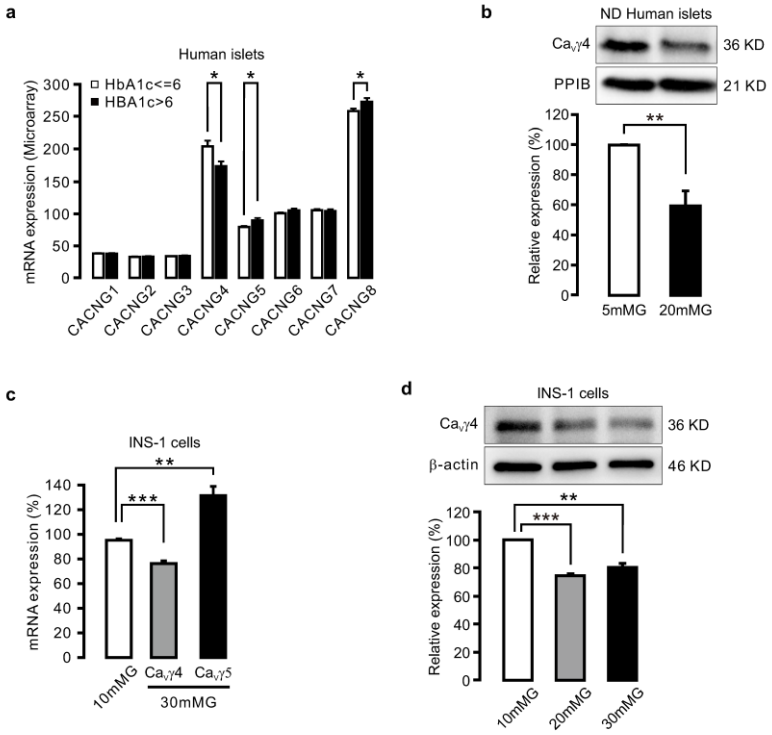
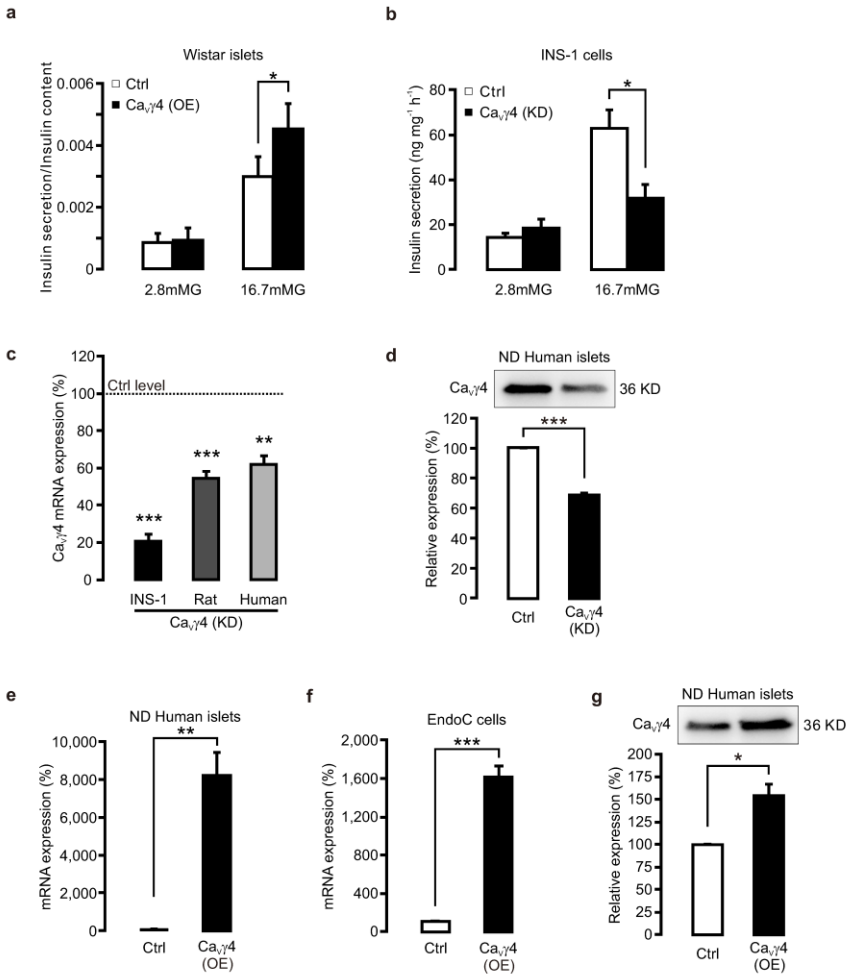
Supplementary Figure 1



