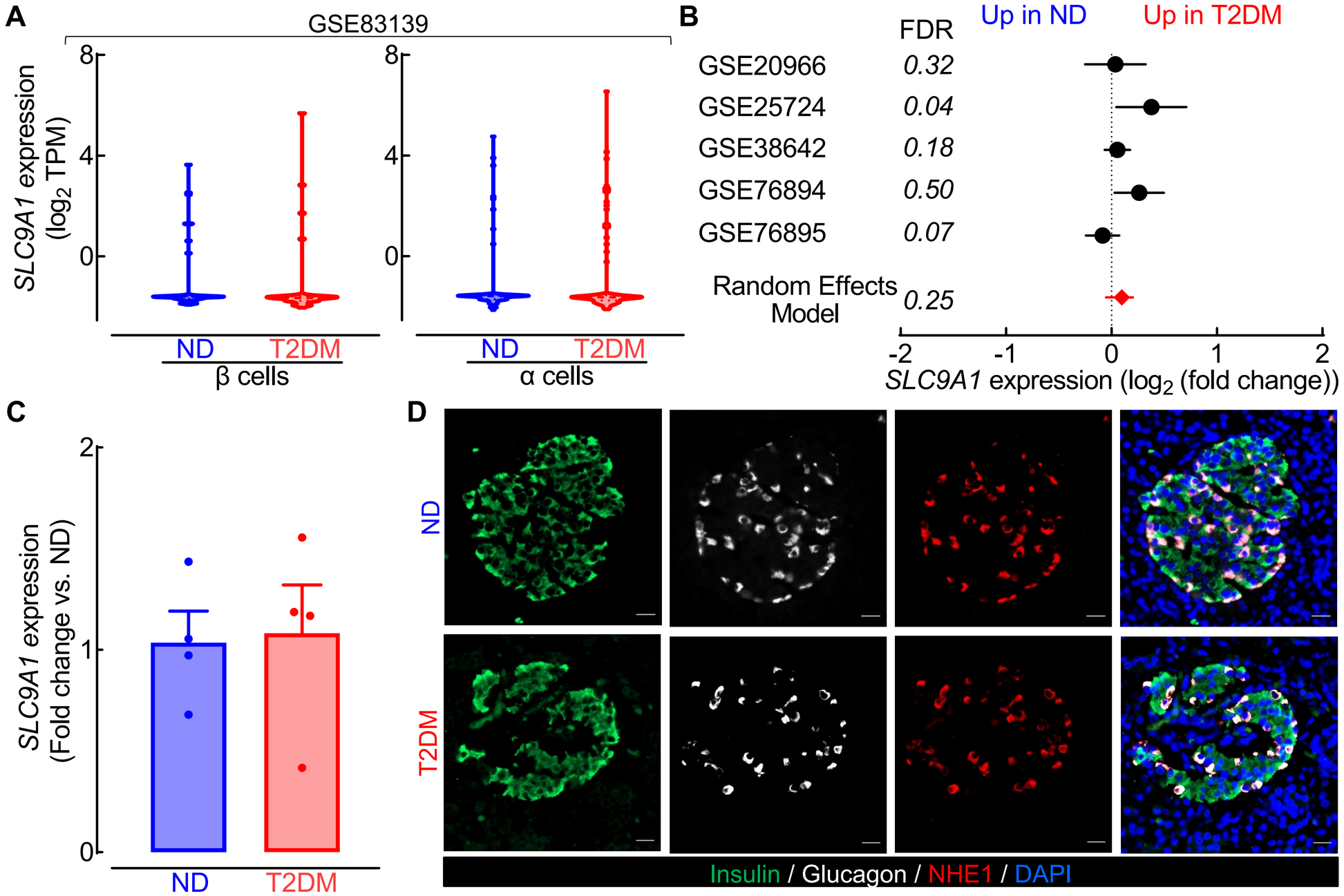
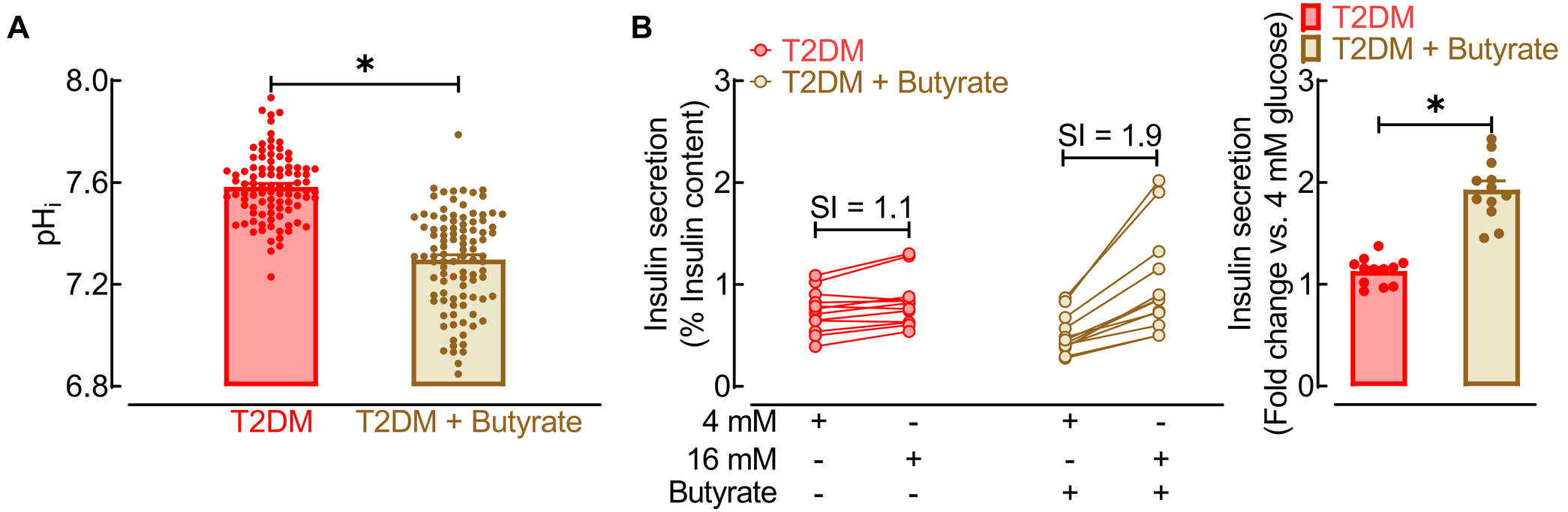
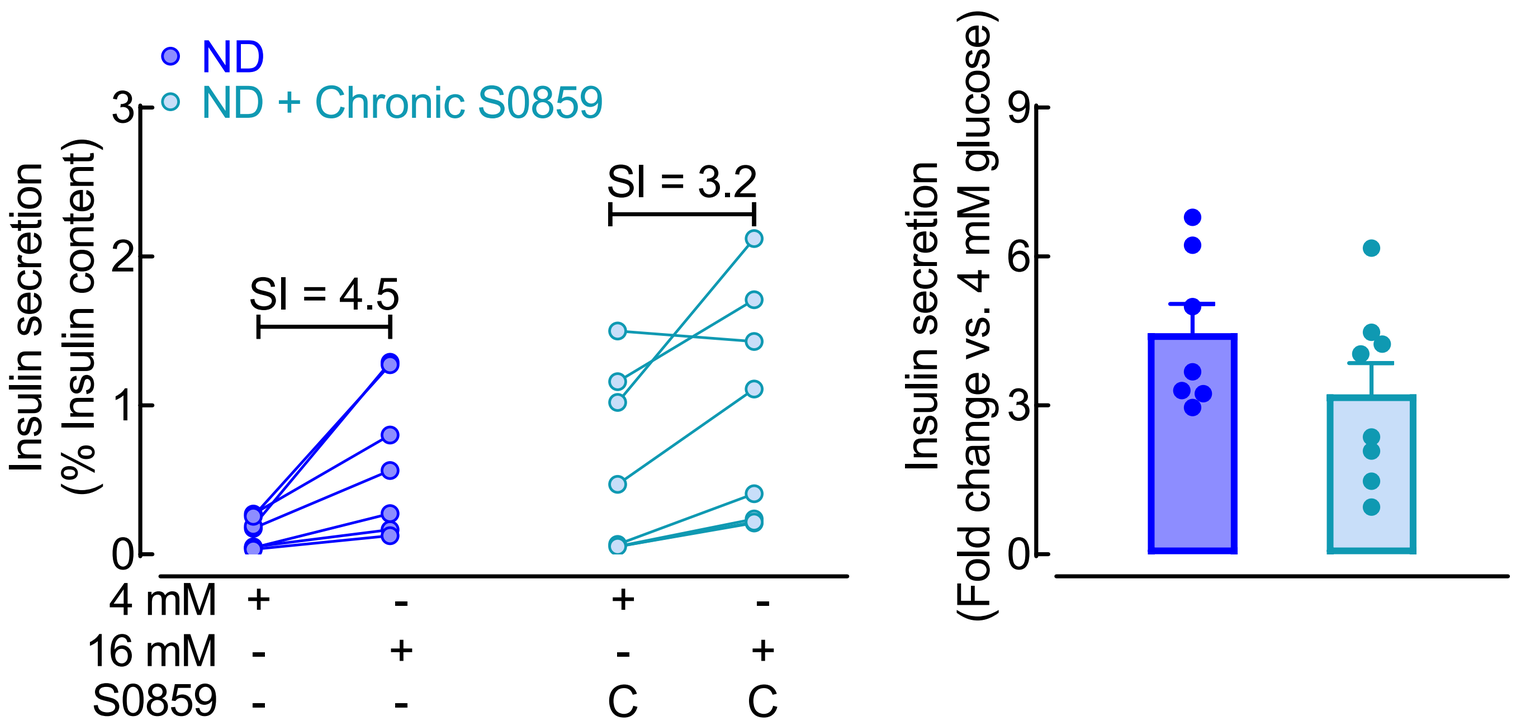


