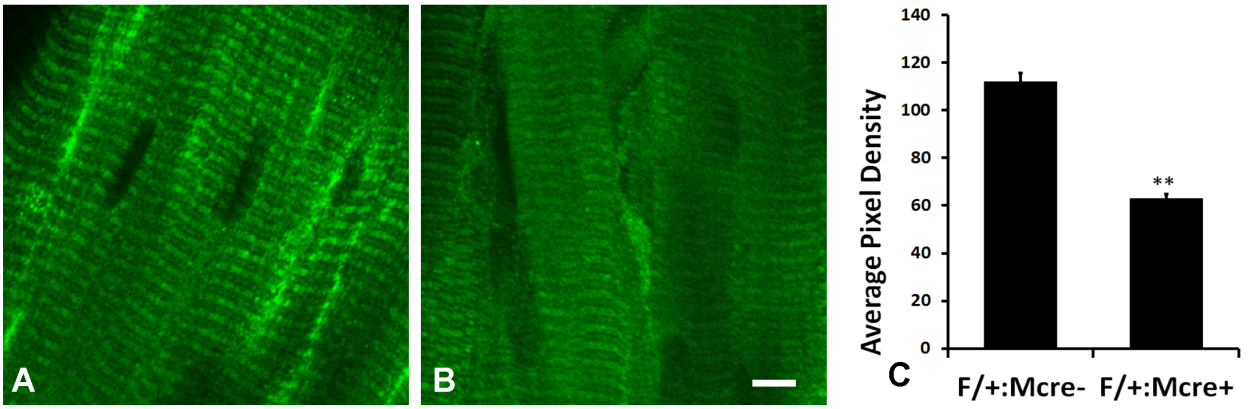
Supplementary Material



Supplementary Figure 1
Characterization of $Na_V1.1$ staining levels in heart tissue of F/+:MCre+ mice. To determine if tamoxifen-induced Mer-Cre activation in our (F/+) mice effectively reduces the expression of Nav1.1 protein in heart tissue, the relative density of Nav1.1 staining was compared between F/+:MCre+ and F/+:MCre- mice. Following intra-cardial perfusion with 4% paraformaldehyde heart tissue was removed and 40 mm sections were processed for immunocytochemistry as described previously (25). Digital images were collected on a Leica SL confocal microscope using constant gain and offset and were then analyzed using the region of interest function (ROI) in the program Igor (Wavemetrics). A. Representative tissue section of cardiac ventricle from F/+:MCre- mice stained with Nav1.1 antibodies illustrating normal patterns of Nav1.1 in heart. B. Representative tissue section of cardiac ventricle from F/+:MCre+ mice stained with Nav1.1 antibodies following induction of MCre using tamoxifen. C. Analysis of average pixel density of staining from multiple sections from F/+:MCre- and F/+:MCre+ groups illustrating that stain intensity is reduced to 55% of wild-type. These results demonstrate that the expression of Mer-Cre has effectively decreased the level of Nav1.1 protein in heart tissue. (**) denotes significance at $P< 0.01$ between the Mer-Cre- and Mer-Cre+ groups. Scale bar=10 μm.

Table 1

Effects of global or conditional knock-out of *Scn1a* on resting interictal heart rate and cardiac autonomic tone.

Table of resting heart rates and their changes in *Scn1a* knock-out mice and controls after acute intraperitoneal administration of saturating dose of atropine (1 mg/kg), propranolol (4 mg/kg), and combined atropine (1 mg/kg) + propranolol (4 mg/kg). Suppressed resting heart rate in F/+:MCre^{+} mice alone was observed. No significant difference in the effects of each drug on resting heart rate was observed in mutant mice compared to controls. All values are mean ± SD. (*) denotes significance at P< 0.05 between the mutant mice and respective controls. Abbreviations: DS: Dravet syndrome mice; F/+:Dlx-Cre^{+} and F/+:Dlx-Cre^{-}: forebrain interneuron specific *Scn1a* knock-out mice and littermate controls; F/+:MCre^{+} and F/+:MCre^{-}: cardiac specific *Scn1a* knock-out mice and littermate controls.

Genotype	Resting HR	Change in resting HR (%)		
	(BPM)	*Atropine*	*Propranolol*	*Atropine + Propranolol*
DS	583.3 ± 50	19.7 ± 3.9	-18.3 ± 1.7	-24.4 ± 2.0
WT	554.5 ± 50	25.6 ± 2.9	-21.9 ± 2.6	-31.6 ± 4.3
F/+:MCre+	582.2 ± 44	25.6 ± 3.7	-19.9 ± 3.9	-30.9 ± 4.0
F/+:Mcre-	565.0 ± 46	28.0 ± 3.0	-23.0 ± 4.0	-32.5 ± 4.5
F/+:DlxCre+	513.1 ± 37 *	23.7 ± 3.5	-24.5 ± 2.0	-34.3 ± 3.4
F/+:DlxCre-	558.0 ± 47	27.3 ± 2.8	23.2 ± 3.0	-30.0 ± 4.6

Table 2

Effects of global or conditional knock-out of *Scn1a* on heart rate variability.