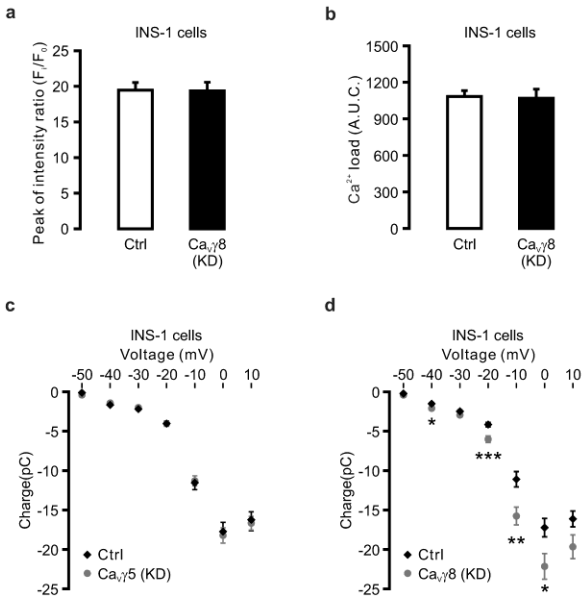
Supplementary Figure 1. $Ca_V\gamma4$ expression is reduced in beta-cells in response to glucotoxicity. **(a)** Microarray gene profile showing all $Ca_V\gamma$ subunit genes mRNA expression in human pancreatic islets. n = 77 donors for HbA1c ≤ 6, 36 donors for HbA1c > 6, *p = 0.028 ($Ca_V\gamma4$), *p = 0.012 ($Ca_V\gamma5$), *p = 0.037 ($Ca_V\gamma8$). **(b)** Decreased $Ca_V\gamma4$ protein expression in ND human islets cultured at 5 or 20 mM glucose (48h). n = 3 donors, **p = 0.003. See also Supplementary figure 7l, but cultured for 72h. n = 5 donors, not significant. **(c)** $Ca_V\gamma4$ and $Ca_V\gamma5$ mRNA expression in INS-1 cells cultured at 10 or 30 mM glucose for 24h. n = 3, ***p < 0.001 ($Ca_V\gamma4$), **p = 0.001 ($Ca_V\gamma5$). **(d)** Immunoblotting of $Ca_V\gamma4$ in INS-1 cells cultured at 10, 20 or 30 mM glucose for 72 h. n = 4, ***p < 0.001 (20 mMG), **p = 0.009 (30 mMG). Data are presented as Mean ± SEM and were analyzed with two-tailed unpaired Student's *t*-test; and the significance in (c-d) were corrected by Holm-Bonferroni method.