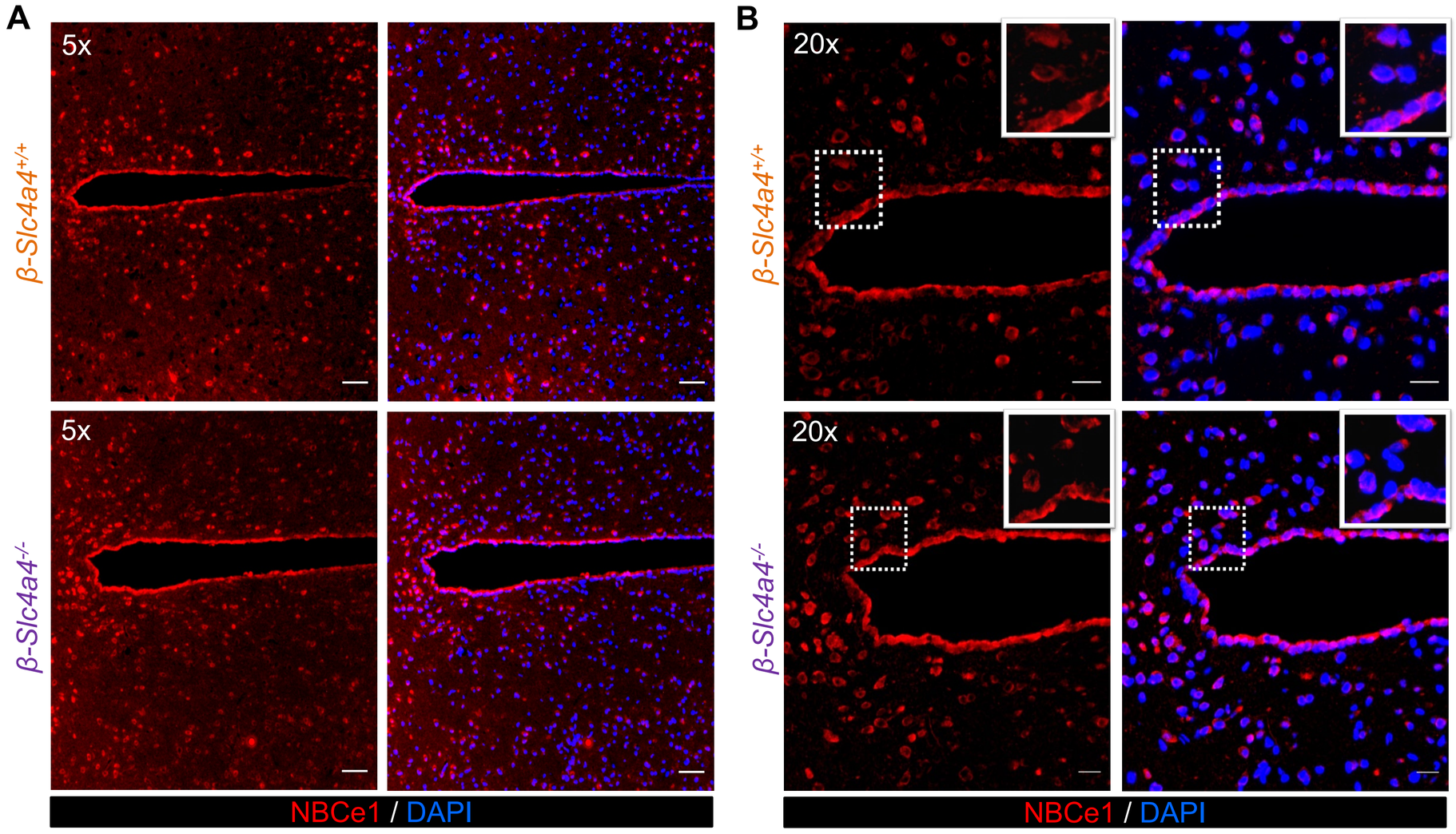
Supplemental Figure 1. *SLC9A1* and NHE1 are not differentially expressed in T2DM β cells. (A) *SLC9A1* expression in human non-diabetic (ND) and type 2 diabetic (T2DM) β cells and α from GSE83139 (n=38-100 cells). **(B)** Meta-analysis of *SLC9A1* expression in ND and T2DM islets from five independent whole-gene transcriptomic array studies. FDR<.05, denotes statistical significance (Benjamini-Hochberg method). **(C)** mRNA expression of *SLC9A1* in ND and T2DM isolated human islets (n=4 independent ND and T2DM human islet shipments). **(D)** Representative images of human pancreatic sections from lean ND and obese T2DM subjects immunostained for NHE1 (red), Insulin (green), Glucagon (white), and nuclear marker DAPI (blue) imaged at 20x magnification. Images are representative of 3 ND and 3 T2DM subjects. Scale bars represent 20 μm in all images. Values are represented as mean ± SEM.



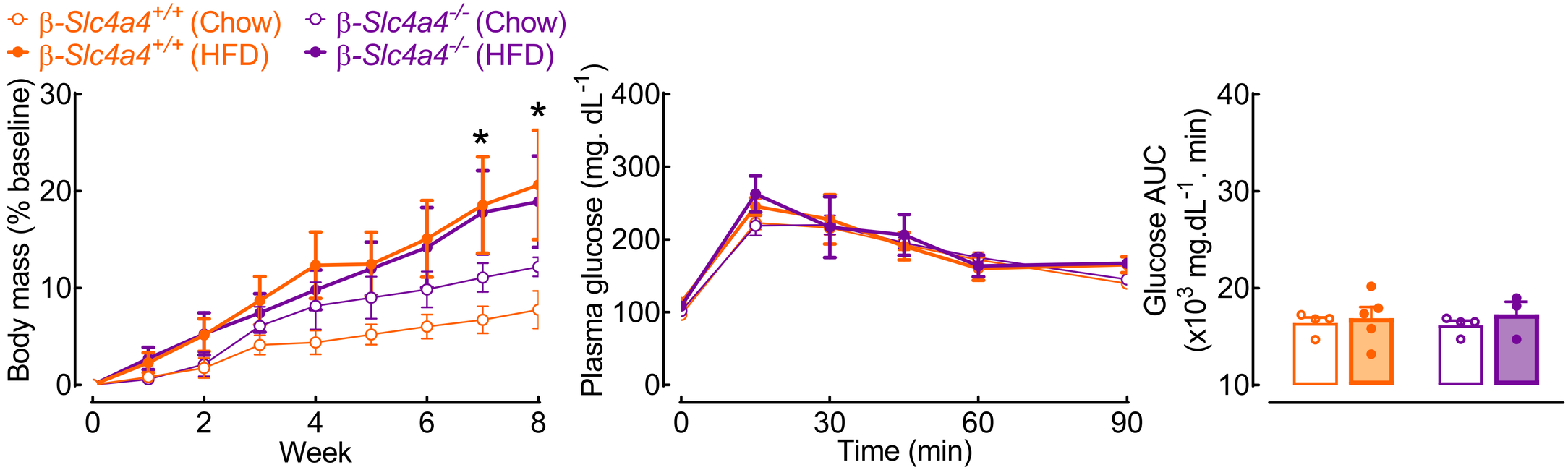
Supplemental Figure 2. Intracellular acidification enhances β cell function in T2DM. (A) Intracellular pH (pH_i) measurements in T2DM human islet cells exposed to either vehicle or 100 μM sodium butyrate in 4 mM glucose KRBH buffer. *p<.05 denotes statistical significance (unpaired, two-tailed t-test; n=86-99 independent cells from 3 T2DM islet shipments). **(B)** Glucose-stimulated insulin secretion (GSIS) during 30 min static incubations at hyperglycemic 16 mM glucose and basal 4 mM glucose concentration in isolated T2DM human islets exposed to either vehicle or 100 μM sodium butyrate in KRBH buffer (left). Quantification of fold change in insulin secretion (16 vs. 4 mM glucose; right). *p<.05 denotes statistical significance (unpaired, two-tailed t-test; n=12 independent experiments from 2 T2DM human islet shipments). All values are represented as mean ± SEM.



