene T2D module	1.42E-04
rs5975111	<i>SMARCA1</i>	Eigengene T2D module	1.99E-04
rs5932625	<i>SMARCA1</i>	Eigengene T2D module	1.42E-04
rs11796659	<i>SMARCA1</i>	Eigengene T2D module	1.99E-04
rs5932624	<i>SMARCA1</i>	Eigengene T2D module	2.19E-04
rs5977087	<i>SMARCA1</i>	Eigengene T2D module	1.99E-04
rs1408301	<i>SMARCA1</i>	Eigengene T2D module	1.99E-04
rs10505917	<i>SOX5</i>	Eigengene T2D module	1.28E-03
rs7314161	<i>SOX5</i>	Eigengene T2D module	1.19E-03
rs11047351	<i>SOX5</i>	Eigengene 168 genes	1.67E-03
rs17498948	<i>SOX5</i>	Eigengene 168 genes	1.67E-03
rs4569092	<i>SOX5</i>	Eigengene 168 genes	1.15E-03
rs4963749	<i>SOX5</i>	Eigengene 168 genes	1.67E-03

Associations between donor genotype (n=64 donors) and the eigengenes of the T2D-related module and the 168 open chromatin genes, respectively, were analyzed by linear regression using age, sex and BMI as covariates. The nearest genes to each SNP and the p-values from the linear regression are shown.

Supplementary Table 9. Direction of change of signature genes in INS-1 832/13 cells with Sox5 knockdown or Sox5 overexpression

Sox5-kd:	Same as in T2D	Same as in T2D	No change	No change
Sox5 OE:	Opposite to T2D (n=50)	No change (n=28)	Opposite to T2D (n=37)	No change (n=24)
	<i>ABCC9</i>	<i>ABHD10</i>	<i>ACVR1C</i>	<i>CHODL</i>
	<i>ADAMTS2</i>	<i>AGBL4</i>	<i>CACNB2</i>	<i>DIRAS2</i>
	<i>BARX2</i>	<i>ANKS1B</i>	<i>CADM1</i>	<i>DSCAM</i>
	<i>BMP5</i>	<i>ATRNL1</i>	<i>CNTN1</i>	<i>FOXC1</i>
	<i>CACNA1H</i>	<i>DCX</i>	<i>CPE</i>	<i>MAGI2</i>
	<i>CACNA2D1</i>	<i>DGKB</i>	<i>EML5</i>	<i>MAPK10</i>
	<i>CADPS</i>	<i>ELAVL4</i>	<i>FAM135B</i>	<i>MEIS3</i>
	<i>CNTN4</i>	<i>FAM19A4</i>	<i>GABRA1</i>	<i>MMP16</i>
	<i>DZIP3</i>	<i>FGF14</i>	<i>GAD2</i>	<i>MYO3A</i>
	<i>ENAM</i>	<i>GABRB3</i>	<i>GLP1R</i>	<i>NECAB2</i>
	<i>FAM135A</i>	<i>GRIK2</i>	<i>GNAI1</i>	<i>NEGR1</i>
	<i>FAM84A</i>	<i>JAKMIP2</i>	<i>GPM6A</i>	<i>NKX6-1</i>
	<i>FOXP2</i>	<i>KCNB2</i>	<i>HS6ST3</i>	<i>PAM</i>
	<i>GABRG2</i>	<i>KCNK16</i>	<i>IAPP</i>	<i>PCDH20</i>
	<i>GDAP1</i>	<i>LRRTM3</i>	<i>IGSF11</i>	<i>PCP4</i>
	<i>GPR27</i>	<i>LSAMP</i>	<i>KLHL1</i>	<i>PDK4</i>
	<i>GRIA2</i>	<i>NALCN</i>	<i>MCTP2</i>	<i>PDX1</i>
	<i>GRIA4</i>	<i>NMNAT3</i>	<i>MEIS2</i>	<i>PRUNE2</i>
	<i>HMGCLL1</i>	<i>NR3C2</i>	<i>NRXN1</i>	<i>RNF150</i>
	<i>ISL1</i>	<i>PGR</i>	<i>OXGR1</i>	<i>SGCZ</i>
	<i>KCNMA1</i>	<i>PVRL3</i>	<i>PCDH17</i>	<i>SULT4A1</i>
	<i>KL</i>	<i>RALYL</i>	<i>PDZRN3</i>	<i>SYT14</i>
	<i>LIG4</i>	<i>RORB</i>	<i>RGS4</i>	<i>TSPYL5</i>
	<i>LIMCH1</i>	<i>SLC18A2</i>	<i>RNF180</i>	<i>ZSCAN18</i>
	<i>MAP9</i>	<i>ST18</i>	<i>ROR1</i>	
	<i>NEUROD1</i>	<i>ST8SIA3</i>	<i>RTN1</i>	
	<i>NOL4</i>	<i>TMEM63C</i>	<i>SCG2</i>	
	<i>PAX6</i>	<i>TSHZ3</i>	<i>SLC30A8</i>	
	<i>PCLO</i>		<i>SLC35F4</i>	
	<i>PRKACB</i>		<i>SLCO1A2</i>	
	<i>RAB3C</i>		<i>SOX6</i>	
	<i>RASEF</i>		<i>ST6GALNAC5</i>	
	<i>RGS17</i>		<i>STXBP5L</i>	
	<i>RIMBP2</i>		<i>SYT4</i>	
	<i>RIMS2</i>		<i>TMEM132D</i>	
	<i>ROBO2</i>		<i>TRPM3</i>	
	<i>SCGB2A1</i>		<i>TSC22D1</i>	