Supplementary Figure 2



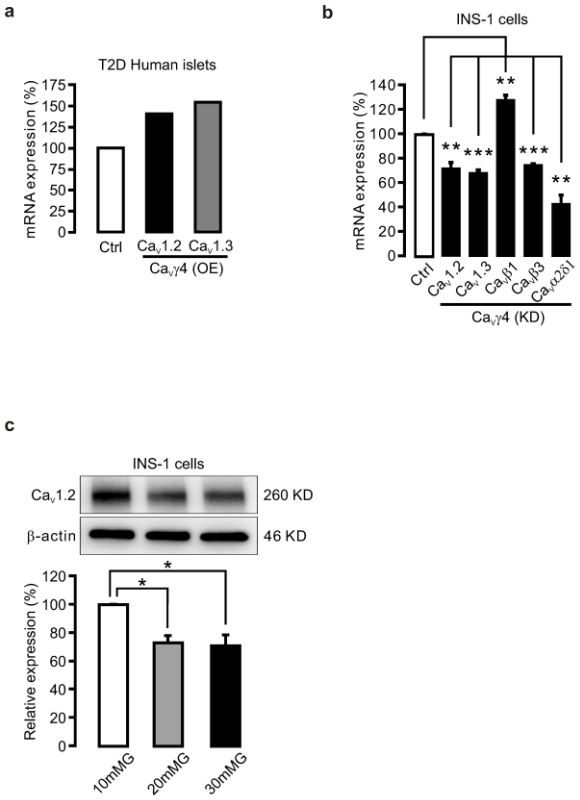
Supplementary Figure 2. Successful siRNA and lentiviral transfection of Ca$_V$γ4 in human beta-cells and the effects on glucose-stimulated insulin secretion (GSIS). (a) GSIS in Ca$_V$γ4 overexpressed Wistar rat islets. n = 3, *p = 0.027. **(b)** As in (a) but in Ca$_V$γ4 silenced INS-1 cells. n = 4, *p = 0.024. **(c)** Ca$_V$γ4 mRNA expression in Ca$_V$γ4 silenced INS-1 cells, Wistar rat islets and ND human islets to validate the silencing effect of Ca$_V$γ4 siRNA. n = 7 (INS-1, ***p < 0.001), 4 (rat, ***p < 0.001) and 3 (human, **p = 0.001). **(d)** Ca$_V$γ4 protein expression in Ca$_V$γ4 silenced ND human islets normalized by total protein (see Supplementary figure 7n). n = 3 donors, ***p < 0.001. **(e)** Ca$_V$γ4 mRNA expression in Ca$_V$γ4 overexpressed ND human islets to validate the Ca$_V$γ4 lentiviral overexpressing efficiency. n = 3 donors, **p = 0.002. **(f)** As in (e) but in Ca$_V$γ4 overexpressed EndoC cells. n = 4, ***p < 0.001. **(g)** As in (d) but in Ca$_V$γ4 overexpressed ND human islets normalized by total protein (see Supplementary figure 7o). n = 3 donors, *p = 0.014. Data are presented as Mean ± SEM and were analyzed with two-tailed paired (a) and unpaired (b-g) Student's *t*-test.