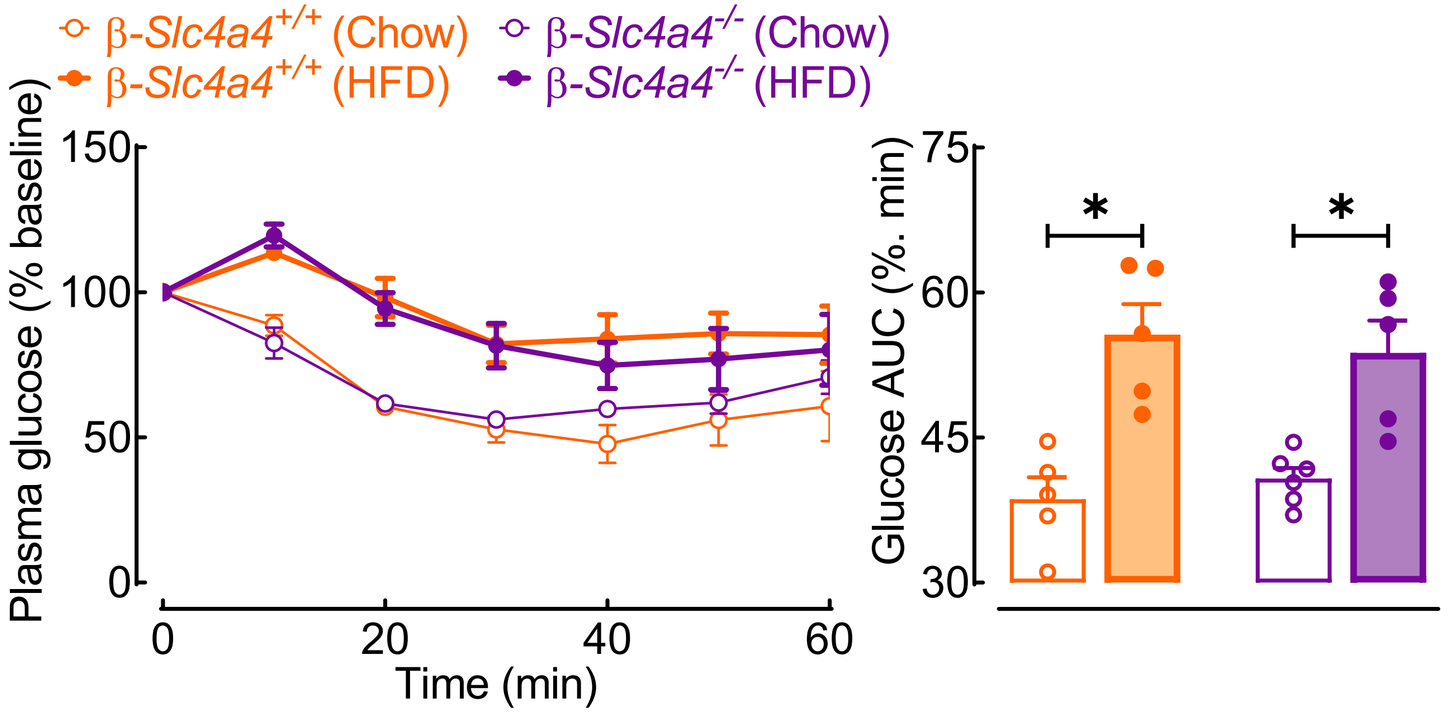
Supplemental Figure 3. Chronic inhibition of NBCe1 does not modulate β cell function of ND islets. Glucose-stimulated insulin secretion (GSIS) during 30 min static incubations at hyperglycemic 16 mM glucose and basal 4 mM glucose concentrations in human non-diabetic (ND) islets. Islets were treated with vehicle or chronic NBCe1 inhibition (30 μM S0859) for 72 h. Islets exposed to chronic NBCe1 inhibition were not exposed to S0859 during GSIS procedure (left). Quantification of fold change in insulin secretion (16 mM vs. 4 mM glucose; unpaired, two-tailed t-test; n=7-8 independent experiments from 2 independent ND islet shipments). All values are represented as mean ± SEM.



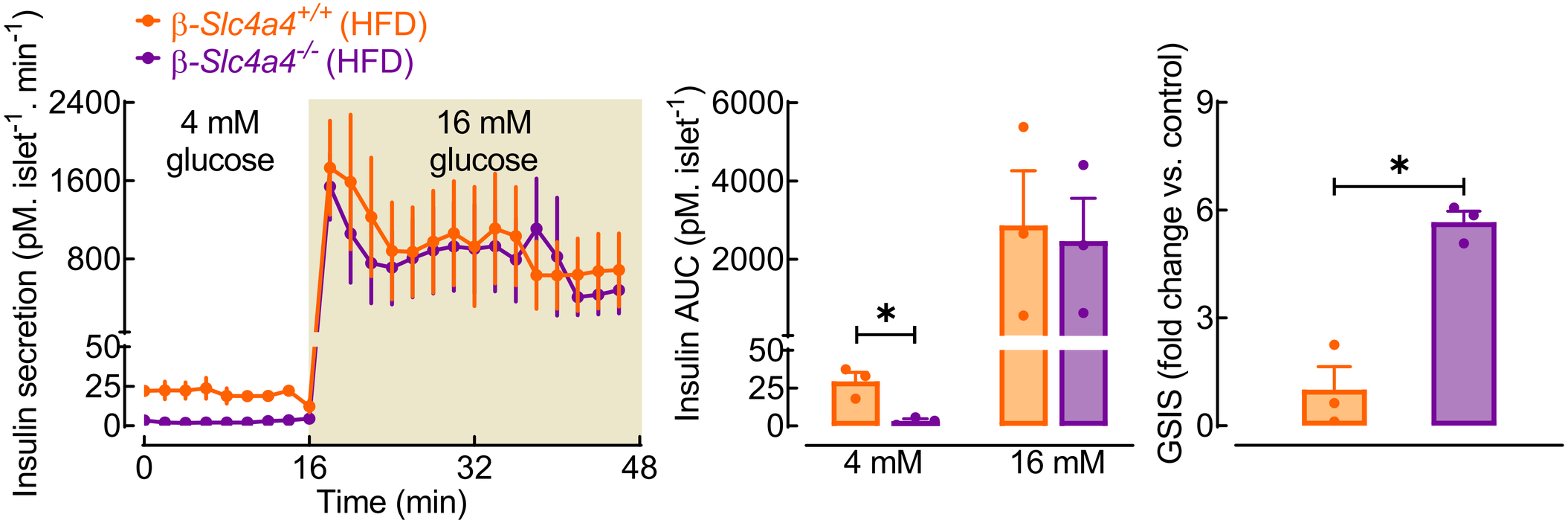
Supplemental Figure 4. RIP-Cre mediated *Slc4a4* deletion does not modulate hypothalamic NBCe1 expression. Representative examples of hypothalamic immunostaining for NBCe1 (red) and DAPI (blue) imaged at **(A)** 5x (Scale bars represent 50 μm) and **(B)** 20x (Scale bars represent 20 μm) obtained from *β-Slc4a4*$^{+/+}$ (*Slc4a4*$^{fl/fl}$+/+) and *β-Slc4a4*$^{-/-}$ (*Slc4a4*$^{fl/fl}$*Ins2*$^{Cre/+}$) mice. Images are representative of n=3 independent repeats per group.