SERPINI2
SGCB
SIM1
SLC17A6
SLC5A1
SLC5A8
SLC7A2
SNAP91
SPATA7
SPTB
TMEM132B
TMEM196
TTC8

INS-1 832/13 cells were transfected with Sox5 siRNA (*Sox5*-kd) or a Sox5 plasmid (*Sox5* OE). The table displays genes in the T2D-associated module that exhibited a statistically significant change in expression in the same or opposite direction to that observed in T2D vs. non-diabetic islets or no change.

Supplementary Table 10. Genes involved in glucose metabolism that are affected in response to Sox5-knockdown

Gene symbol	Gene name	Microarray		qPCR	
		Fold-change	P-value	Fold-change	P-value
<i>Cs</i>	Citrate synthase	-1.21	0.0480	-1.03	0.614
<i>Fh</i>	Fumarate hydratase	-1.31	0.00500	-1.34	0.00613
<i>Suclg2</i>	Succinate-CoA ligase, GDP-forming, beta subunit	-1.24	0.00130	-1.30	0.00587
<i>Sucla2</i>	Succinate-CoA ligase, ADP-forming, beta subunit	-1.70	0.000300	-1.71	0.000421
<i>Pdha1</i>	Pyruvate dehydrogenase (lipoamide) alpha 1	-1.52	0.00120	-1.60	0.00209
<i>Ldhb</i>	Lactate dehydrogenase B	1.34	0.00300	1.48	0.0396
<i>Ndufa10</i>	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 10	-1.53	3.80E-05	-1.39	0.000983
<i>Ndufv3</i>	NADH dehydrogenase (ubiquinone) flavoprotein 3	-1.37	0.0410	-1.19	0.139
<i>Sdha</i>	Succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	-1.44	4.90E-05	-1.65	0.00791
<i>Sdhc</i>	Succinate dehydrogenase complex, subunit C, integral membrane protein	-2.08	0.000200	-2.26	0.00102
<i>Atp5f1</i>	ATP synthase, H ⁺ transporting, mitochondrial Fo complex, subunit B1	-1.92	0.000500	-2.48	0.00437

Genes encoding enzymes that are involved in glucose metabolism were analyzed in the microarrays and changes in expression were also analyzed by qPCR. Fold-change denotes differential gene expression in Sox5-kd cells vs. control cells (n=3-5).

Supplementary Table 11. Signature genes with changed expression in INS-1 832/13 cells after VPA treatment or Sox5 overexpression

