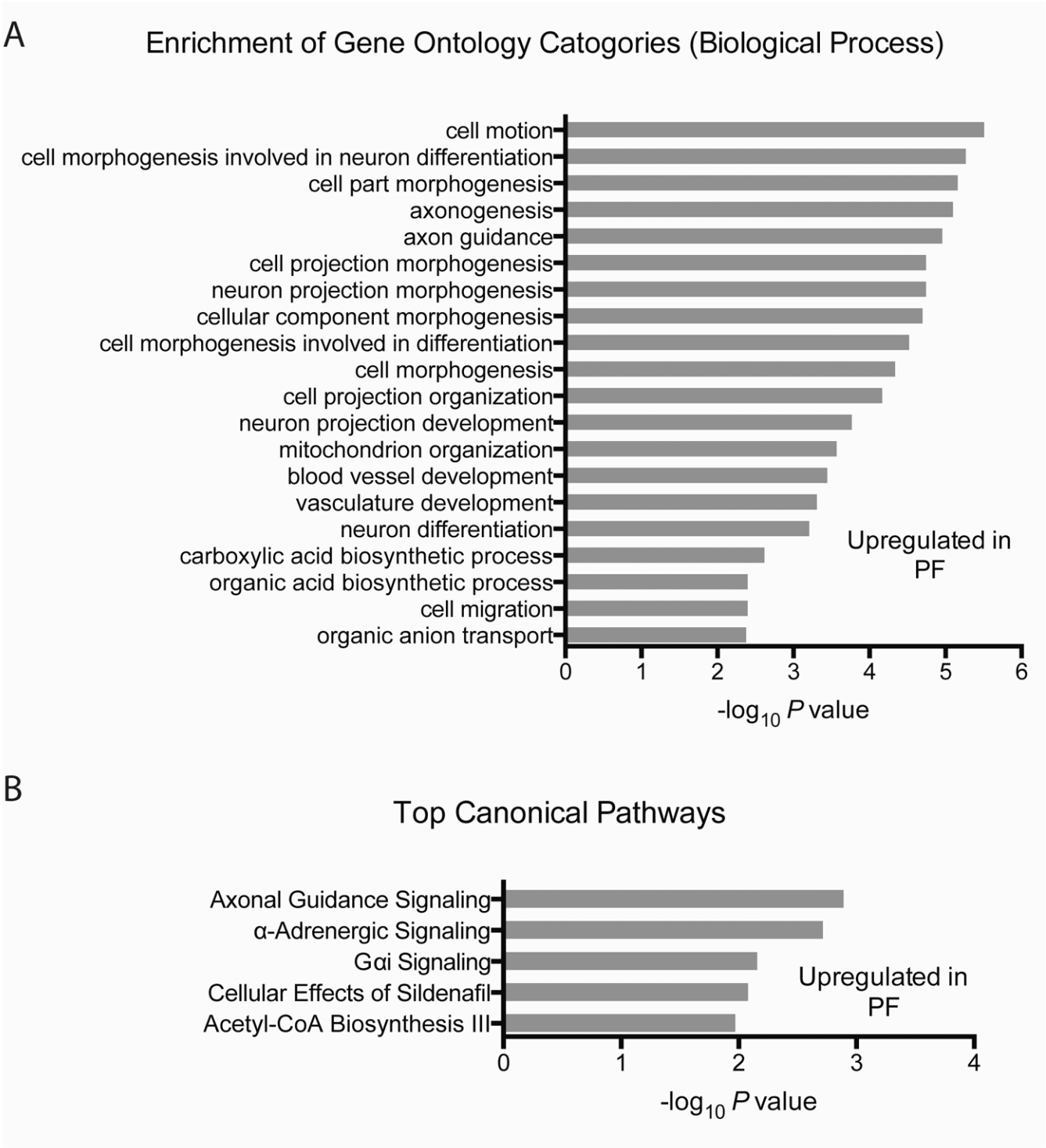
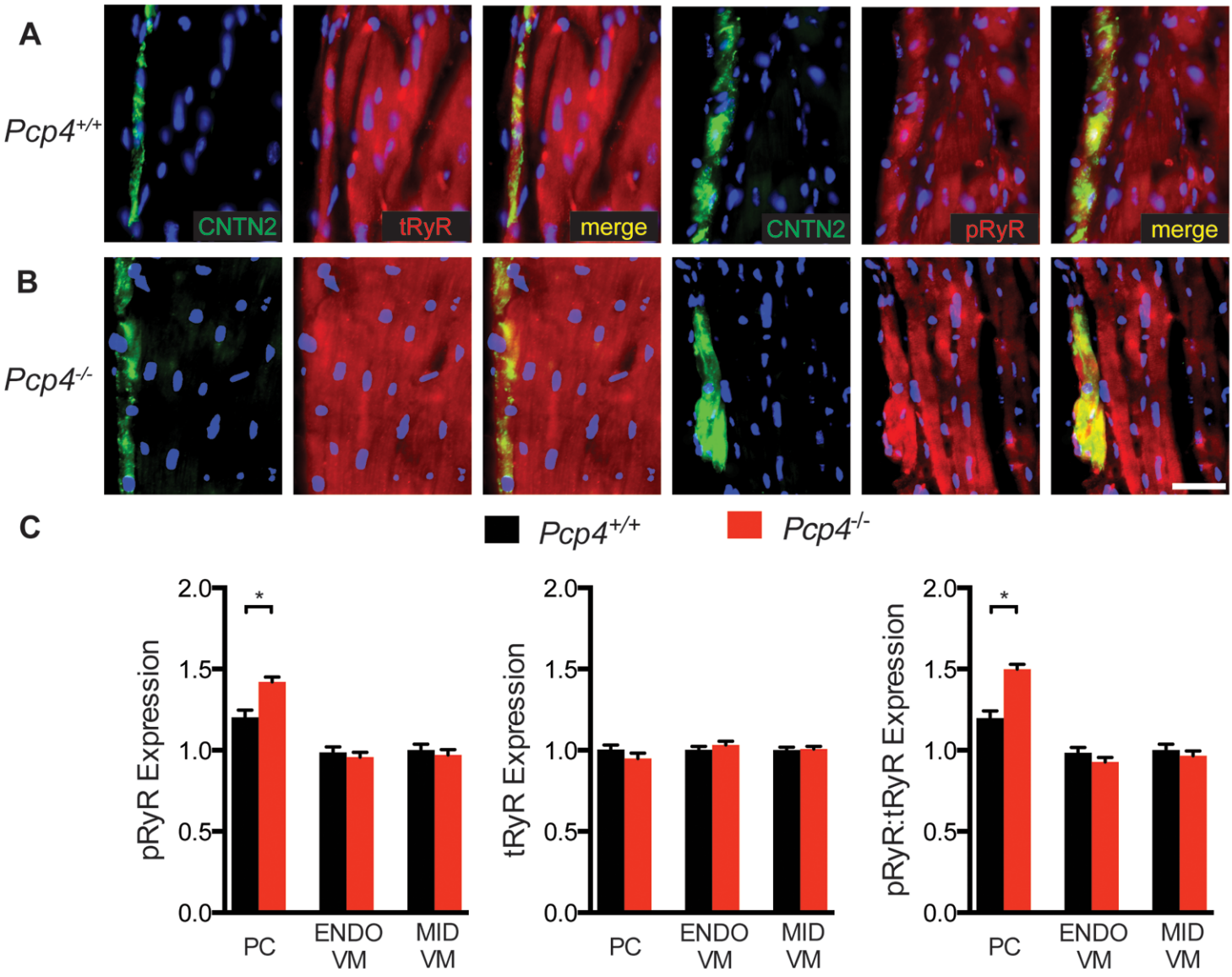
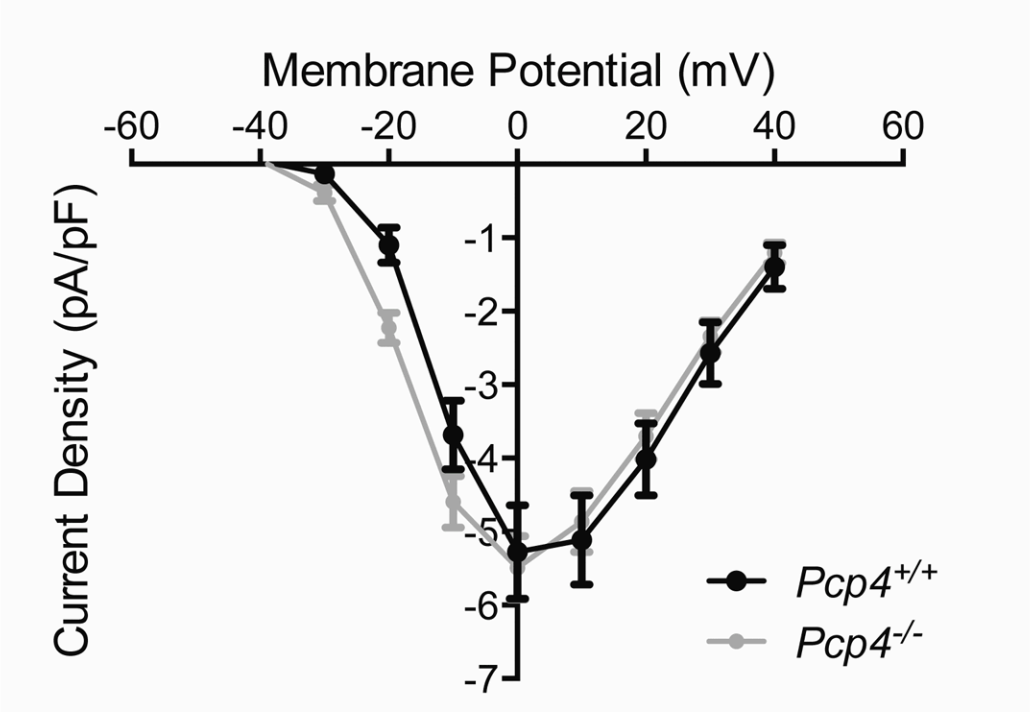


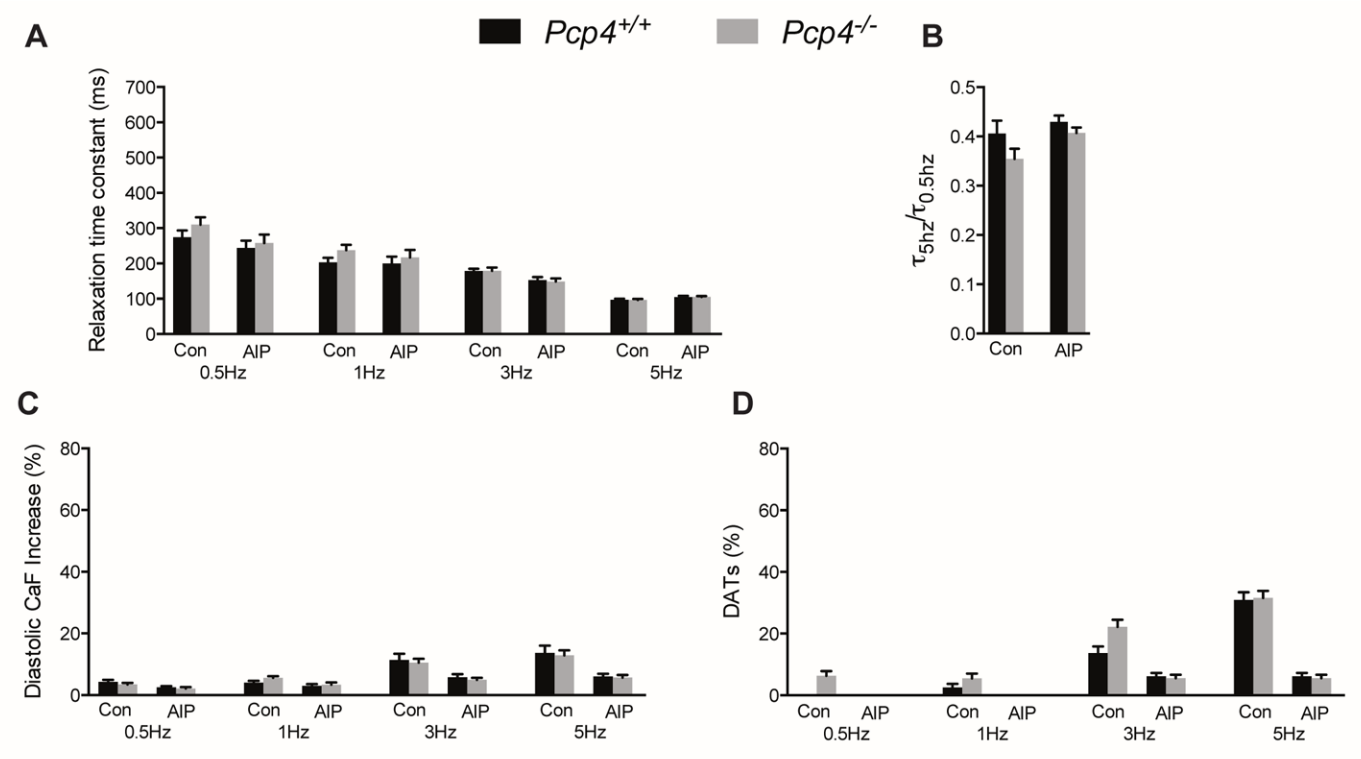
Supplemental Figure 1. Gene ontology functional analysis and canonical pathway analysis (**A**) Gene ontology categories (biological process) for upregulated cardiac Purkinje cell specific genes by DAVID analysis. The top 20 categories are shown. (**B**) Enriched canonical pathway in cardiac Purkinje cells as determined via Ingenuity IPA analysis.