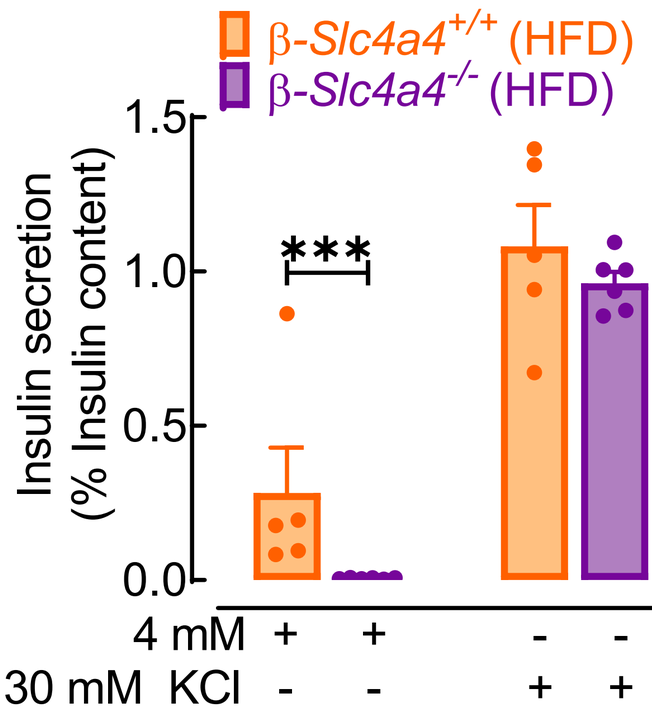
Supplemental Figure 5. Deletion of *Slc4a4* in β cells does not influence response to diet-induced obesity in female mice in vivo. Percent change in body mass from baseline (left), glucose tolerance at week 8 (center), and corresponding glucose tolerance area under the curve (right) of female *β-Slc4a4*$^{+/+}$ (*Slc4a4*$^{fl/fl}$+/+) and *β-Slc4a4*$^{-/-}$ (*Slc4a4*$^{fl/fl}$*Ins2*$^{Cre/+}$) mice exposed to 8 weeks of chow or HFD. *p<.05 denotes statistical significance of *β-Slc4a4*$^{+/+}$ HFD and *β-Slc4a4*$^{-/-}$ HFD vs. *β-Slc4a4*$^{+/+}$ Chow (two-way ANOVA with Dunnet method for multiple comparisons; n=3-5 independent experiments). All values are represented as mean ± SEM.



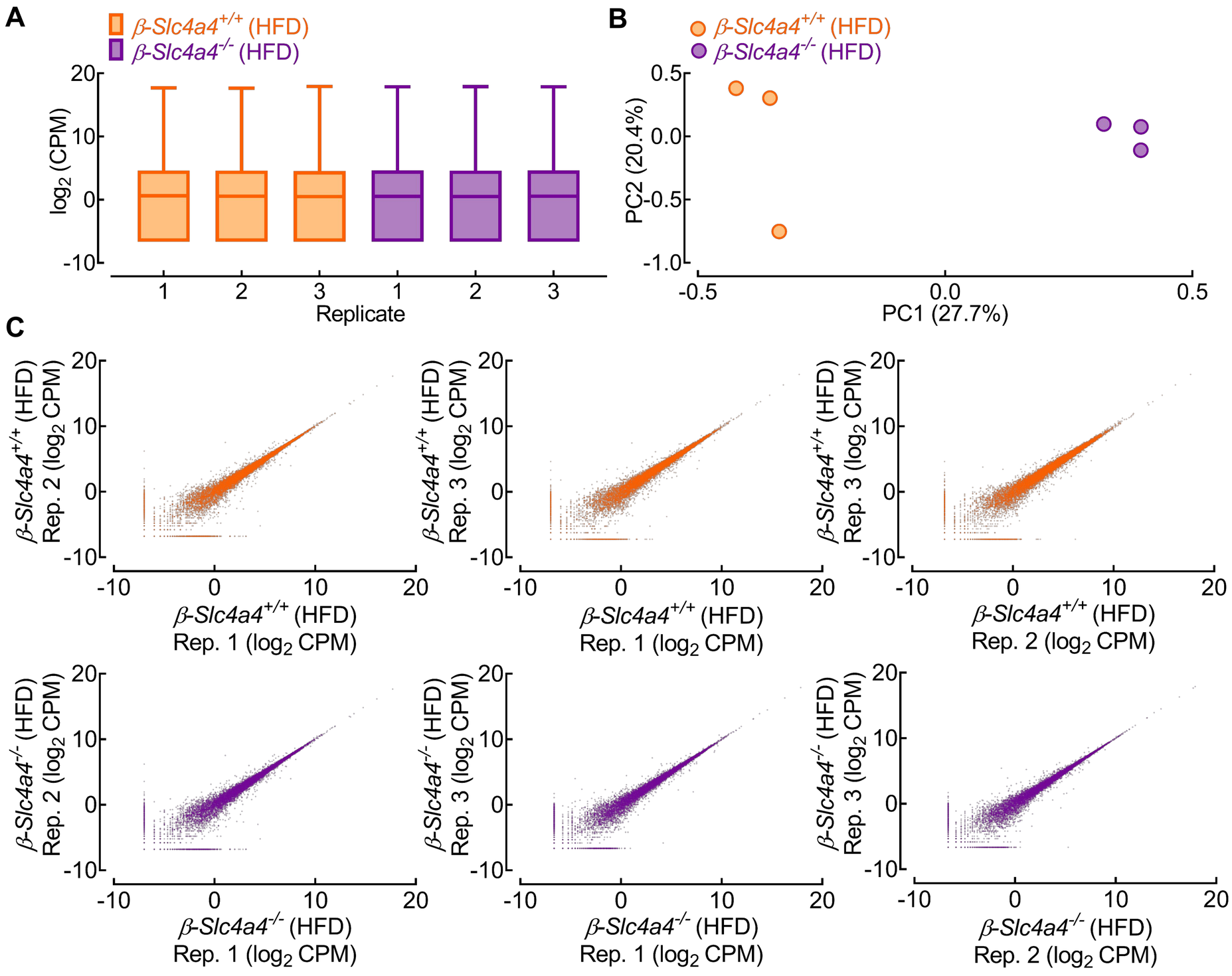
Supplemental Figure 6 Deletion of *Slc4a4* in β cells does not influence changes to diet-induced insulin resistance in male mice. Percent change in plasma glucose from baseline (left) and corresponding insulin tolerance area under the curve (right) of male *β-Slc4a4*$^{+/+}$ (*Slc4a4*$^{fl/fl}$+/+) and *β-Slc4a4*$^{-/-}$ (*Slc4a4*$^{fl/fl}$*Ins2*$^{Cre/+}$) mice exposed to 8 weeks of chow or HFD. *p<.05 denotes statistical significance (unpaired, two-tailed t-test; n=5-6 independent experiments). All values are represented as mean ± SEM.