Same direction of change with VPA and Sox5 OE (n=41)	Genes changed with VPA but not with Sox5 OE (n=38)
<i>ADAMTS2</i>	<i>ACVR1C</i>
<i>AGBL4</i>	<i>CADM1</i>
<i>C1orf168</i>	<i>CPE</i>
<i>C3orf14</i>	<i>DACH1</i>
<i>CACNA1H</i>	<i>DCX</i>
<i>CADPS</i>	<i>DSCAM</i>
<i>CNTN1</i>	<i>ELP4</i>
<i>CNTN4</i>	<i>EML5</i>
<i>ELAVL4</i>	<i>FAM135B</i>
<i>FAM123C</i>	<i>FAM84A</i>
<i>GABRG2</i>	<i>FLJ25770</i>
<i>GRIA2</i>	<i>GABRA1</i>
<i>GRIK2</i>	<i>GABRB3</i>
<i>KBTBD7</i>	<i>GPM6A</i>
<i>KCNB2</i>	<i>HMGCLL1</i>
<i>KIAA0774</i>	<i>IGSF11</i>
<i>KIAA1486</i>	<i>ISL1</i>
<i>KL</i>	<i>KCNMA1</i>
<i>MEIS3</i>	<i>KIAA1383</i>
<i>NALCN</i>	<i>KIAA1804</i>
<i>NBEA</i>	<i>KLHL1</i>
<i>NEUROD1</i>	<i>MAPK10</i>
<i>NKX6-1</i>	<i>MMP16</i>
<i>NOL4</i>	<i>MYO3A</i>
<i>NRXN1</i>	<i>NR3C2</i>
<i>PCDHAC1</i>	<i>OXGR1</i>
<i>PDK4</i>	<i>PAM</i>
<i>RGS4</i>	<i>PAPPA2</i>
<i>RIMBP2</i>	<i>PCLO</i>
<i>RNF180</i>	<i>PRKACB</i>
<i>SLC17A6</i>	<i>PRUNE2</i>
<i>SLC18A2</i>	<i>RNF150</i>
<i>SLC30A8</i>	<i>ROR1</i>
<i>SLC7A2</i>	<i>RTN1</i>
<i>SLCO1A2</i>	<i>SOX6</i>
<i>ST6GALNAC5</i>	<i>TMEM196</i>
<i>ST8SIA3</i>	<i>TSHZ3</i>

SYT14

ZSCAN18

TMEM132B

TRPM3

TTC8

Genes in the T2D signature that were significantly changed in response to treatment with 1 mM VPA or transfection with a Sox5 plasmid (Sox5 OE) relative to control INS-1 832/13 cells (n=3).

Supplementary Table 12. Association between T2D-associated risk variants and gene expression in human islets

SNP		Eigengene for T2D- associated module	Eigengene for the 168 genes (T2D signature)	SOX5 expression
<i>KCNQ1_rs2237895</i>	Effect size	0.0702	0.133	0.0588
	p-value	0.581	0.295	0.644
	N	64	64	64
<i>MTNR1B_rs10830963</i>	Effect size	-0.0002	0.000	-0.0052
	p-value	0.999	1.000	0.968
	N	64	64	64
<i>ADRA2A_rs553668</i>	Effect size	-0.0724	-0.020	0.0152
	p-value	0.573	0.874	0.906
	N	63	63	63
<i>CDKAL1_rs7754840</i>	Effect size	0.0932	-0.098	-0.0438
	p-value	0.464	0.441	0.731
	N	64	64	64
<i>TCF7L2_rs7903146</i>	Effect size	-0.0449	-0.179	-0.1336
	p-value	0.731	0.167	0.305
	N	61	61	61
<i>GIPR_rs10423928</i>	Effect size	0.0569	0.272	0.2329
	p-value	0.658	0.313	0.066
	N	63	63	63
<i>IGF2BP2_rs4402960</i>	Effect size	-0.1701	-0.150	-0.1195
	p-value	0.179	0.236	0.347
	N	64	64	64
<i>SLC30A8_rs13266634</i>	Effect size	-0.0153	0.104	0.1784
	p-value	0.911	0.445	0.188
	N	56	56	56
<i>CAMK1D_rs12779790</i>	Effect size	-0.1775	-0.093	-0.1242
	p-value	0.164	0.469	0.332
	N	63	63	63
<i>FTO_rs9939609</i>	Effect size	-0.0268	-0.077	-0.0249
	p-value	0.834	0.547	0.845
	N	64	64	64

