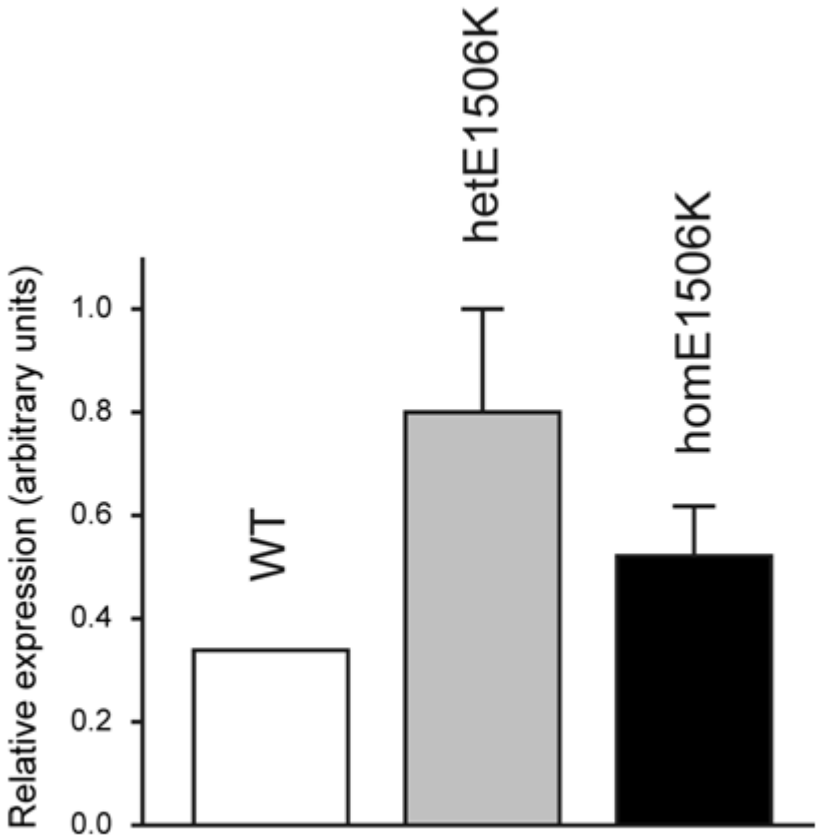
SUPPLEMENTARY DATA

Supplementary Table 1. Electrophysiological properties of wild-type and mutant beta-cells

	Wild-type	**hetE1506K**	**homE1506K** (2-month old)	**homE1506K** (6-month old)
IC_{50} (μM)	33.8±7.4	14.2±1.5	10.2±0.75	9.25±0.91
h	1.14±0.17	0.95±0.09	1.07±0.09	1.09±0.11
n	6	7	7	7
Spiking	0/20	15/30	19/30	21/30
K_{ATP} activity	15/20	20/30	4/30	1/30