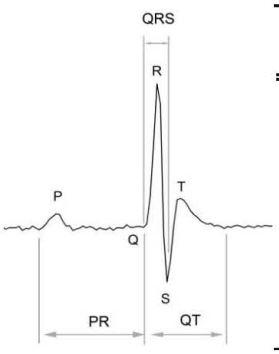
Table of coefficients of variations of resting heart rate (HR CV), standard deviation of normal R-R intervals (SD NN), standard deviation of delta NN (SD of delta NN), and root mean square of differences between adjacent normal R-R intervals (RMSSD) in *Scn1a* mutant mice and controls. Reduced values of HRV indexes for DS and F/+:Dlx-Cre^{+} mice, but elevated values for F/+:MCre^{+} mice. All values are mean ± SD. (*) denotes significance at P< 0.05 between the mutant mice and respective controls. Abbreviations: DS: Dravet syndrome mice; F/+:Dlx-Cre^{+} and F/+:Dlx-Cre^{-}: forebrain interneuron specific *Scn1a* knock-out mice and littermate controls; F/+:MCre^{+} and F/+:MCre^{-}: cardiac specific *Scn1a* knock-out mice and littermate controls.

Genotype	HR CV	SD NN	SD delta	RMSSD
DS	5.5 ± 3.4 *	31.6 ± 21.2 *	8.5 ± 5.8 *	2.5 ± 0.9 *
WT	16.0 ± 6	89.7 ± 34.1	25.1 ± 14.4	7.7 ± 0.8
F/+:MCre+	7.6 ± 3.0 *	43.4 ± 19.3 *	13.2 ± 5.8 *	2.9 ± 0.6 *
F/+:Mcre-	16.0 ± 6	91.1 ± 32.0	24.0 ± 10.0	9.0 ± 3.0
F/+:DlxCre+	7.6 ± 3.0 *	170.8 ± 93.1 *	44.2 ± 16.3 *	9.5 ± 2.0 *
F/+:DlxCre-	16.0 ± 6	90.0 ± 33.0	24.2 ± 13.0	7.1 ± 2.0

Table 3

Effects of global and conditional *Scn1a* knock-out on resting ECG intervals

(Left) Representative example of a WT mouse resting ECG tracing with marked ECG intervals. ECG traces were collected during eight hours of simultaneous video-EEG-ECG recordings from 8:00 AM – 4:00 PM. Stable segments of the ECG records, devoid of movement artifacts, electrical noise, ectopic beats, or arrhythmias were considered for analyses. (Right) Table of resting ECG intervals measured in WT and *Scn1a* knockout mice. All values are mean ± SD. (*) denotes significance at P< 0.05 between the mutant mice and respective controls. (*) denotes significance at P< 0.05 between the mutant mice and respective controls. Abbreviations: DS: Dravet syndrome mice; F/+:Dlx-Cre^{+} and F/+:Dlx-Cre^{-}: forebrain interneuron specific *Scn1a* knock-out mice and littermate controls; F/+:MCre^{+} and F/+:MCre^{-}: cardiac specific *Scn1a* knock-out mice and littermate controls.



Genotype	Ave HR *(BPM)*	Duration *(ms)*	PR *(ms)*	QRS *(ms)*	QT *(ms)*	QTc *(ms)*	n
WT	554.5 ± 50	9.5 ± 1.1	32.2 ± 1.7	9.1 ± 1.0	19.5 ± 1.4	59.4 ± 2.7	6
DS	583.3 ± 50	9.4 ± 1.7	31.8 ± 2.1	8.2 ± 1.0	19.0 ± 1.7	59.6 ± 5.2	9
F/+:Dlx-Cre^{-}	565 ± 46	10 ± 1.1	31 ± 2.0	9.3 ± 1.0	18.8 ± 1.5	59.0 ± 3.8	5
F/+:Dlx-Cre^{+}	582.2 ± 44	10.5 ± 1.1	32.3 ± 1.7	9.3 ± 1.0	21.8 ± 4.5	61.7 ± 5.8	6
F/+:Mcre-	558 ± 47	9.3 ± 1.0	32 ± 0.3	8.8 ± 0.4	19.0 ± 1.0	59.1 ± 1.5	5
F/+:MCre^{+}	**513.1 ± 37***	10.3 ± 1.0	35.4 ± 0.3*	8.3 ± 0.4	20.3 ± 0.3	60.1 ± .5	9