Supplementary Figure 3



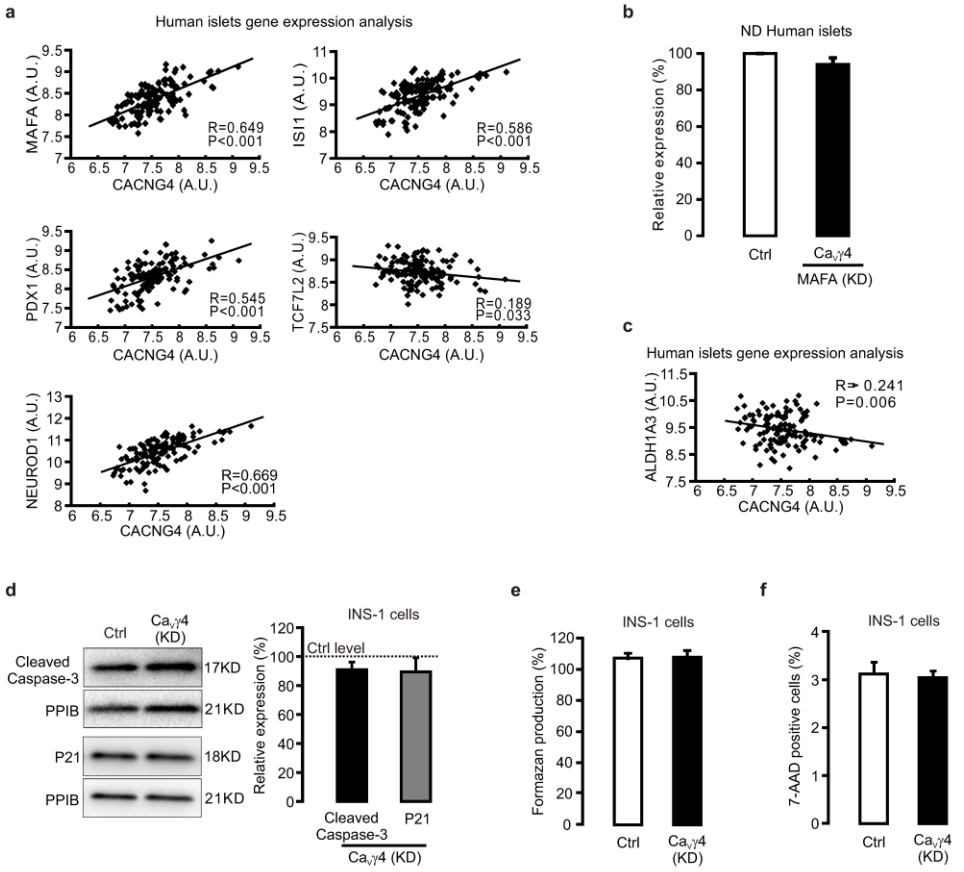
Supplementary Figure 3. Ca^{2+} influx in $Ca_V\gamma8$ silenced INS-1 cells. (a) Comparison of intracellular Ca^{2+} concentration $[Ca^{2+}]_i$ peak intensity (Fi/F0) in control and $Ca_V\gamma8$ silenced INS-1 cells by Ca^{2+} imaging, p = 0.957. **(b)** Integrated Ca^{2+} load (Area Under the Curve, A.U.C.) after the stimulation of 70 mM KCl, 0-180s, p = 0.867, see Figure 3f. n = 62 control and 42 $Ca_V\gamma8$ silencing cells, from 3 independent experiments, for both (a) and (b). **(c)** Integrated whole-cell Ca^{2+} charge-voltage relations in $Ca_V\gamma5$ silenced INS-1 cells. n = 53 control and 57 $Ca_V\gamma5$ silencing cells from 3 independent experiments. **(d)** As in (c) but in $Ca_V\gamma8$ silenced INS-1 cells. n = 41 control and 40 $Ca_V\gamma8$ silencing cells from 3 independent experiments, *p = 0.031 (-40mV), ***p < 0.001 (-20mV), **p = 0.003 (-10mV), *p = 0.017 (0mV). Data are presented as Mean ± SEM and were analyzed with two-tailed unpaired Student's *t*-test.

Supplementary Figure 4



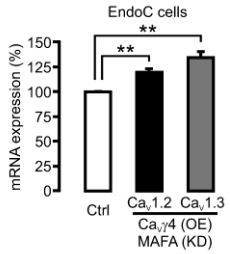
Supplementary Figure 4. $Ca_V\gamma4$ regulates $Ca_V1.2$ and $Ca_V1.3$ expression. (a) Increased tendency of $Ca_V1.2$ and $Ca_V1.3$ mRNA expression in $Ca_V\gamma4$ overexpressed T2D human islets, n = 1 donor. **(b)** Ca_V channels mRNA expression in $Ca_V\gamma4$ silenced INS-1 cells. n = 3, **p = 0.004 ($Ca_V1.2$), ***p < 0.001 ($Ca_V1.3$), **p = 0.002 ($Ca_V\beta1$), ***p < 0.001 ($Ca_V\beta3$), **p = 0.001 ($Ca_V\alpha_2\delta1$). **(c)** $Ca_V1.2$ protein expression in INS-1 cells cultured with 10, 20 or 30 mM glucose. n = 4, *p = 0.012 (20 mMG), *p = 0.028 (30 mMG). Data are presented as Mean ± SEM and were analyzed with two-tailed unpaired Student's *t*-test; and the significance in (a-b) were corrected by Holm-Bonferroni method.