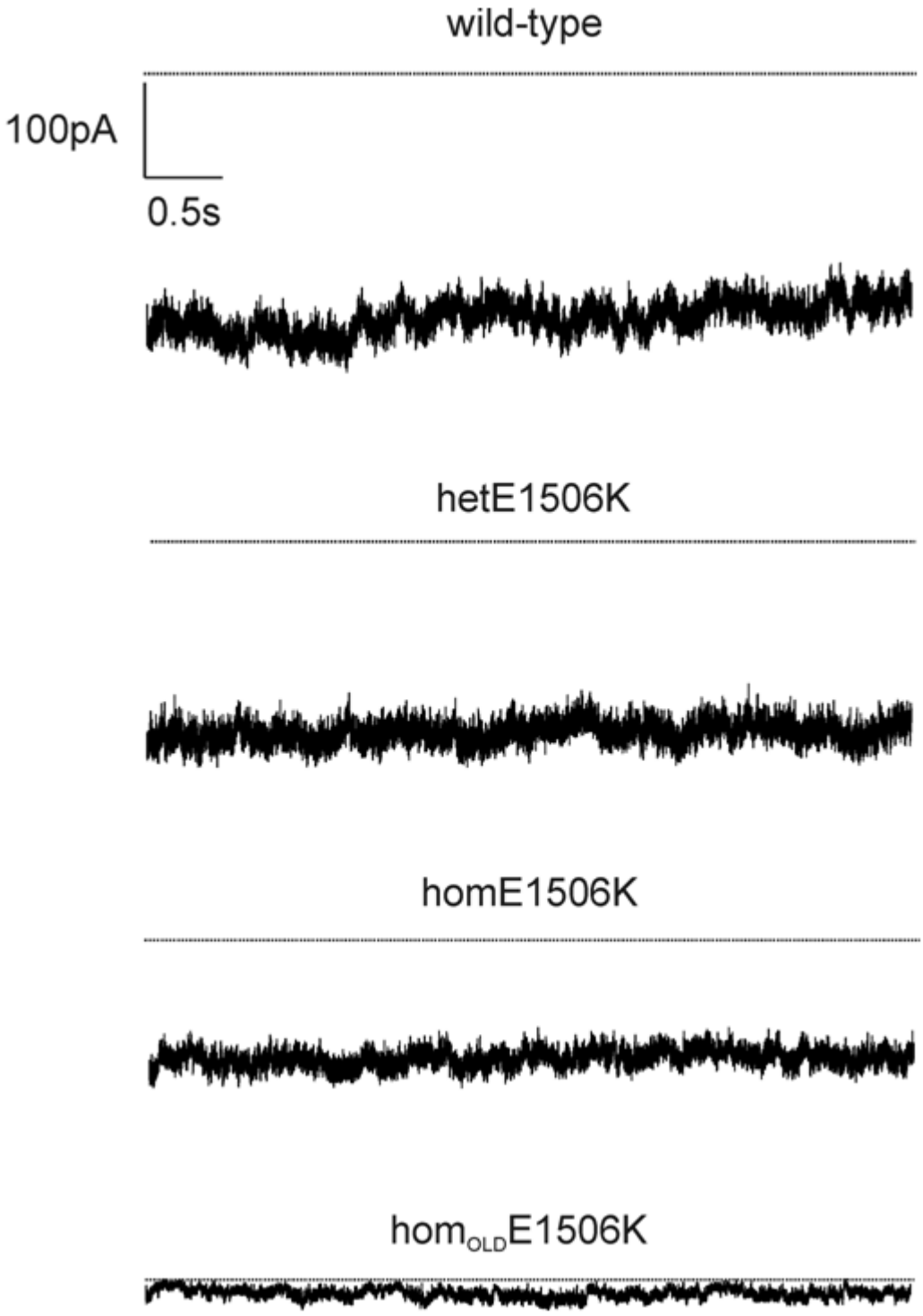
Mean±SEM values for the ATP concentration producing half-maximal inhibition of K_{ATP} currents (IC_{50}), and the slope factor (*h*), used to fit the ATP concentration-inhibition curves for *n* patches. IC_{50} and *h* values are the mean of the fits of equation 1 to the individual dose-response curves. Spiking and K_{ATP} activity data refer to the number of patches exhibiting activity out of the total number of patches measured.

Supplementary Figure 1. Relative expression of the SUR1 gene in 6 month-old WT, hetE1506K and homE1506K islets. Data are expressed relative to a panel of house-keeping genes. Data are the mean ± SEM of WT (n=2), hetE1506K (n=4) and homE1506K (n=4) 6-month-old mice.