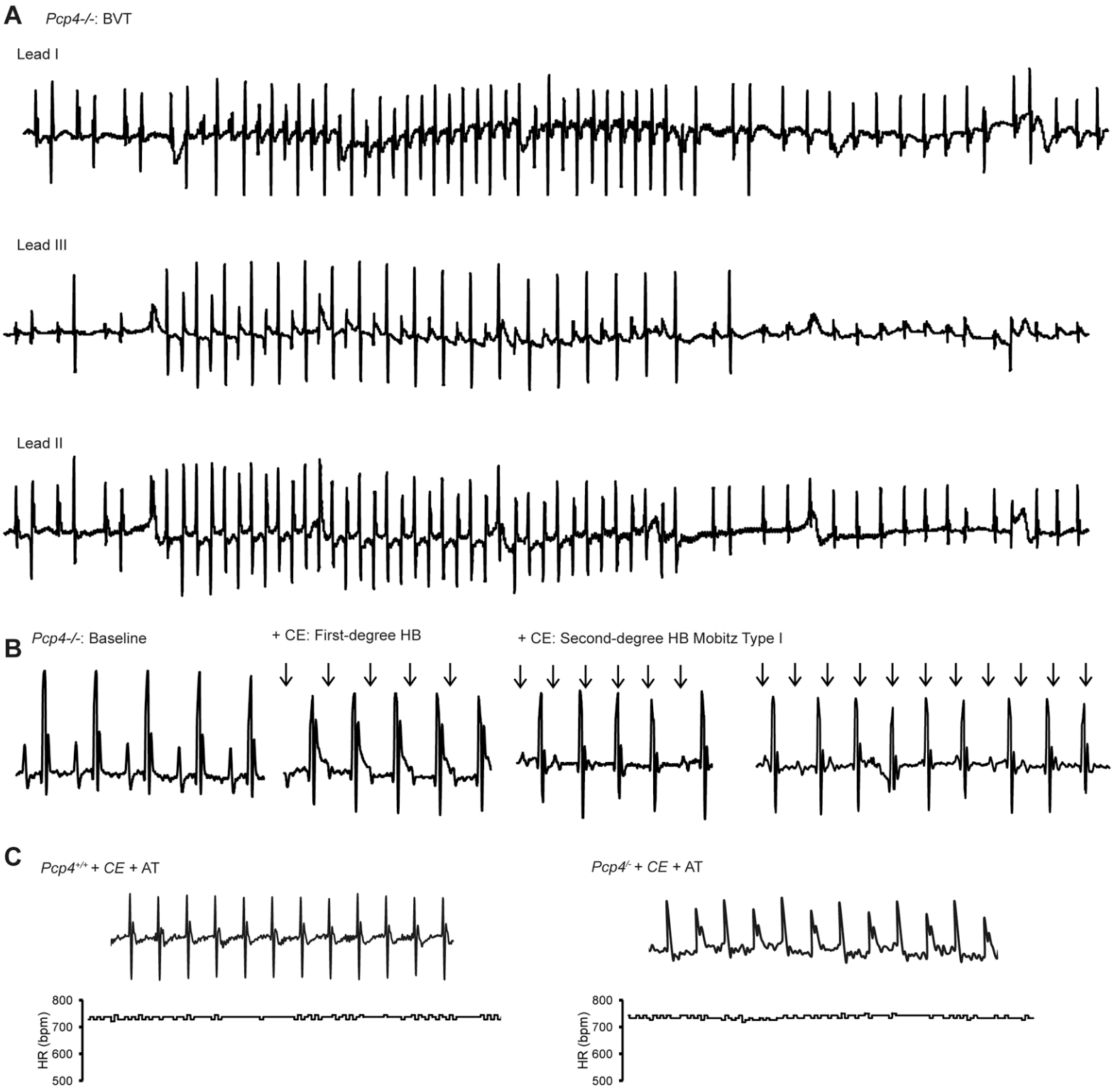
Supplemental Figure 2. Expression patterns of total RyR and phospho-Ser2814-RyR in *Pcp4*-null and control hearts. (**A** and **B**) Representative immunofluorescent staining of total RyR (tRyR) and phospho-Ser2814-RyR (pRyR) in serial sections of (**A**) control and (**B**) *Pcp4*-null hearts. CNTN2 expression identifies PCs. (**C**) Quantitative assessment of the abundance pRyR, tRyR, and the ratio of pRyR : tRyR as assessed by pixel intensity measurements within distinct compartments