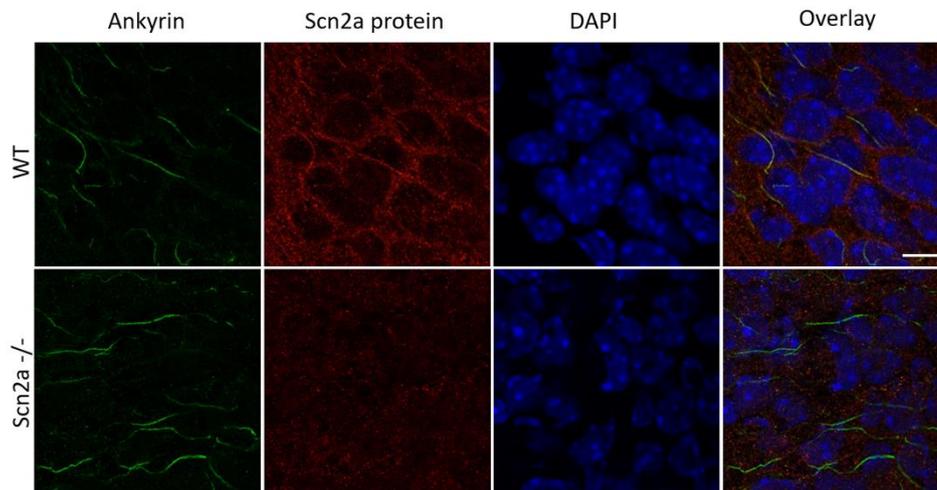
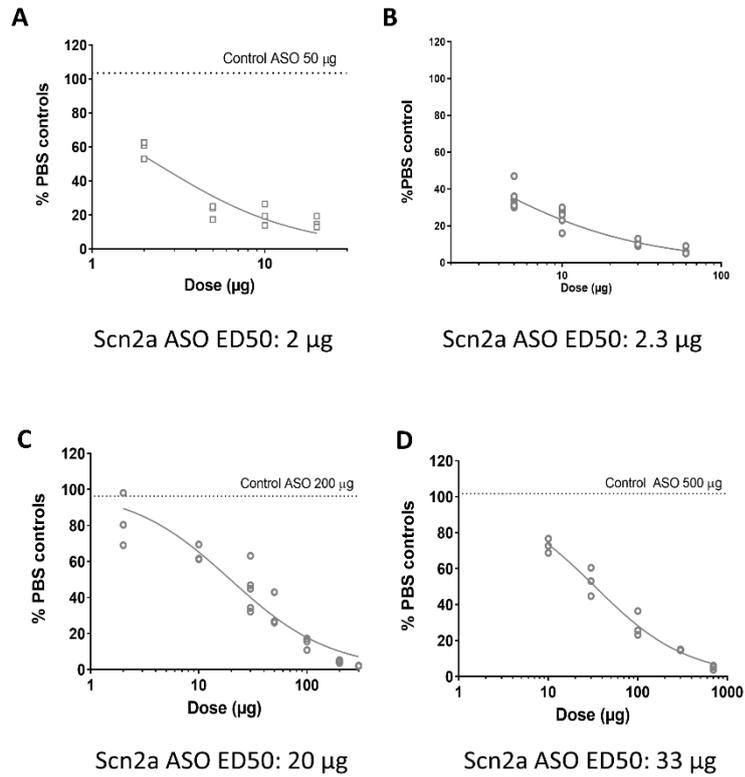


**Supplementary figure 1. Distribution of ASO (ED80, 10 µg) in mouse ICV injected at P1.** (A) Forebrain coronal slice overview fluorescently labelled with DAPI (blue) and ASO antibody (red). Higher resolution images of boxed areas in (A) for neurons labelled with NeuN (gray), ASO (red) and DAPI (blue) showing motor cortex (B); Somatosensory cortex (C); Caudate Putamen (D). (E, H) Hippocampus and cerebellum slice overviews fluorescently labelled with DAPI (blue) and ASO antibody (red). Higher resolution images of boxed areas shown are CA1 (F) and CA3 (G) for NeuN (gray), ASO (red) and DAPI (blue) and brainstem neurons (I). (J) Cerebellum slice image shows an example of the Calbindin (blue) and brainstem neurons (I).