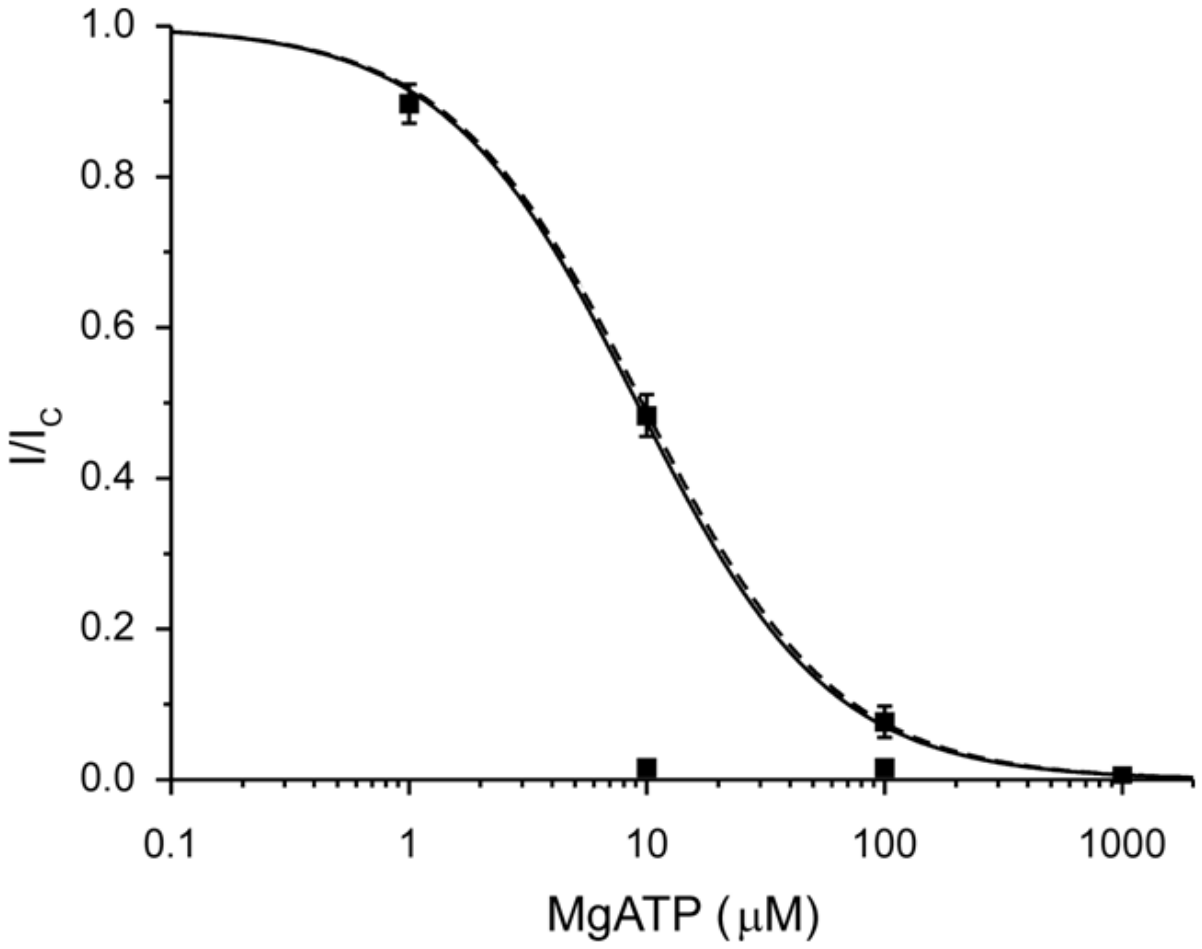
SUPPLEMENTARY DATA

Supplementary Figure 2. Examples of peak macroscopic K_{ATP} currents recorded from inside-out patches immediately after patch excision, from 2-month-old wild-type, hetE1506K and homE1506K mice as indicated and from 6-month old (hom_{OLD}E1506K) mice, as indicated. Currents were recorded at -60mV in nucleotide-free solutions. The dotted line indicates zero current level.