of *Pcp4*-null and control animals: Purkinje network (PC; 10 - 40 μm from endocardium), subendocardial VMs (ENDO VM; 75 – 125 μm from endocardium) and mid-myocardial VMs (MID VM; 250-300 μm from endocardium). Scale, 50 μm. The data are mean ± SEM *$P < 0.05$.



Supplemental Figure 3. Comparison of current-voltage (I-V) relationship of I_{Ca} in *Pcp4*-null (n = 9) and control (n = 7) VMs. Representative whole cell recordings of I_{Ca} evoked by voltage steps from -40 to +40 mV in 10 mV increments from a holding potential of -50 mV with a 30 ms prepulse to -30 mV. The data are mean ± SEM. No significant differences by one-way ANOVA.



Supplemental Figure 4. Effect of *Pcp4*-null mutation on ventricular myocyte calcium cycling. (**A** and **B)** Kinetics of intracellular calcium decay. (**A**) The relaxation time constant (τ) at various stimulation frequencies and (**B**) the frequency dependent acceleration of relaxation (FDAR) index ($\tau_{5Hz}/\tau_{0.5Hz}$) between *Pcp4*-null VMs and control VMs in the presence or absence of AIP. Comparison of (**C**) the intracellular calcium concentration with repetitive stimulation and (**D**) the frequency of delayed aftertransients (DATs) between VMs of *Pcp4*-null and control mice at various stimulation frequencies in the presence or absence of AIP. No EATs were observed in VMs of either genotype. Con, vehicle. For **A**-**C**, n = 30-45 cells per group. For **D** n = 4-6 hearts per group. 8-12 cells were recorded from each heart. The data are mean ± SEM. No significant differences by one-way ANOVA.



