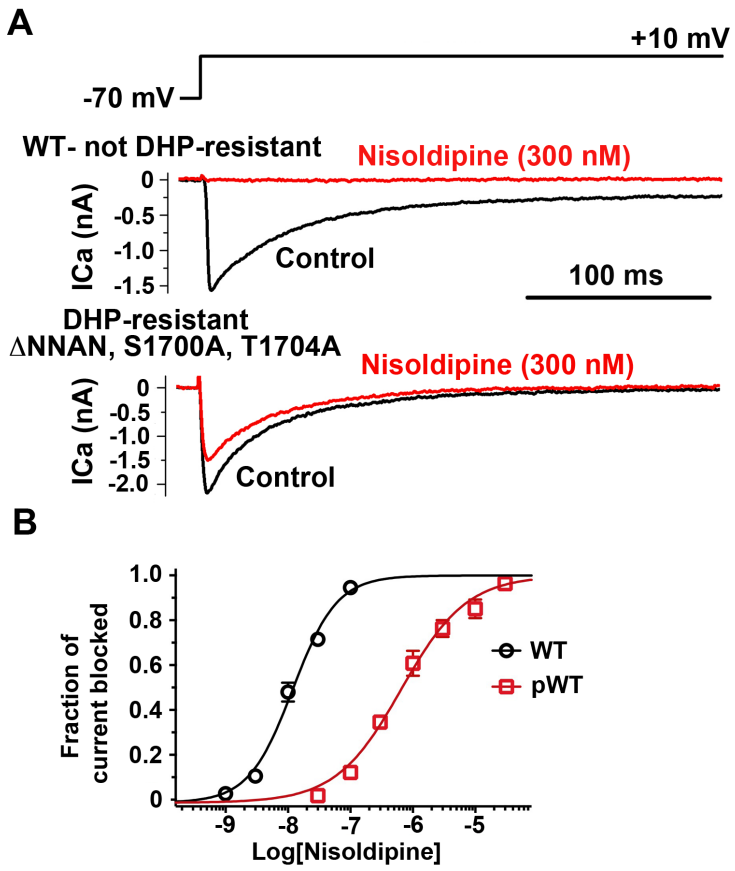
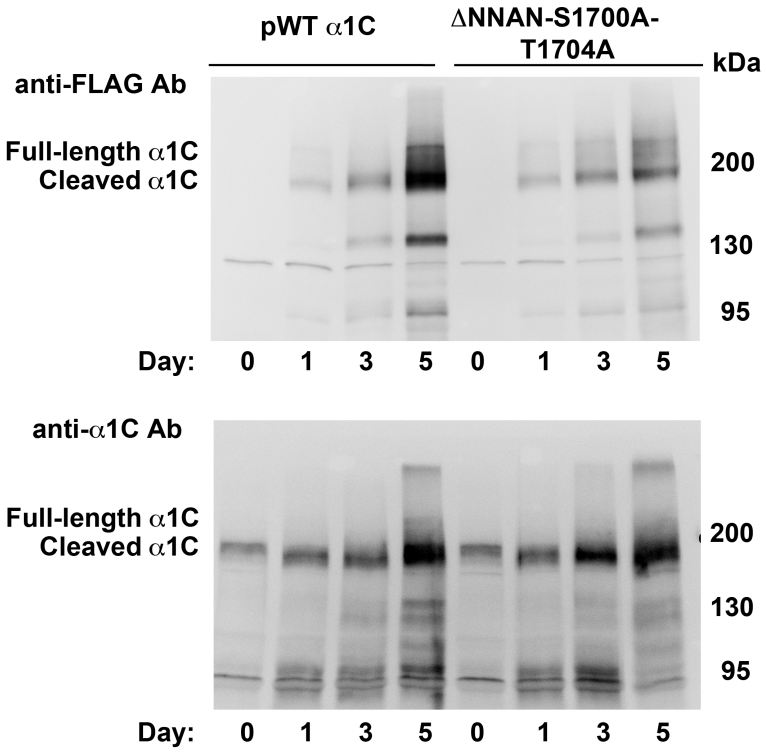
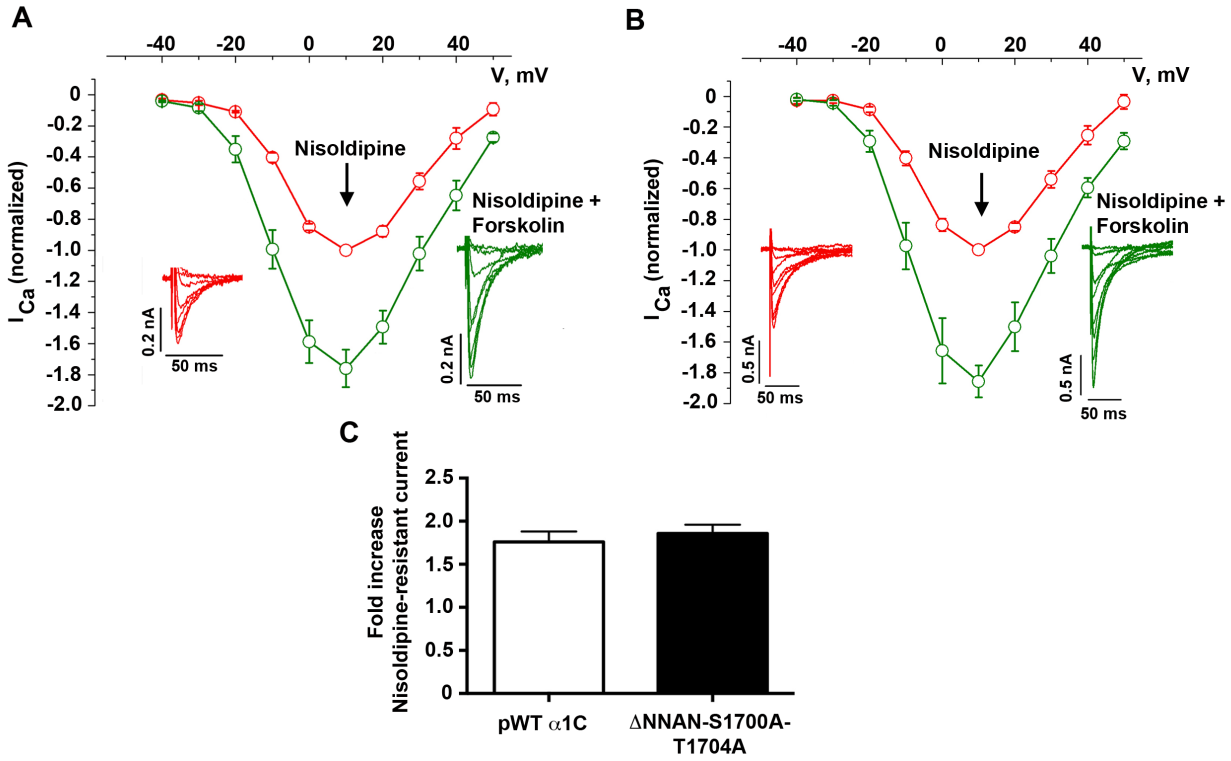
SUPPLEMENTAL MATERIAL