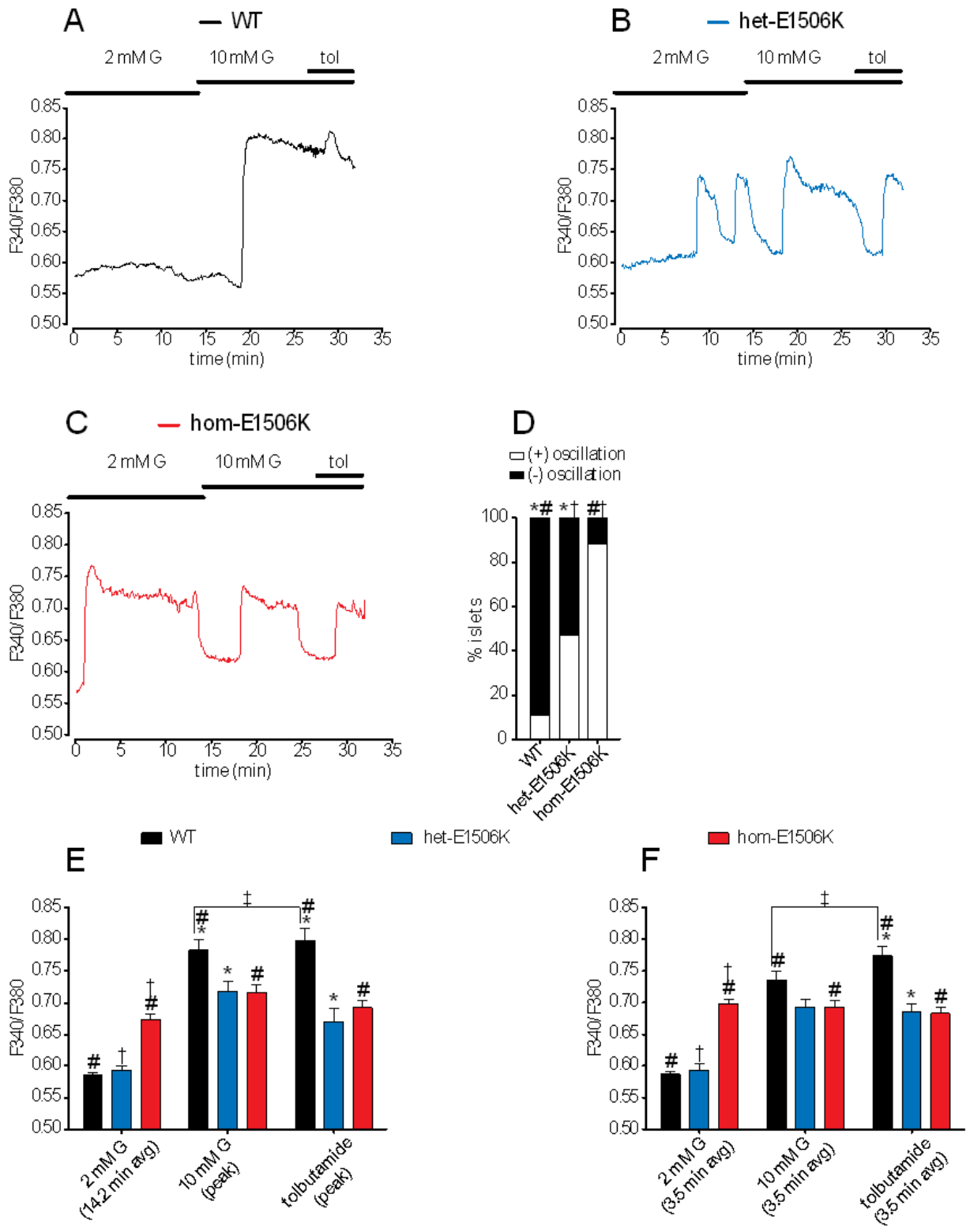
SUPPLEMENTARY DATA

Supplementary Figure 3. Mean±SEM MgATP concentration-inhibition relationships for K_{ATP} currents recorded from beta-cells isolated from 6-month old homE1506K (black circles, n=7 patches, 3 mice) mice. Current (I) is expressed relative to that in ATP-free solution (I_c). The solid line is the best fit of equation 1 to the mean data with IC_{50}=9.1μM, h=1.1. The dashed line indicates the mean fit to the data obtained from 2-month-old homE1506K mice.