Supplemental Figure 5. ECG tracings of arrhythmias observed in *Pcp4*-null mice. (**A**) Representative 3 lead ECG (I, II, III) in mutant mouse after administration of caffeine and epinephrine (CE) demonstrates bidirectional ventricular tachycardiac preceded by PVCs in bigeminy. (**B**) Representative mutant mouse ECG at baseline, along with examples of CE induced 1st and 2nd degree Mobitz type I heart block. Arrows denote P waves. In examples of 2nd degree Mobitz type I heart block, note progressive PR interval prolongation, progressive RR interval shortening, and grouped beating. (**C**) Representative ECG tracings and graphical plot of heart rate in mutant and WT mice after administration of Caffeine, Epinephrine(CE), and atropine (AT)

Supplemental Tables

Supplemental Table 1. Effect of *Pcp4*-null mutation and cardiac disease models on echocardiographic parameters.

	Pcp4$^{+/+}$	*Pcp4*$^{-/-}$	C57BL/6	C57BL/6 + PE	C57BL/6 + TAC
N	5	5	6	3	4
Heart Rate (BPM)	424.7 + 16.5	448.9 + 29.2	450.6 + 10.7	480.1 + 26.2	478.2 + 32.3
End Diastolic Volume (ul)	81.1 + 1.4	80.7 + 1.5	77.3 + 2.8	52.5 + 2.6*	113.4 + 13.1*
End Systolic Volume (ul)	30.6 + 1.7	30.7 + 2.4	32.0 + 1.6	17.4 + 2.0*	81.1 + 15.0*
Cardiac Output (ml/min)	21.4 + 0.7	22.5 + 1.9	20.5 + 1.0	16.9 + 1.6*	15.2 + 0.6*
Ejection Fraction (%)	62.3 + 2.2	62.1 + 2.3	58.7 + 0.6	66.9 + 2.1*	30.0 + 4.6*
SX Fractional Shortening (%)	28.7 + 0.6	27.6 + 1.7	29.4 + 1.2	45.3 + 3.5*	22.5 + 3.2*
Stroke Volume (ul)	50.5 + 2.2	50.0 + 1.0	45.4 + 1.2	35.1 + 0.7*	32.3 + 2.3*
LV Anterior Wall Thickness, diastole (mm)	0.79 + 0.03	0.80 + 0.01	0.85 + 0.05	1.07 + 0.05*	1.13 + 0.04*
LV Anterior Wall Thickness, systole (mm)	1.25 + 0.01	1.25 + 0.03	1.26 + 0.02	1.75 + 0.02*	1.78 + 0.12*
LV Posterior Wall Thickness, diastole (mm)	0.79 + 0.01	0.84 + 0.02	0.80 + 0.04	1.04 + 0.02*	1.24 + 0.09*
LV Posterior Wall Thickness, systole (mm)	1.21 + 0.03	1.21 + 0.02	1.20 + 0.04	1.71 + 0.07*	1.71 + 0.14*

Supplemental Table 2. Effect of *Pcp4*-null mutation and cardiac disease models on electrocardiographic parameters.

	Pcp4$^{+/+}$	*Pcp4*$^{-/-}$	C57BL/6	C57BL/6 + PE	C57BL/6 + TAC
N	5	5	6	3	4
Heart Rate (BPM)	458.7 + 36.9	432.2 + 27.5	431.7 + 17.1	423.4 + 38.6	445.9 + 37.1
PR (ms)	40.2 + 1.4	39.1 + 1.0	39.9 + 1.8	42.4 + 2.8	47.4 + 1.8*
QRS (ms)	11.2 + 0.3	11.5 + 0.6	11.8 + 0.3	16.4 + 0.8*	17.2 + 1.2*
QT (ms)	19.9 + 0.6	20.8 + 0.5	20.3 + 0.8	24.2 + 1.3*	24.7 + 1.7*