Supplementary Figure 5



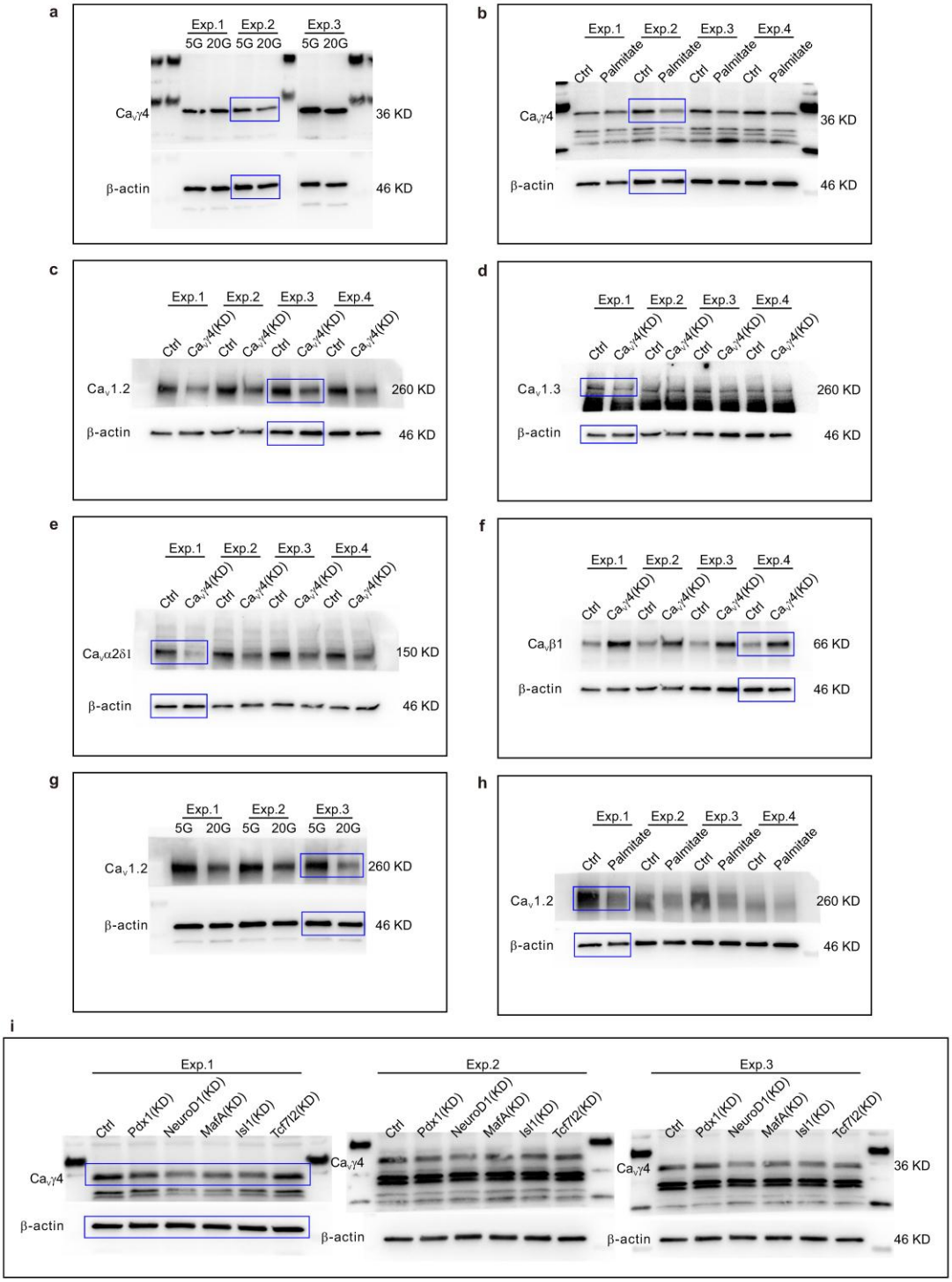
Supplementary Figure 5. Effect of $Ca_V\gamma4$ on beta-cell health. (a) Correlation of mRNA expressions (Microarray) between $Ca_V\gamma4$ (*CACNG4*) and transcription factors *MAFA*, *ISL1*, *PDX1*, *TCF7L2* and *NEUROD1* in human islets. n = 128 donors. Pearson correlation coefficient (*R*) was tested (*t*-test) and labeled alongside with p values. **(b)** $Ca_V\gamma4$ mRNA expression in MAFA silenced ND human islets. n = 3 donors, p = 0.237. **(c)** Correlation of mRNA expressions (Microarray) between $Ca_V\gamma4$ (*CACNG4*) and *ALDH1A3* in human islets. n = 128 donors. **(d)** Cleaved Caspase-3 and P21 immunoblotting and means of expression in $Ca_V\gamma4$ silenced INS-1 cells. n = 4 each, p = 0.155 and p = 0.356, respectively. **(e)** Cellular viability (formazan production) measured in $Ca_V\gamma4$ silenced INS-1 cells. n = 4, p = 0.945. **(f)** Cell viability test by 7-AAD staining in $Ca_V\gamma4$ silenced INS-1 cells. n = 3, p = 0.782. Data are presented as Mean ± SEM and were analyzed with two-tailed unpaired Student's *t*-test.