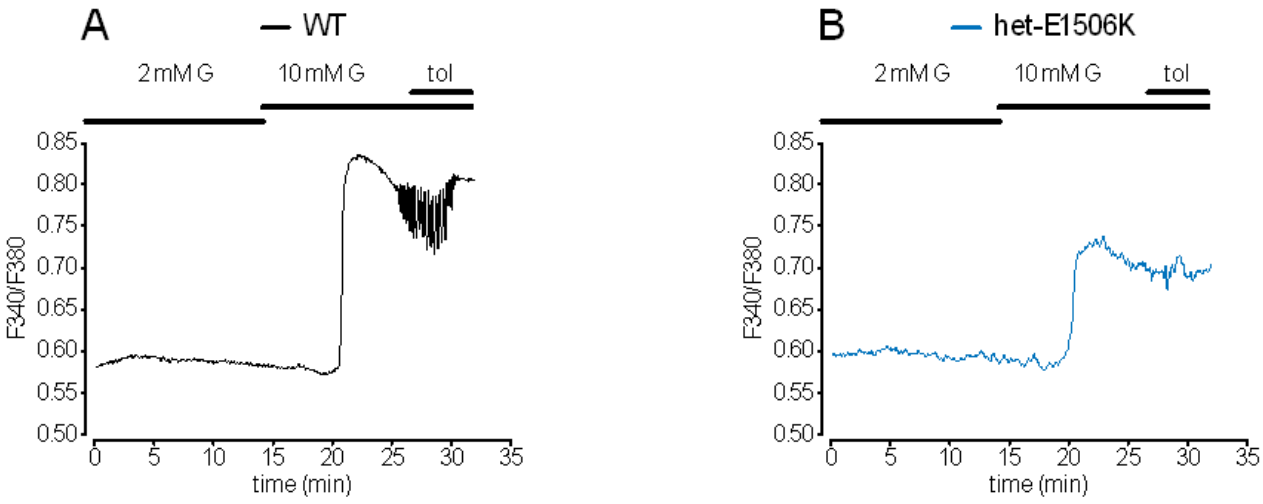
Supplementary Figure 4. A-C. Representative Ca^{2+} responses recorded from 5-6 week-old wild-type (A), het-E1506K (B) and hom-E1506K (C) islets. D. Percentage of islets showing spontaneous Ca^{2+} oscillations in 2 mM glucose (WT = 2/18, het-E1506K = 8/17, hom-E1506K = 21/25). Significance was verified by the Fisher's exact test. E. Mean data (± SEM) showing the average Ca^{2+} level in 2 mM glucose, the peak value in 10 mM glucose and the peak value in 0.2 mM tolbutamide plus 10 mM glucose. Black bars, WT; blue bars, hetE1506K; red bars, homE1506K. F. Mean data (± SEM) showing Ca^{2+} responses averaged over 3.5 min in 2 mM glucose, 10 mM glucose and 0.2 mM tolbutamide plus 10 mM glucose. Black bars, WT; blue bars, hetE1506K; red bars, homE1506K.D-F. Data are the mean ± SEM of 18 islets isolated from 4 WT mice, 17 islets isolated from 3 het-E1506K mice and 25 islets from 3 hom-E1506K mice. Significance was tested using a One-Way ANOVA test and the Bonferroni post-test. Compared groups: WT with het-E1506K (*), WT with hom-E1506K (#) and het-E1506K with hom-E1506K (†). As islets were stimulated consecutively with glucose and tolbutamide, the paired t-test (‡) was used to compare the data between different stimuli.*,#,†,‡ $p < 0.05$.

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

Supplementary Figure 5. A-C. Representative Ca^{2+} responses recorded from 7-14 month-old wild-type (A), het-E1506K (B) and hom-E1506K (C) islets. D. Percentage of islets showing spontaneous Ca^{2+} oscillations in 2 mM glucose (WT = 0/11, het-E1506K = 4/22, hom-E1506K = 0/11). Data were not significantly different (Chi-square test). E. Mean data (± SEM) showing the average Ca^{2+} level at 2 mM glucose, the peak value at 10 mM glucose and the peak value at tolbutamide plus 10 mM glucose. Black bars, WT; blue bars, hetE1506K; red bars, homE1506K. F. Mean data (± SEM) showing Ca^{2+} responses averaged over 3.5 min at 2 mM glucose, 10 mM glucose and tolbutamide plus 10 mM glucose. Black bars, WT; blue bars, hetE1506K; red bars, homE1506K. D-F. Data are the mean ± SEM of 11 islets (2 WT mice), 22 islets (5 het-E1506K mice) and 11 islets (2 hom-E1506K mice). E,F. Significance was tested using a One-Way ANOVA test and the Bonferroni post-test. Compared groups: WT with het-E1506K (*), WT with hom-E1506K (#) and het-E1506K with hom-E1506K (†).*,#,†,‡ $p < 0.05$.