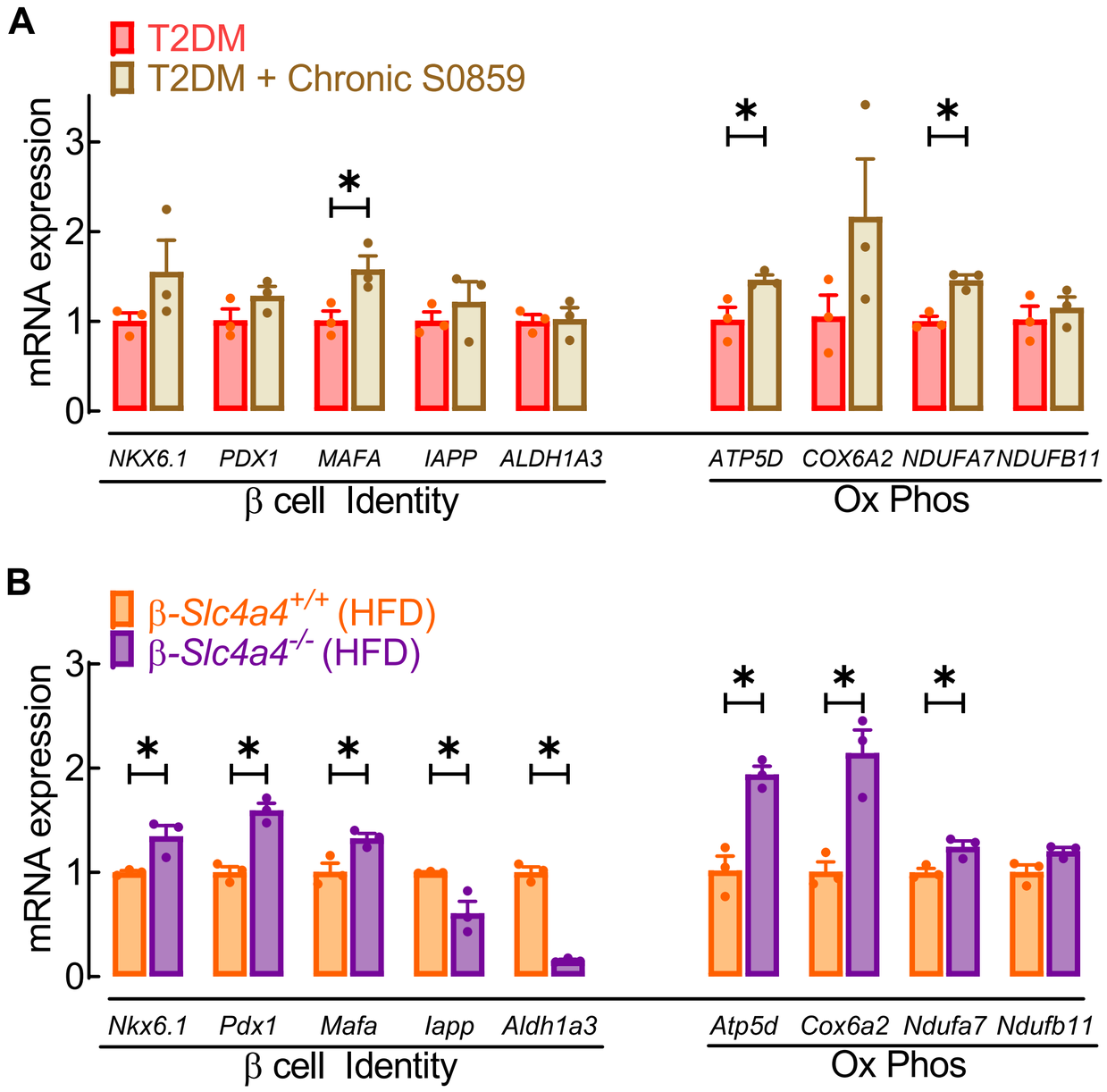
Supplemental Figure 7. Deletion of *Slc4a4* mediates protection from diet-induced glucose tolerance through reduction in basal hyperinsulinemia. Mean glucose-stimulated insulin secretion (GSIS) in response to hyperglycemic 16 mM glucose (16-48 min) and basal 4mM glucose (0-16 min) concentrations in *β-Slc4a4*$^{+/+}$ (*Slc4a4*$^{fl/fl}$*+/+)* and *β-Slc4a4*$^{-/-}$ (*Slc4a4*$^{fl/fl}$ *Ins2*$^{Cre/+}$) islets exposed to 8 weeks of HFD (left). Corresponding area under the curve calculated from integration of insulin secretion during exposure to 4 mM and 16 mM glucose (center) and GSIS normalized to fold change in insulin secretion (16 vs. 4 mM glucose) in control *β-Slc4a4*$^{+/+}$ HFD (right). **p*<.05 denotes statistical significance (unpaired, two-tailed t-test; n=3 independent experiments from 3 mice per group). All values are represented as mean ± SEM.



Supplemental Figure 8. Deletion of *Slc4a4* in β cells does not influence depolarization-induced insulin secretion. Depolarization-stimulated insulin secretion at depolarizing 30 mM KCl and basal 4 mM glucose concentrations in islets from *β-Slc4a4*$^{+/+}$ (*Slc4a4*$^{fl/fl}$*+/+)* and *β-Slc4a4*$^{-/-}$ (*Slc4a4*$^{fl/fl}$ *Ins2*$^{Cre/+}$) mice exposed to 8 weeks of HFD. ****p*<.001 denotes statistical significance (unpaired, two-tailed t-test; n=5-6 independent experiments from 2-3 mice). All values are represented as mean ± SEM.



Supplemental Figure 9. Quality control of RNA-sequencing. (A) Log_2 normalized mean gene expression expressed as counts per million reads (CPM) in *β-Slc4a4*$^{+/+}$ (*Slc4a4*$^{fl/fl}$*+/+)* and *β-Slc4a4*$^{-/-}$ (*Slc4a4*$^{fl/fl}$ *Ins2*$^{Cre/+}$) islets exposed to 8 weeks of HFD. Values expressed as mean ± min/ max log_2 CPM. Global mean transcript levels were not found to be statically significant (one-way ANOVA with Dunnet method for multiple comparisons). **(B)** Principal component analysis (PCA) visualizing principal component 1 (27.7% of variance) and 2 (20.4% of variance) from global transcriptome of *β-Slc4a4*$^{+/+}$ and *β-Slc4a4*$^{-/-}$ islets exposed to 8 weeks of HFD. **(C)** Linear correlation analysis between independent RNA-seq replicates. All replicates had linear correlation coefficient, R^2 >0.95.



Supplemental Figure 10. Pharmacological and genetic inhibition of NBCe1 enhances expression of key regulators of oxidative phosphorylation in islets. (A) mRNA expression of key genes related to β cell identity/ dedifferentiation and oxidative phosphorylation in human type 2 diabetic (T2DM) islets exposed to either vehicle or 30 μM S0859 for 72 h. *p<.05 denotes statistical significance (unpaired, two-tailed t-test; n=3 independent experiments from one T2DM islet shipment). **(B)** mRNA expression of key genes related to β cell identity/ dedifferentiation and oxidative phosphorylation in islets from *β-Slc4a4*$^{+/+}$ (*Slc4a4*$^{fl/fl}$+/+) and *β-Slc4a4*$^{-/-}$ (*Slc4a4*$^{fl/fl}$ *Ins2*$^{Cre/+}$) mice exposed to 8 weeks of HFD. *p<.05 denotes statistical significance (unpaired, two-tailed t-test; n=3 independent experiments). All values are reported as mean ± SEM.

Supplemental Table 1. Donor characteristics associated with cadaveric human islets used for studies.

Human Islets for Studies																		
Unique Identifier	HP-15162	HP-16012	HP-18270	HP-18275	HP-18032	HP-19051	HP-18068	HP-19053	HP118038	HP18103	HP18243	HP18017	HP16280	HP18032	HP-20268	HP-20346	SAMN17833574	SAMN17831932
Donor Age (y)	27	42	31	30	45	53	55	47	45	35	51	57	52	45	55	37	45	60
Donor Sex (M/F)	M	M	M	F	M	M	M	F	M	F	M	F	M	M	M	F	M	M
Donor BMI (kg/m^2)	29.7	43.7	22.0	40.1	29.6	30.1	29.9	32.7	27.3	34.0	37.3	21.4	22.0	29.6	23	26.1	35.6	41.3
Donor HbA1c	4.9%	6.6%	5.5%	6.5%	5.1%	7.8%	8.5%	5.3%	6.7%	7.1%	6.2%	5.8%	5.6%	5.1%	4.7%	5.0%	5.0%	7.5%
Source of Islets	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	UNOS	IIDP	IIDP
Islet Isolation Center	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	Prodo Laboratories	University of Pennsylvania	Southern California Islet Resource Center
Donor History of Diabetes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes
For T2DM donors																		
Diabetes Duration (years)	-	Not Reported	-	Not Reported	-	Not Reported	Not Reported	-	Not Reported	0.5	25	-	-	-	-	-	0 to 5	Not Reported
Glucose Lowering Therapy	-	Not Reported	-	Diet	-	Glipizide, Januvia	Not Reported	-	Diet	Diet	Diet/Oral Medications	-	-	-	-	-	Diet, Insulin	Not Reported

Supplemental Table 2. Clinical characteristics associated with human pancreatic autopsy specimens used for studies. Lean non-diabetic donors (n=8), obese non-diabetic donors (n=6), and obese, documented type 2 diabetic donors (n=8).

Clinical Characteristics of Lean Non-Diabetic								
Case Id	1	2	3	4	5	6	7	8
Age (y)	86	81	67	84	85	78	84	64
Sex (M/F)	M	M	M	M	M	F	M	F
BMI (kg/ m^2)	24.7	26.1	16.3	23.3	24.6	16.6	29.4	20.7
Cause of Death	Sepsis	Acute bronchopneumonia	Adenocarcinoma of the lung, stage IV	Aspiration pneumonia	Cardiogenic shock	Intracranial hemorrhage	Acute bronchopneumonia	Fibrinous pneumonia
Clinical Characteristics of Obese Non-Diabetic								
Case Id	1	2	3	4	5	6		
Age (y)	62	72	59	75	78	57		
Sex (M/F)	M	M	F	M	F	M		
BMI (kg/ m^2)	33.5	32.3	43.7	34.6	37.6	29.8		
Cause of Death	Ischemic heart disease	Multiple organ system failure	Liver failure associated with cirrhosis	Hypotension, arrhythmias, and right ventricular tamponade	Pulmonary hypertension	non-penetrating blunt force trauma		
Clinical Characteristics of Obese Type 2 Diabetic								
Case Id	1	2	3	4	5	6	7	8
Age (y)	49	58	63	70	66	61	69	67
Sex (M/F)	F	F	F	M	M	F	M	M
BMI (kg/ m^2)	46.1	50.1	37.0	48.1	38.2	49.8	40.7	32.6
Cause of Death	ARDS	Aspiration of bilious gastric contents	Ischemic heart disease	Dissecting thoracoabdominal aneurysm	Acute myocardial ischemia	Hypoxic encephalopathy	Dilated cardiomyopathy	Hypertensive and atherosclerotic CV disease
Length of Diabetes (y)	5	5	5	8	22	25	3.5	-
Medication	Sulfonylurea	Sulfonylurea	Insulin	Diet	Insulin	Insulin; Glucophage	Insulin	Insulin

Supplemental Table 3. Deletion of *Slc4a4* in β cells does not influence changes to in vivo blood gas and metabolite concentration. Blood gas and metabolite concentration (with specified unit) in male *β-Slc4a4*$^{+/+}$ (*Slc4a4*$^{fl/fl}$*+/+)* and *β-Slc4a4*$^{-/-}$ (*Slc4a4*$^{fl/fl}$ *Ins2*$^{Cre/+}$) mice exposed to 8 weeks of chow or HFD (One-way ANOVA with Dunnet's method for multiple comparisons; n=4-5 independent experiments). No statistically significant metabolites or gases were identified. All values are represented as mean with SEM in parentheses.