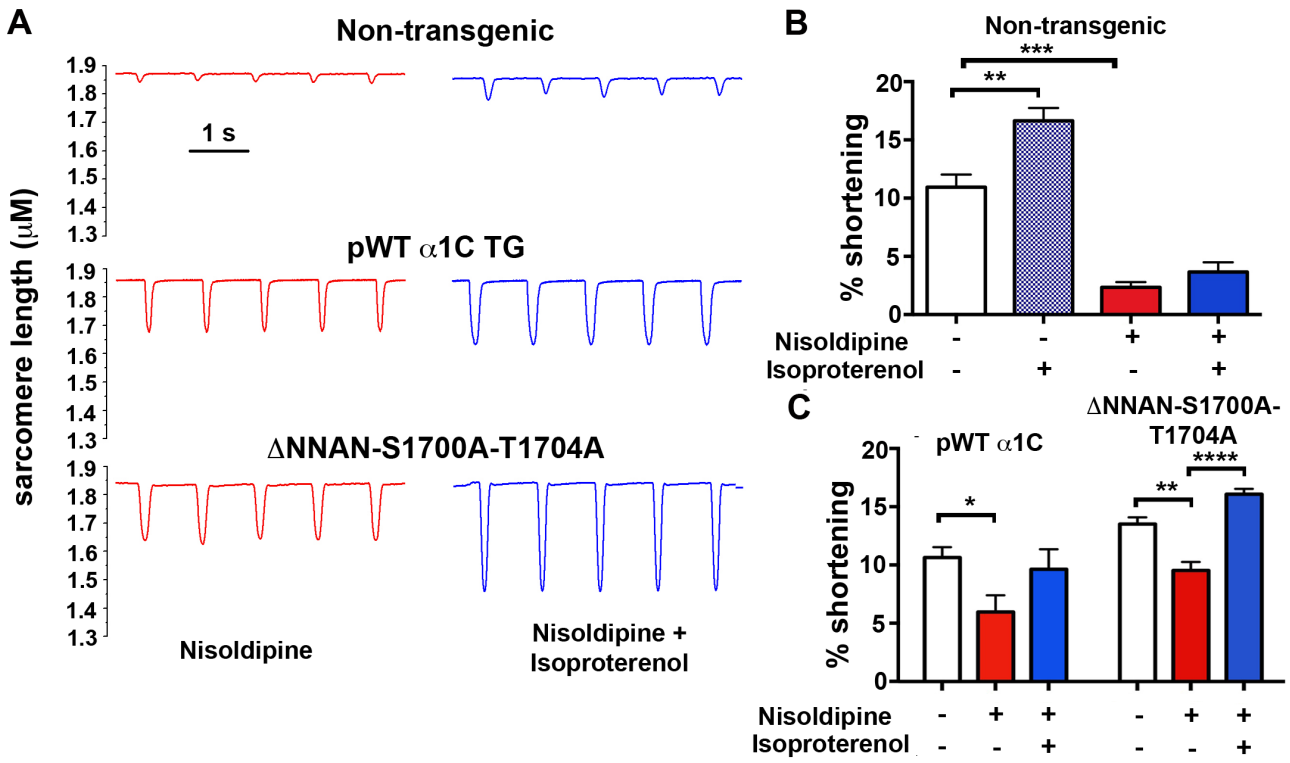
Online Figure I. DHP-resistant currents in tsA-201 cells. (A) Exemplar whole cell current traces recorded from -70 mV to +10 mV before and after 300 nM nisoldipine. (B) Semi-log plot of dose-response relationship of nisoldipine and fraction of current blocked. IC_{50}= 12 nM for WT; 650 nM for DHP-resistant, pWT α_{1C}. N= 11 for WT and N= 12 for DHP-resistant, pWT α_{1C}. Mean $\pm$ SEM.