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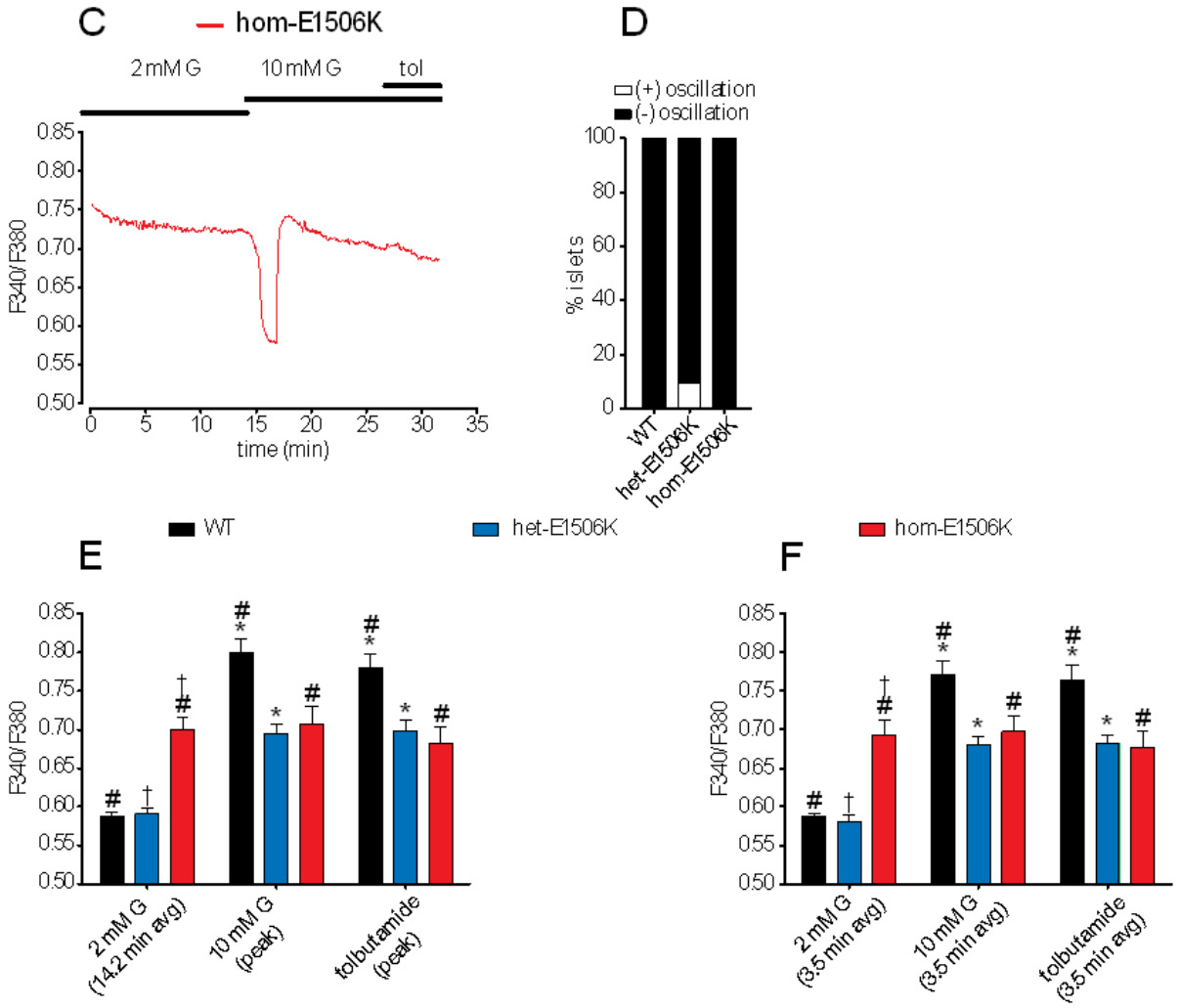
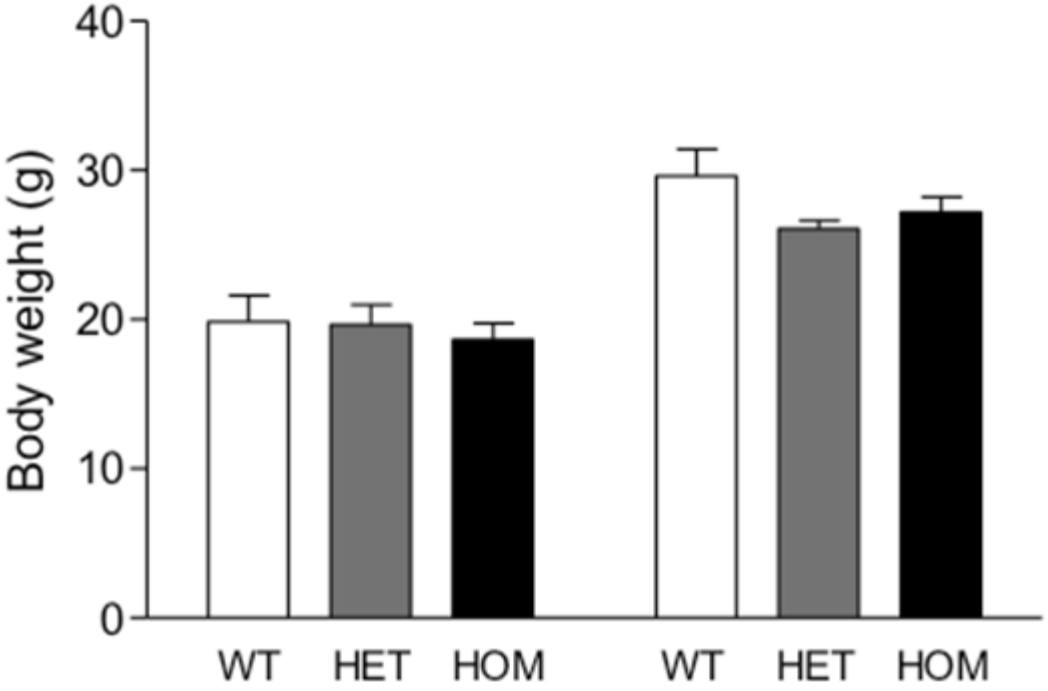