	***β-Slc4a4*$^{+/+}$ Chow**	***β-Slc4a4*$^{+/+}$ HFD**	***β-Slc4a4*$^{-/-}$ Chow**	***β-Slc4a4*$^{-/-}$ HFD**
Na^+ (mM)	151.2 (0.4)	148.5 (0.9)	150.7 (0.3)	148.6 (0.9)
K^+ (mM)	7.8 (0.2)	6.4 (0.2)	7.2 (0.1)	7.4 (0.2)
Cl^- (mM)	114.2 (0.3)	116.3 (0.5)	113.4 (0.4)	116.0 (0.5)
pH	7.31 (0.02)	7.34 (0.02)	7.36 (0.00)	7.34 (0.01)
HCO_3^- (mM)	17.1 (0.3)	17.4 (0.4)	17.9 (0.3)	17.1 (0.8)
BUN (mg/dL)	21.3 (0.3)	21.2 (1.0)	16.8 (0.2)	21.2 (0.3)
Lactate (mM)	5.9 (0.3)	6.1 (0.3)	5.5 (0.1)	6.2 (0.4)
Osm (mOsm/kg)	307.9 (0.7)	305.3 (2.0)	305.7 (0.4)	306.5 (1.6)
PCO_2 (mmHg)	31.4 (0.9)	29.8 (0.9)	31.0 (0.5)	33.1 (0.7)
PO_2 (mmHg)	45.7 (1.1)	46.8 (1.9)	45.2 (0.4)	47.0 (1.5)
Hct (%)	43.6 (0.5)	43.3 (0.2)	43.0 (0.5)	44.2 (0.2)

Supplemental Table 4. Significantly enriched KEGG pathways annotated to transcripts up-regulated in *β-Slc4a4*$^{-/-}$ HFD islets.

Id	Description	LogP	Terms/List	Symbols
mmu04932	Non-alcoholic fatty liver disease (NAFLD)	-6.48	24/151	Akt1,Cox6a1,Cox6a2,Ddit3,Ndufa2,Ndufv1,Pik3r2,Srebf1,Uqcrc1,Map3k11,Mlxipl,Uqcr10,Ndufa7,Uqcr11,Ndufb7,Ndufa13,Ndufc2,Ndufb10,Ndufa11,Ndufs7,Ndufb11,Ndufs8,Irs2,Ndufa4l2
mmu05016	Huntington's disease	-6.02	27/194	Ap2a1,Cox6a1,Cox6a2,Dctn1,Grin1,Hap1,Ndufa2,Ndufv1,Uqcrc1,Creb3l1,Dnal4,Atp5d,Uqcr10,Ndufa7,Polr2e,Uqcr11,Ndufb7,Ndufa13,Atp5g2,Ndufc2,Ndufb10,Ndufa11,Ndufs7,Ndufb11,Bbc3,Ndufs8,Ndufa4l2
mmu00190	Oxidative phosphorylation	-5.65	21/134	Atp6v0c,Cox17,Cox6a1,Cox6a2,Ndufa2,Ndufv1,Uqcrc1,Atp5d,Uqcr10,Ndufa7,Uqcr11,Ndufb7,Ndufa13,Atp5g2,Ndufc2,Ndufb10,Ndufa11,Ndufs7,Ndufb11,Ndufs8,Ndufa4l2
mmu05012	Parkinson's disease	-5.14	21/144	Cox6a1,Cox6a2,Ndufa2,Ndufv1,Uchl1,Uqcrc1,Park7,Atp5d,Uqcr10,Ndufa7,Uqcr11,Ndufb7,Ndufa13,Atp5g2,Ndufc2,Ndufb10,Ndufa11,Ndufs7,Ndufb11,Ndufs8,Ndufa4l2
mmu03040	Spliceosome	-5.13	20/133	Hspa1b,Hspa2,Sf3a2,Sart1,Srsf5,Snrnp70,Snrpb,Cherp,Lsm4,Snrpa,Ddx39b,Prpf40b,Acin1,Srsf4,Sf3b5,Xab2,Ccdc12,Sf3b4,Hspa1a,U2af1l4
mmu05010	Alzheimer's disease	-3.87	21/175	Apoe,Cox6a1,Cox6a2,Grin1,Ndufa2,Ndufv1,Uqcrc1,Atp5d,Uqcr10,Ndufa7,Uqcr11,Ndufb7,Ndufa13,Atp5g2,Ndufc2,Ndufb10,Ndufa11,Ndufs7,Ndufb11,Ndufs8,Ndufa4l2
mmu04950	Maturity onset diabetes of the young	-3.61	7/27	Mnx1,Foxa2,Nkx6-1,Pdx1,Hnf1a,Gck,Mafa
mmu04330	Notch signaling pathway	-2.62	8/49	Ctbp1,Jag2,Notch1,Numbl,Ncor2,Dll4,Dtx2,Dtx3
mmu04213	Longevity regulating pathway - multiple species	-2.52	9/62	Akt1,Foxa2,Hspa1b,Hspa2,Pik3r2,Rps6kb2,Akt1s1,Hspa1a,Irs2
mmu04152	AMPK signaling pathway	-2.05	13/126	Akt1,Cpt1b,Pfkl,Pik3r2,Srebf1,Stk11,Creb3l1,Rps6kb2,Akt1s1,Crtc2,Cpt1c,Scd4,Irs2
mmu04211	Longevity regulating pathway	-1.90	10/90	Akt1,Atf6b,Pik3r2,Stk11,Creb3l1,Rps6kb2,Akt1s1,Ehmt2,Sesn2,Irs2
mmu04612	Antigen processing and presentation	-1.87	10/91	H2-Ab1,H2-Eb1,H2-Q2,H2-T23,Hspa1b,Hspa2,Psme2,Rfxank,Tap2,Hspa1a
mmu00532	Glycosaminoglycan biosynthesis - chondroitin sulfate / dermatan sulfate	-1.83	4/20	B3gat3,Chpf,Chpf2,B4galt7
mmu05221	Acute myeloid leukemia	-1.76	7/55	Akt1,Jup,Pik3r2,Pim2,Ppard,Map2k2,Rps6kb2
mmu04931	Insulin resistance	-1.75	11/109	Akt1,Cpt1b,Pik3r2,Srebf1,Nr1h2,Creb3l1,Slc27a1,Mlxipl,Rps6kb2,Crtc2,Irs2
mmu04911	Insulin secretion	-1.64	9/85	Fxyd2,Atf6b,Gna11,Pdx1,Rab3a,Abcc8,Vamp2,Creb3l1,Gck
mmu05169	Epstein-Barr virus infection	-1.63	18/220	Akt1,H2-Q2,H2-T23,Hdac5,Hspa1b,Hspa2,Nfkbib,Pik3r2,Ncor2,Psmd3,Map2k7,Polr3e,Irf3,Akap8l,Adrm1,Polr2e,Polr3d,Hspa1a
mmu02010	ABC transporters	-1.62	6/46	Abcg1,Abcc8,Tap2,Abca7,Abcb9,Abcc10
mmu04140	Autophagy - animal	-1.59	12/130	Akt1,Dapk3,Pik3r2,Stk11,Map2k2,Rps6kb2,Akt1s1,Atg16l2,Atg16l1,Atg4d,Atg2a,Irs2
mmu04930	Type II diabetes mellitus	-1.54	6/48	Pdx1,Pik3r2,Abcc8,Gck,Mafa,Irs2
mmu05168	Herpes simplex infection	-1.45	17/215	H2-Ab1,H2-Eb1,H2-Q2,H2-T23,Nfkbib,Per1,Per2,Per3,Cfp,Srsf5,Tap2,Mcrs1,Nxf1,Irf3,Srsf4,Nop53,Cdc34
mmu05164	Influenza A	-1.44	14/168	Akt1,H2-Ab1,H2-Eb1,Hspa1b,Hspa2,Nfkbib,Furin,Pik3r2,Map2k2,Map2k7,Nxf1,Ddx39b,Irf3,Hspa1a
mmu04915	Estrogen signaling pathway	-1.34	9/96	Akt1,Atf6b,Hspa1b,Hspa2,Pik3r2,Map2k2,Creb3l1,Hspa1a,Shc2

Supplemental Table 5. Significantly enriched KEGG pathways annotated to transcripts up-regulated in *β-Slc4a4*$^{+/+}$ HFD islets.