<i>HHEX_rs1111875</i>	Effect size	0.2088	0.134	0.1193
	p-value	0.098	0.291	0.348
	N	64	64	64
<i>KCNJ11_rs5219</i>	Effect size	-0.0639	-0.114	-0.1444
	p-value	0.616	0.371	0.255
	N	64	64	64
<i>TSPAN8_LGR5_rs7961581</i>	Effect size	0.0730	0.067	0.1082
	p-value	0.567	0.600	0.395
	N	64	64	64
<i>JAZF1_rs864745</i>	Effect size	0.0857	0.029	0.0591
	p-value	0.504	0.820	0.645
	N	63	63	63
<i>WFS1_10010131</i>	Effect size	-0.0490	-0.056	-0.0898
	p-value	0.707	0.670	0.491
	N	61	61	61
<i>CDKN2A2B_rs10811661</i>	Effect size	-0.0085	-0.025	-0.0778
	p-value	0.948	0.848	0.545
	N	63	63	63
<i>PPARG_rs1801282</i>	Effect size	0.0070	0.022	0.0181
	p-value	0.956	0.861	0.887
	N	64	64	64
<i>NOTCH2_rs10923931</i>	Effect size	0.1628	-0.013	-0.0023
	p-value	0.199	0.921	0.986
	N	64	64	64
<i>ADAMTS9_rs4607103</i>	Effect size	-0.0095	0.173	0.2245
	p-value	0.941	0.172	0.075
	N	64	64	64
<i>G6PC2_rs560887</i>	Effect size	-0.0019	0.157	0.1471
	p-value	0.988	0.214	0.246
	N	64	64	64
<i>GCK_rs4607517</i>	Effect size	0.0348	-0.012	-0.0387
	p-value	0.790	0.929	0.767
	N	61	61	61
<i>GCKR_rs780094</i>	Effect size	0.2438	0.253	0.3570

	p-value	0.052	0.438	0.038
	N	64	64	64
<i>THADA_rs7578597</i>	Effect size	-0.0550	0.016	-0.0125
	p-value	0.674	0.902	0.924
	N	61	61	61
<i>ADCY5_rs11708067</i>	Effect size	0.0278	-0.010	-0.1851
	p-value	0.828	0.938	0.146
	N	63	63	63
<i>TCF2_rs757210</i>	Effect size	-0.2421	-0.248	-0.2016
	p-value	0.072	0.065	0.136
	N	56	56	56
<i>DGKB-TMEM195_rs2191349</i>	Effect size	0.0683	0.047	0.1013
	p-value	0.634	0.744	0.479
	N	51	51	51
<i>FADS1_rs174550</i>	Effect size	0.0138	-0.168	-0.2057
	p-value	0.919	0.210	0.125
	N	57	57	57
<i>IGF1_rs35767</i>	Effect size	0.1291	0.118	0.1547
	p-value	0.309	0.354	0.222
	N	64	64	64
<i>MADD_rs7944584</i>	Effect size	-0.261	0.062	0.0086
	p-value	0.370	0.629	0.946
	N	64	64	64
<i>CRY2_rs11605924</i>	Effect size	-0.2313	-0.121	-0.0960
	p-value	0.086	0.374	0.482
	N	56	56	56
<i>SLC2A2_rs11920090</i>	Effect size	0.1216	0.077	0.0904
	p-value	0.346	0.551	0.485
	N	62	62	62
<i>GLIS3_rs7034200</i>	Effect size	0.0758	0.121	0.0959
	p-value	0.558	0.349	0.459
	N	62	62	62
<i>PROX1_rs340874</i>	Effect size	-0.0137	-0.033	-0.0147
	p-value	0.914	0.794	0.908

	N	64	64	64
<i>C2CD4B_rs11071657</i>	Effect size	0.0049	-0.038	-0.1413
	p-value	0.972	0.784	0.304
	N	55	55	55
<i>VPS13C_rs17271305</i>	Effect size	-0.0072	-0.053	-0.0533
	p-value	0.956	0.684	0.683
	N	61	61	61

Islet donors (n=64) were genotyped for 35 common single-nucleotide polymorphisms (SNPs) that have previously been associated with increased risk for T2D or glucose intolerance. Associations between donor genotype and the eigengene for the T2D-associated co-expression module, the eigengene for the 168 genes with islet-selective open chromatin (the T2D signature) and *SOX5* expression, respectively, was analyzed by linear regression using age, sex and BMI as covariates. Displayed p-values are not corrected for multiple testing.

Supplementary Table 13. Expression of 8 key markers of differentiated β -cells in human islets from non-diabetic (ND) and T2D donors

Gene symbol	Gene expression (a.u.) in ND (n=46)	Gene expression (a.u.) in T2D (n=19)	Ratio (T2D/ND)
<i>GAD2</i>	1105	891	0.81
<i>GLP1R</i>	320	208	0.65
<i>MAFA</i>	201	164	0.82
<i>NKX6-1</i>	261	191	0.73
<i>PCSK1</i>	3641	2557	0.70
<i>PDX1</i>	172	137	0.80
<i>SLC2A2</i>	221	113	0.51
<i>SLC30A8</i>	4421	3541	0.80

Gene expression as analyzed by microarray.