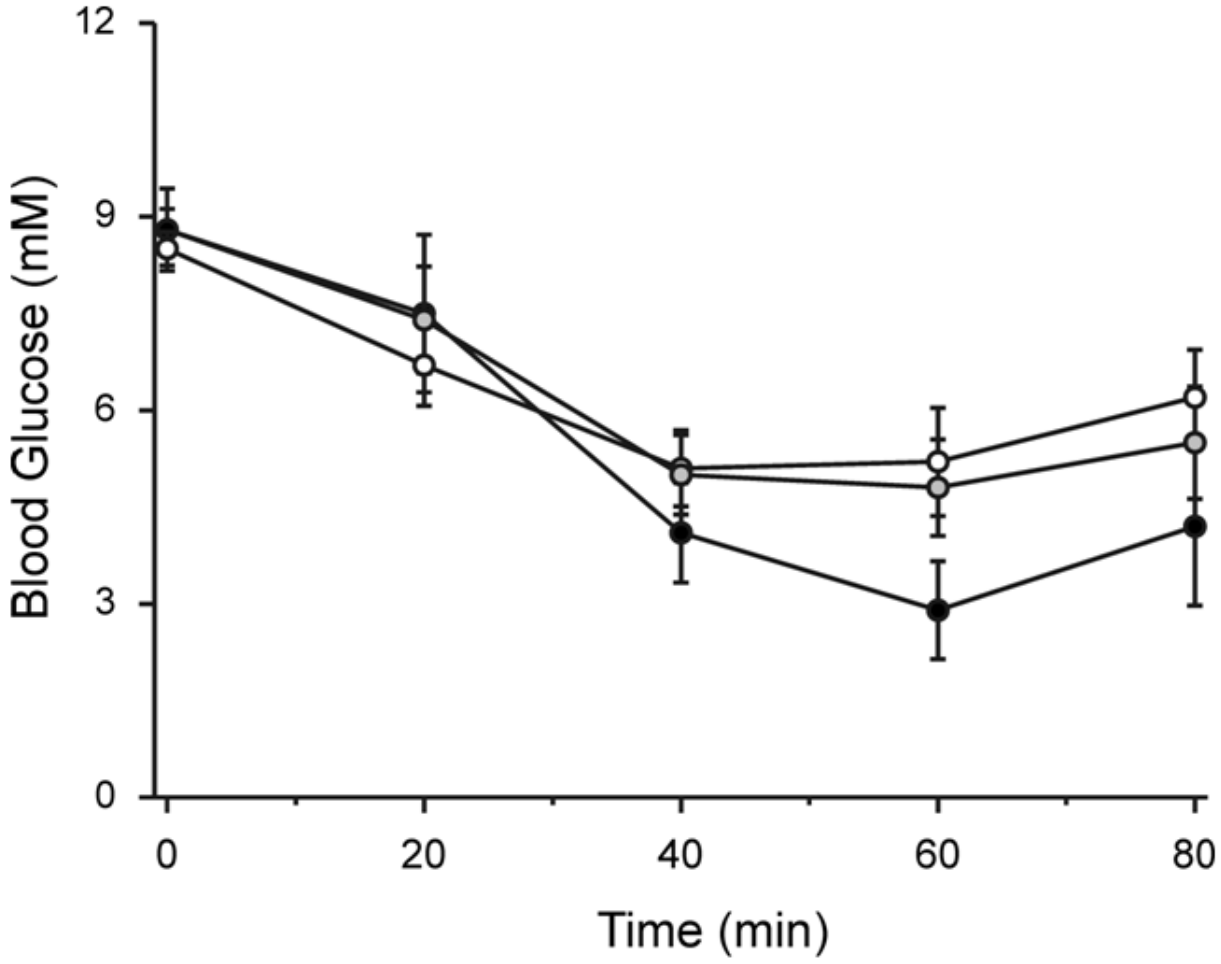
SUPPLEMENTARY DATA

Supplementary Figure 6. Mean±SEM body weight of 2-month-old WT n=5), hetE1506K (grey bar, n=8) and homE1506K (black bar, n=6) mice; and of 6-month old WT (n=4), hetE1506K (n=4) and homE1506K (n=4) mice.



SUPPLEMENTARY DATA

Supplementary Figure 7. Insulin tolerance test for 12-month-old WT (n=11), hetE1506K (n=12) and homE1506K (n=9) mice. Mice were fasted for 4 hours and a fasted blood sample was taken prior to intraperitoneal administration of 0.25mU/g insulin. Subsequent blood samples were taken over time from a tail vein under local anaesthesia (5% Emla cream, AstraZeneca) for glucose measurement. Glucose was measured using a Precision Xtra glucometer (Abbott)



SUPPLEMENTARY DATA

Supplementary Figure 8. A. Mean±SEM post-prandial plasma glucose levels in 2-month-old WT (n=5), hetE1506K (n=8) and homE1506K (n=6) mice. Glucose was measured at 2pm. B. Mean±SEM plasma insulin levels in 2-month-old WT (n=5), hetE1506K (n=5) and homE1506K (n=5) mice. Mice were fasted overnight and insulin was measured 30min after injection of 2g/kg body weight glucose.