Online Figure II. Inducible, cardiac-specific FLAG-tagged α_{1C}-expressing transgenic mice. Anti-FLAG antibody (upper) and anti-α_{1C} antibody (lower) immunoblots showing FLAG-epitope tagged α_{1C} expression in tsA-201 cells transfected with FLAG-tagged α_{1C} and expression in isolated cardiomyocytes from either pWT α_{1C} or ΔNNAN-S1700A-T1704A transgenic mice before doxycycline and after doxycycline-impregnated food for 1, 3 and 5 days.



Online Figure III. Forskolin-induced stimulation of transgenic $Ca_V1.2$ currents. (A-B) Current-voltage relationships of pWT α_{1C} (A) and ΔNNAN-S1700A-T1704A $Ca_V1.2$ (B) acquired in 300 nM nisoldipine, before (red traces) and 3 minutes after superfusion of 10 μM forskolin (green traces). Insets: Series of whole-cell $Ca_V1.2$ currents recorded from a series of pulses between -40 mV and + 50 mV from a holding potential of -70 mV before (red traces) and 3 minutes after forskolin (green traces). (C) Bar graph depicting the forskolin-induced fold-increase in peak current. Mean + SEM. P= not significant by Student's t-test.



Online Figure IV. Effect of isoproterenol on fractional shortening in non-transgenic mice and doxycycline-fed transgenic mice. (A) Changes in sarcomere length in response to field stimulation at 1-Hz. Cardiomyocytes were incubated for at least 2 minutes with 300 nM nisoldipine-containing solution (red traces). Isoproterenol (200 nM) was then superfused with 300 nM nisoldipine (blue traces). Sarcomere length was determined after 3 minutes. (B-C) Bar graphs of % shortening in absence and presence of nisoldipine and isoproterenol. Mean ± SEM. N= 14 cardiomyocytes for all conditions. One-way Anova with Sidak post hoc test. * $P<0.05$, ** $P<0.01$, **** $P<0.0001$

DETAILED METHODS:

Extent of non-transgenic current in fraction of nisoldipine-resistant current

The fraction of nisoldipine-resistant current is

$$R = I_{Nis}/I_{Tot} \quad (1)$$

where I_{Tot} is the total peak current at +10 mV before nisoldipine, and I_{Nis} is the peak current at +10 mV in the presence of 300 nM nisoldipine.

The nisoldipine-resistant current at +10 mV is

$$I_{Nis} = I_{Tot} * X * m + I_{Tot} * (1-X) * n \quad (2)$$

where X is the fraction of endogenous current of total current, m is the fraction of current remaining in non-transgenic cardiomyocytes in the presence of 300 nM nisoldipine, and n is the fraction of remaining current of DHP-resistant transgenic channels in the presence of 300 nM nisoldipine (assessed in tsA-201).

Dividing Eq. 2 by I_{Tot} and substituting Eq. 1 R in Eq. 2, we obtain

$$R = X* m + (1-X) * n \quad (3)$$

Solving for X:

$$X = (R-n) / (m-n) \quad (4)$$

In our experiments, m = 0.07 (see Fig. 3), n =0.66. Therefore, when R=0.4, X= 0.44 and when R=0.3, X = 0.61.

In the presence of nisoldipine, the fraction of non-transgenic (NTG) current of the total current is:

$$Fraction_{NTG} = (X * 0.07) / ((1-X) * 0.66) + (X * 0.07) \quad (5)$$

For R=0.4: $Fraction_{NTG} = 0.08$
For R=0.3: $Fraction_{NTG} = 0.14$