Supplementary Figure 6

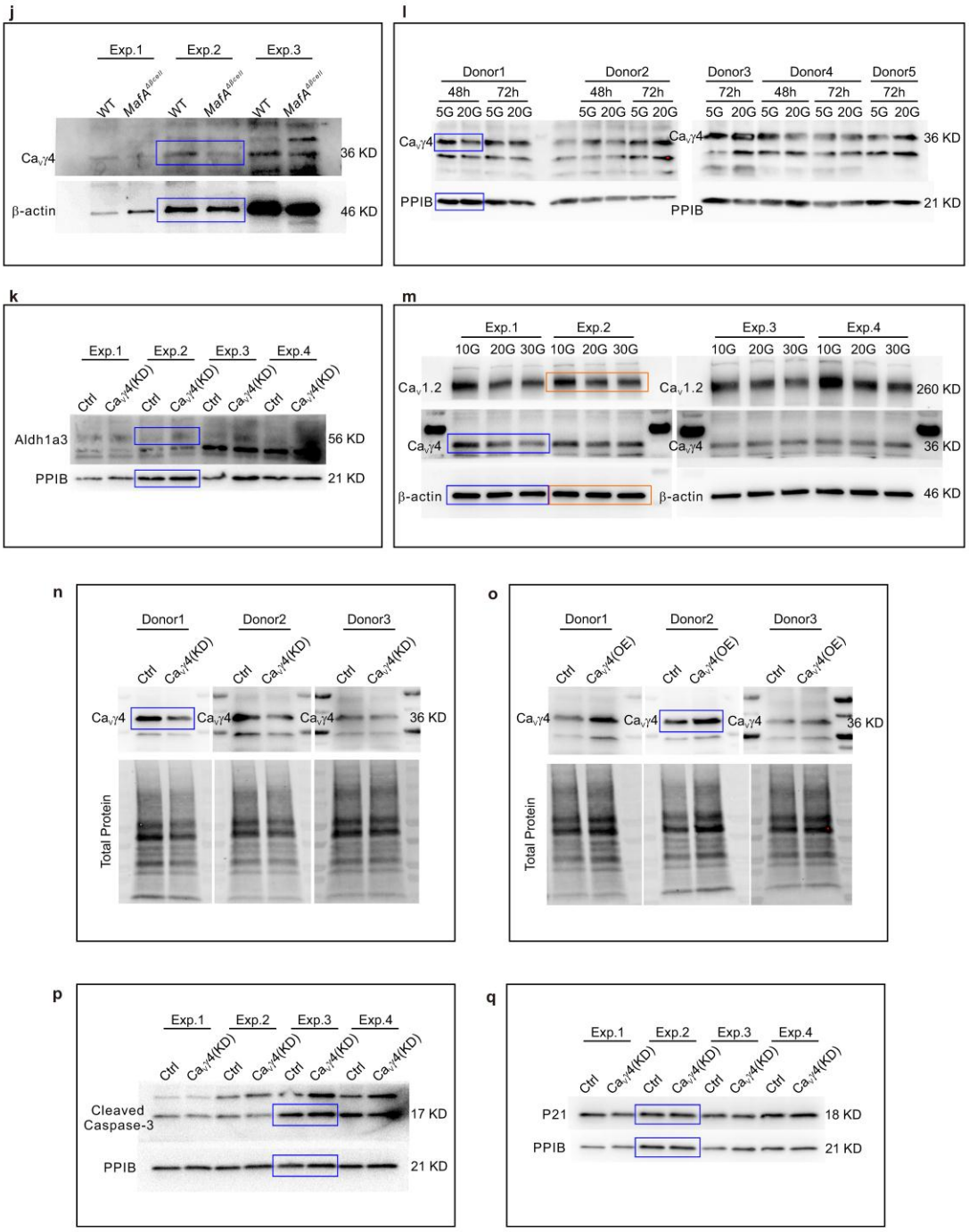


Supplementary Figure 6. $Ca_V1.2$ and $Ca_V1.3$ expression in $Ca_V\gamma4$ overexpressed and MAFA silenced beta-cells. Increased $Ca_V1.2$ and $Ca_V1.3$ mRNA expression in $Ca_V\gamma4$ overexpressed and simultaneously MAFA silenced human EndoC cells. n = 4, **p = 0.002 ($Ca_V1.2$), **p = 0.001 ($Ca_V1.3$). Data are presented as Mean ± SEM and were analyzed with two-tailed unpaired Student's *t*-test; and the significance were corrected by Holm-Bonferroni method.

Supplementary Figure 7



Supplementary Figure 7



Supplementary Figure 7. Full pictures of protein blots presented in the main paper. Protein blots from which the blue or orange boxes correspond, with similar band order, to Figure 1g-h **(a-b)**, Figure 4d **(c-f)**, Figure 4e-f **(g-h)**, Figure 5c-d and h **(i-k)**, Supplementary Figure 1b and d **(l and m (blue))**, Supplementary Figure 2d and g **(n-o)**, Supplementary Figure 4c **(m (orange))**, and Supplementary Figure 5d **(p-q)**.

Supplementary Table 1

Supplementary Table 1. Characteristics of human islet donors used for experiment.

	All (n=51)	Non-diabetic (n=37)	T2D (n=14)
Age (years)	61 ± 11	60 ± 12	64 ± 9
Sex (female/male)	20/31	16/21	4/10
BMI (kg m^{-2})	27.1 ± 5.7 *	26.1 ± 4.7 *	29.5 ± 7.4
HbA1c (%)	5.9 ± 0.8 **	5.5 ± 0.4 **	6.9 ± 0.5
Purity (%)	73 ± 20	70 ± 21	78 ± 12
Days cultured	3 ± 1	3 ± 1	2 ± 1

Data are presented as mean ± s.d.

* 1 missing value

** 2 missing values