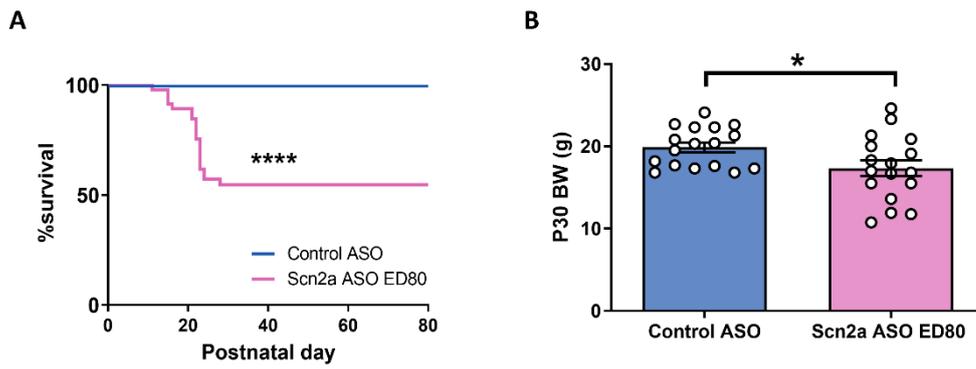
positive Purkinje neurons (gray), DAP (blue) and ASO (red). **(K-M)** No primary controls for ASO antibody **(K)**, NeuN antibody **(L)** and DAPI **(M)**. Scale bar is 20  $\mu\text{m}$ .



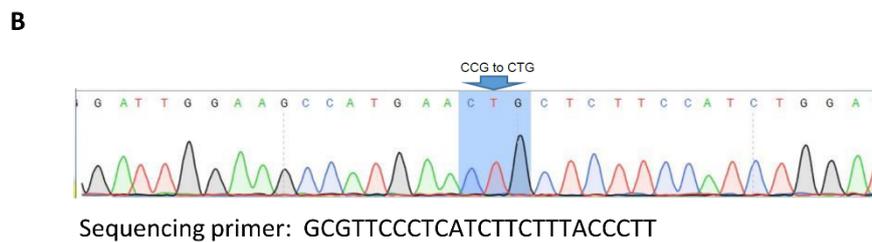
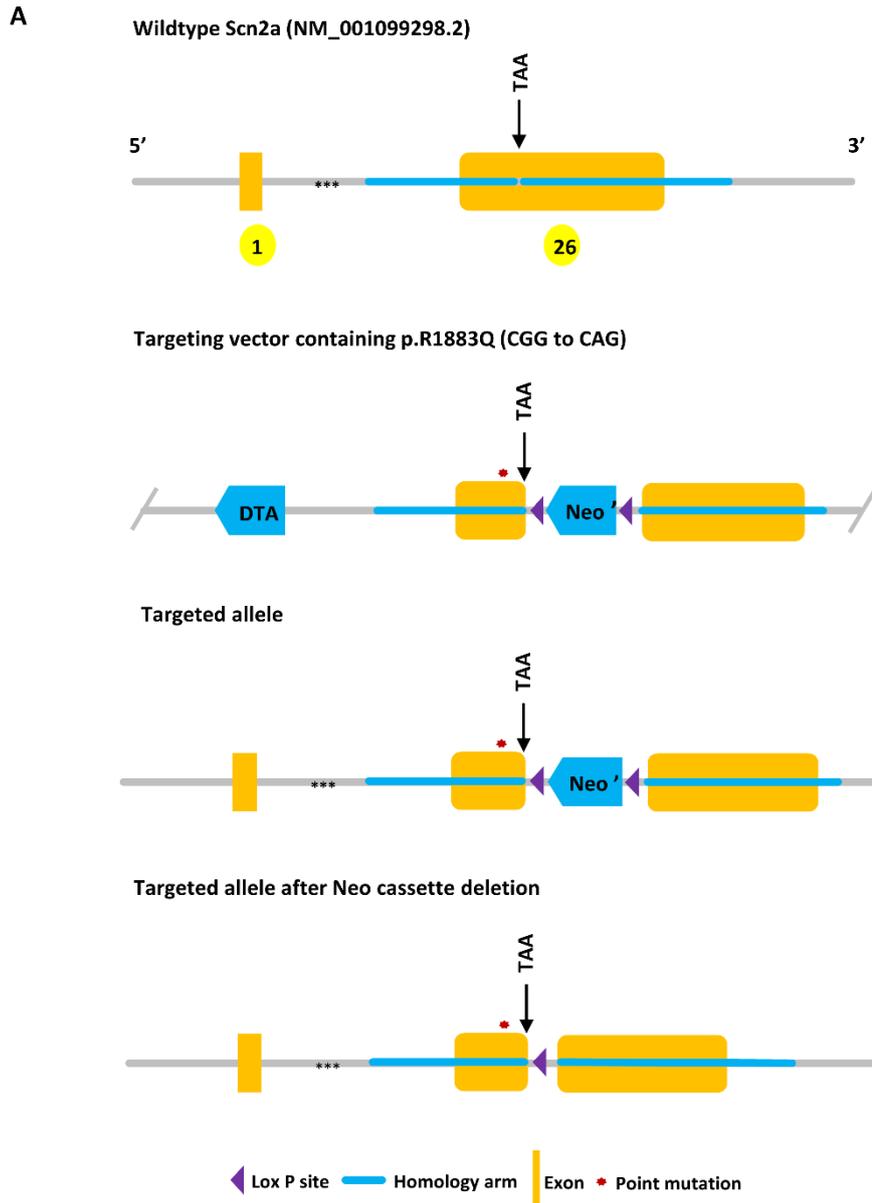
**Supplementary figure 2.** Brain sections were collected from *Scn2a* homozygous knockout (*Scn2a*  $-/-$ ) and wildtype mice at P0. Sections were stained with anti-ankyrin G and anti-Scn2a protein antibody and DAPI. Scale bar indicates 10  $\mu$ m.