Id	Description	LogP	Terms/List	Symbols
mmu04110	Cell cycle	-7.56	23/124	Atm,Bub1,Ccna2,Ccnb2,Ccnd1,Ccne2,Cdc25c,Cdk1,Cdkn2c,Hdac2,Mcm3,Prkdc,Rb1,Stag1,Stag2,Smc1a,Orc4,Mad2l1,Espl1,Cdc20,Cdc27,Atr,Ccnb1
mmu04914	Progesterone-mediated oocyte maturation	-6.08	17/87	Bub1,Ccna2,Ccnb2,Cdc25c,Cdk1,Gnai3,Hsp90aa1,Igf1r,Pde3b,Pik3r1,Mapk10,Mad2l1,Cpeb4,Braf,Rps6ka3,Cdc27,Ccnb1
mmu04120	Ubiquitin mediated proteolysis	-5.38	21/140	Xiap,Brca1,Birc6,Socs3,Trip12,Herc2,Ube2b,Ube3a,Cop1,Cul3,Ube2d2a,Huwe1,Ube2c,Ubr5,Cul2,Cul4b,Ube3c,Cdc20,Ube2q2,Cdc27,Herc1
mmu04114	Oocyte meiosis	-4.91	18/116	Bub1,Calm2,Ccnb2,Ccne2,Cdc25c,Cdk1,Igf1r,Ppp1cb,Ppp2ca,Ppp3r1,Smc1a,Mad2l1,Cpeb4,Espl1,Cdc20,Rps6ka3,Cdc27,Ccnb1
mmu04071	Sphingolipid signaling pathway	-4.60	18/122	Asah1,Degs1,Gna13,Gnai3,Gnaq,Pik3r1,Prkca,Ppp2ca,Pten,Rock1,Rock2,Sgpl1,Mapk10,Asah2,Sgms2,Sgpp1,Sgms1,Ppp2r3a
mmu04150	mTOR signaling pathway	-3.78	19/153	Chuk,Eif4e,Fzd6,Grb10,Igf1r,Lrp6,Pik3r1,Prkca,Pten,Sos1,Rragd,Seh1l,Rictor,Deptor,Atp6v1h,Braf,Rps6ka3,Fnip1,Fnip2
mmu04141	Protein processing in endoplasmic reticulum	-3.73	20/167	Canx,Hsp90aa1,Stt3a,Hspa4l,Mapk10,Ero1a,Ube2d2a,Ngly1,Uggt2,Erlec1,Edem3,Ssr3,Ero1b,Stt3b,Tram1,Svip,Sec63,Edem1,Mbtps2,Dnajc3
mmu04510	Focal adhesion	-3.54	22/199	Xiap,Arhgap5,Ctnnb1,Ccnd1,Cdc42,Igf1r,Itga2,Itga6,Met,Pak3,Pik3r1,Prkca,Ppp1cb,Pten,Rock1,Rock2,Sos1,Spp1,Mapk10,Braf,Rap1a,Rap1b
mmu05200	Pathways in cancer	-3.36	35/393	Apc,Xiap,Birc5,Ctnnb1,Ccnd1,Ccne2,Cdc42,Chuk,Fzd6,Gna13,Gnai3,Gnaq,Gng12,Hdac2,Hif1a,Hsp90aa1,Igf1r,Itga2,Itga6,Met,Pik3r1,Prkca,Pten,Rb1,Rock1,Rock2,Sos1,Tgfbr1,Mapk10,Cks2,Arhgef12,Cul2,Appl1,Tpr,Braf
mmu05205	Proteoglycans in cancer	-3.33	22/206	Ctnnb1,Ccnd1,Cd44,Cdc42,Dcn,Fzd6,Hif1a,Igf1r,Itga2,Met,Pdcd4,Pik3r1,Prkca,Ppp1cb,Rdx,Rock1,Rock2,Sos1,Timp3,Arhgef12,Ank2,Braf
mmu05211	Renal cell carcinoma	-2.95	10/65	Cdc42,Hif1a,Met,Pak3,Pik3r1,Sos1,Cul2,Braf,Rap1a,Rap1b
mmu04919	Thyroid hormone signaling pathway	-2.86	14/115	Atp1b1,Ctnnb1,Ccnd1,Dio1,Hdac2,Hif1a,Kat2b,Pik3r1,Prkca,Thrb,Med14,Med13l,Med13,Med12l
mmu04720	Long-term potentiation	-2.85	10/67	Cacna1c,Calm2,Gnaq,Prkca,Ppp1cb,Ppp3r1,Braf,Rap1a,Rps6ka3,Rap1b
mmu04115	p53 signaling pathway	-2.80	10/68	Atm,Ccnb2,Ccnd1,Ccne2,Ccng1,Cdk1,Pten,Cop1,Atr,Ccnb1
mmu00310	Lysine degradation	-2.68	9/59	Ezh2,Nsd1,Setmar,Nsd2,Acat1,Ash1l,Kmt2a,Kmt2c,Setd2
mmu04520	Adherens junction	-2.61	10/72	Ctnnb1,Cdc42,Csnk2a1,Igf1r,Met,Afdn,Ptprj,Tgfbr1,Yes1,Nectin3
mmu05202	Transcriptional misregulation in cancer	-2.60	18/177	Atm,Bcl2a1a,Cdkn2c,Etv1,Hdac2,Igf1r,Met,Pbx1,Cdk14,Prom1,Ptcra,Sp1,Kdm6a,Fut8,Gria3,Nupr1,Nsd2,Kmt2a
mmu05210	Colorectal cancer	-2.53	9/62	Apc,Birc5,Ctnnb1,Ccnd1,Pik3r1,Tgfbr1,Mapk10,Appl1,Braf
mmu05215	Prostate cancer	-2.49	11/87	Ctnnb1,Ccnd1,Ccne2,Chuk,Hsp90aa1,Igf1r,Pik3r1,Pten,Rb1,Sos1,Braf
mmu03013	RNA transport	-2.49	17/167	Eef1a1,Eif4a2,Eif4e,Eif4g2,Fxr1,Eif3e,Ranbp2,Strap,Eif2s3x,Nup37,Seh1l,Xpot,Eif3j1,Xpo1,Tpr,Eif5,Thoc2
mmu01212	Fatty acid metabolism	-2.47	8/52	Acadl,Cpt1a,Acsl4,Acaa2,Fads2,Elovl5,Acat1,Acsl5
mmu04024	cAMP signaling pathway	-2.45	19/197	Atp1b1,Cacna1c,Calm2,Gnai3,Afdn,Oxtr,Pde3b,Pde4b,Pik3r1,Ppp1cb,Rock1,Rock2,Mapk10,Gria3,Ghrl,Braf,Rap1a,Rap1b,Gpr119
mmu05214	Glioma	-2.44	9/64	Calm2,Ccnd1,Igf1r,Pik3r1,Prkca,Pten,Rb1,Sos1,Braf
mmu04810	Regulation of actin cytoskeleton	-2.39	20/214	Apc,Cdc42,Gna13,Gng12,Itga2,Itga6,Pak3,Pik3r1,Pikfyve,Ppp1cb,Rdx,Rock1,Rock2,Sos1,Nckap1,Diaph2,Arpc5,Arhgef12,Braf,Iqgap3
mmu04972	Pancreatic secretion	-2.37	12/103	Atp1b1,Bst1,Gnaq,Prkca,Try4,Pla2g2f,Rab11a,1810009J06Rik,Try5,Rap1a,Rap1b,Gm10334
mmu01521	EGFR tyrosine kinase inhibitor resistance	-2.27	10/80	Eif4e,Igf1r,Jak2,Met,Nf1,Pik3r1,Prkca,Pten,Sos1,Braf
mmu03018	RNA degradation	-2.24	10/81	Btg1,Btg3,Ddx6,Hspd1,Dcp2,Dhx36,Pan3,Ttc37,Cnot6l,Cnot1
mmu04010	MAPK signaling pathway	-2.22	22/252	Cacna1c,Cacna2d1,Cdc42,Chuk,Gng12,Il1r1,Stmn1,Nf1,Prkca,Ppp3r1,Dusp1,Sos1,Tgfbr1,Map3k2,Map4k1,Mapk10,Braf,Rap1a,Rps6ka3,Rap1b,Taok1,Rasa1

Supplemental Table 5. Significantly enriched KEGG pathways annotated to transcripts up-regulated in *β-Slc4a4*$^{+/+}$ HFD islets. (continued)

mmu05166	HTLV-I infection	-2.22	24/283	Apc,Xiap,Atm,Canx,Ctnnb1,Ccnb2,Ccnd1,Cdkn2c,Chuk,Dlg1,Egr1,Fzd6,Il1r1,Kat2b,Pik3r1,Ppp3r1,Rb1,Tgfbr1,Mad2l1,Trp53inp1,Xpo1,Cdc20,Cdc27,Atr
mmu04070	Phosphatidylinositol signaling system	-2.16	11/96	Calm2,Mtm1,Pik3c2a,Pik3r1,Pikfyve,Prkca,Pten,Pik3c3,Ppip5k2,Impad1,Ocrl
mmu05222	Small cell lung cancer	-2.16	10/83	Xiap,Ccnd1,Ccne2,Chuk,Itga2,Itga6,Pik3r1,Pten,Rb1,Cks2
mmu04611	Platelet activation	-2.13	13/124	Col3a1,Gna13,Gnai3,Gnaq,Itga2,Pik3r1,Ppp1cb,Rock1,Rock2,Snap23,Arhgef12,Rap1a,Rap1b
mmu05412	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	-2.10	9/72	Cacna1c,Cacna2d1,Ctnnb1,Dsc2,Dsg2,Itga2,Itga6,Slc8a1,Dsp
mmu00600	Sphingolipid metabolism	-2.09	7/48	Asah1,Degs1,Sgpl1,Asah2,Sgms2,Sgpp1,Sgms1
mmu00071	Fatty acid degradation	-2.04	7/49	Acadl,Adh7,Cpt1a,Acsl4,Acaa2,Acat1,Acsl5
mmu04730	Long-term depression	-2.04	8/61	Gna13,Gnai3,Gnaq,Igf1r,Prkca,Ppp2ca,Gria3,Braf
mmu05213	Endometrial cancer	-1.99	7/50	Apc,Ctnnb1,Ccnd1,Pik3r1,Pten,Sos1,Braf
mmu05212	Pancreatic cancer	-1.92	8/64	Ccnd1,Cdc42,Chuk,Pik3r1,Rb1,Tgfbr1,Mapk10,Braf
mmu04068	FoxO signaling pathway	-1.91	13/132	Atm,Ccnb2,Ccnd1,Chuk,Igf1r,Pik3r1,Pten,Sos1,Tgfbr1,Mapk10,Fbxo32,Braf,Ccnb1
mmu04728	Dopaminergic synapse	-1.86	13/134	Arntl,Cacna1c,Calm2,Gnai3,Gnaq,Gng12,Kif5b,Prkca,Ppp1cb,Ppp2ca,Mapk10,Gria3,Ppp2r3a
mmu04014	Ras signaling pathway	-1.80	19/228	Calm2,Cdc42,Chuk,Gng12,Igf1r,Met,Afdn,Nf1,Pak3,Pik3r1,Prkca,Sos1,Mapk10,Pla2g2f,Rap1a,Rap1b,Rasa1,Rasal2,Rab5a
mmu05031	Amphetamine addiction	-1.77	8/68	Cacna1c,Calm2,Fosb,Pdyn,Prkca,Ppp1cb,Ppp3r1,Gria3
mmu05220	Chronic myeloid leukemia	-1.67	8/71	Ccnd1,Chuk,Hdac2,Pik3r1,Rb1,Sos1,Tgfbr1,Braf
mmu05223	Non-small cell lung cancer	-1.66	7/58	Ccnd1,Pik3r1,Prkca,Rb1,Sos1,Eml4,Braf
mmu05224	Breast cancer	-1.63	13/144	Apc,Brca1,Ctnnb1,Ccnd1,Fzd6,Igf1r,Lrp6,Pik3r1,Pten,Rb1,Sos1,Sp1,Braf
mmu04670	Leukocyte transendothelial migration	-1.56	11/117	Arhgap5,Ctnnb1,Cdc42,Gnai3,Afdn,Pik3r1,Prkca,Rock1,Rock2,Rap1a,Rap1b
mmu04974	Protein digestion and absorption	-1.51	9/90	Atp1b1,Col3a1,Mep1a,Slc8a1,Try4,Ace2,1810009J06Rik,Try5,Gm10334
mmu01522	Endocrine resistance	-1.43	9/93	Ccnd1,Cdkn2c,Igf1r,Pik3r1,Rb1,Sos1,Sp1,Mapk10,Braf
mmu04961	Endocrine and other factor-regulated calcium reabsorption	-1.33	6/54	Atp1b1,Gnaq,Prkca,Slc8a1,Rab11a,Cltc
mmu04360	Axon guidance	-1.33	14/175	Bmpr2,Cdc42,Gnai3,Met,Pak3,Pik3r1,Prkca,Plxna2,Ppp3r1,Rock1,Rock2,Arhgef12,Rasa1,Robo2
mmu05218	Melanoma	-1.30	7/69	Ccnd1,Igf1r,Met,Pik3r1,Pten,Rb1,Braf
mmu04270	Vascular smooth muscle contraction	-1.30	11/129	Cacna1c,Calm2,Gna13,Gnaq,Prkca,Ppp1cb,Rock1,Rock2,Pla2g2f,Arhgef12,Braf

Supplemental Table 6. Gene Specific Primers

Primer	Sequence
Mouse	
Nkx6.1	F-CTGCACAGTATGGCCGAGATG
	R-CCGGGTTATGTGAGCCCAA
Iapp	F-CTGTGGCACTGAACCACTTGA
	R-TGTTGCACTTCCGTTTGTCCA
Aldh1a3	F-ATCAACAACGACTGGCACGAA
	R-CACATCGGGCTTATCTCCTTC
Slc4a4	F-AGGAGGAGGACATGGTGACT
	R-GCCCAGGAAACTCTCCAACA
Cox6a2	F-CTGCTCCCTTAACTGCTGGAT
	R-GATTGTGGAAAAGCGTGTGGT
Mafa	F-ATCATCACTCTGCCCACCAT
	R-TGGAGCTGGCACTTCTCGCT
Pdx1	F-GAACCCGAGGAAAACAAGAGG
	R-GTTCAACATCACTGCCAGCTC
Atp5d	F-TGCTTCAGGCGCGTACATAC
	R-CACTTGCTTGACGTTGGCA
Ndufa7	F-TCCGCTACTCGCGTTATCCA
	R-GATTGAGGGAGGCACAACTTC
Ndufb11	F-CTCCAGGGCTGTAATCGCC
	R-CGCGTAGACGTTTTCGTCCT
Actin	F-GCAGGAGTACGATGAGTCCG
	R-ACGCAGCTCAGTAACAGTCC
Human	
SLC4A4	F-AGCACCTCACTATCTGAAAGGC
	R-CACAACTTGACTGGTTGGCG
SLC9A1	F-GCCTTCTCTCTGGGCTACCT
	R-CTTGTCCTTCCAGTGGTGGT
ATP5D	F-AAACTTGGAGAAGGCCCAG
	R-GATTCGGATCTGGATCTCTGC
NDUFA7	F-TCATCATGTCGTCGCAGAAG
	R-GACAGCTCCCACCTCTTTATG
NDUFB11	F-TGAGAGGCTTGTGAAATACCG
	R-CAACTGGTCACTCATCCTCTG
COX6A2	F-ACTCAACAGGTGATTGGCCC
	R-GTTGGTAGGGACGGAACTCG
ALDH1A3	F-ATCTCGACAAAGCCCTGAAG
	R-CGTATTCACCTAGTTCTCTGCC
NKX6.1	F-TCAACAGCTGCGTGATTTTC
	R-CCAAGAAGAAGCAGGACTCG
PDX1	F-TGAAGTCTACCAAAGCTCACG
	R-GGAACTCCTTCTCCAGCTCTA
MAFA	F-ATTCTGGAGAGCGAGAAGTGCCAA
	R-CGCCAGCTTCTCGTATTTCTCCTT
IAPP	F-AGCTGCAAGTATTTCTCATTGTG
	R-CATTTCCGCTTTTCCACCTG
ACTIN	F-GCCGTCTTCCCCTCCATC
	R-AATCCTTCTGACCCATGCCC
GAPDH	F-GAAGGTGAAGGTCGGAGTC
	R-GAAGATGGTGATGGGATTTC