**Supplementary figure 3. Dose-response curves of ASO mediated *Scn2a* mRNA reduction at different age of administration.** Control ASO or a range of *Scn2a* ASO doses was ICV injected into P1 Q/+ mice (A), P1 +/+ mice (B), P15 +/+ mice (C) or P30 +/+ mice (D). The *Scn2a* mRNA level was assessed 14-15 days post ICV injection, and ED<sub>50</sub> was determined by Motulsky regression fit, N = 3-5 per dose.



**Supplementary figure 4. Effect of administering *Scn2a* ASO ED<sub>80</sub> into P1 +/+ mice. (A)** Survival curves (control ASO n = 32, *Scn2a* ASO ED<sub>80</sub> n = 47), \*\*\*\**P* < 0.0001, Log-rank test. **(B)** Body weight (control ASO n = 17, *Scn2a* ASO ED<sub>80</sub> n = 17) \* *P* < 0.05 (t = 2.241, df = 32), unpaired t-test.



**Supplementary figure 5. Targeting vector used for *Scn2a* p.R1883Q mouse model generation.** (A) Schematic diagram illustrating the strategy of introducing the point mutation CCG to CTG into exon 26 of the *Scn2a* gene. (B) Chromatogram from sequencing validating the point mutation was inserted into the *Scn2a* gene.

Supplementary table 1 Quantification of ASO positive neurons

ROI	Subregions									% ASO positive neurons	
	1	2	3	4	5	6	7	8	9		
<b>Motor cortex (M1, M2)</b>											% ASO positive neurons
Cell count mean	177.8	142.3	156.0	155.0	140.8	107.8					97.6 ± 0.3
Cell count s.e.m.	30.2	18.5	19.9	24.0	16.3	9.8					
ASO negative neuron mean	4.0	3.3	3.8	6.0	1.5	3.0					
ASO negative neuron s.e.m.	1.6	1.3	1.1	1.2	0.4	0.7					
<b>Somatosensory cortex (S1, BF)</b>											% ASO positive neurons
Cell count mean	163.75	153.5	158.5	209.75	195.5	210.5	152.75	142.75	145.5	145.5	97.9 ± 0.6
Cell count s.e.m.	19.4	41.1	25.0	43.6	37.1	47.3	33.1	24.6	36.3	36.3	
ASO negative neuron mean	5.0	3.8	3.5	4.5	4.0	3.8	4.0	3.5	3.5	3.5	
ASO negative neuron s.e.m.	1.5	2.1	1.0	1.8	1.6	1.5	2.4	1.7	1.4	1.4	
<b>Basal Ganglia (Cpu, GP/SNR)</b>											% ASO positive neurons
Cell count mean	122.3	117.3	157.0	155.5	108.8	118.3	80.3	65.8	68.0	68.0	96.6 ± 0.2
Cell count s.e.m.	44.8	26.6	32.0	13.0	19.3	22.5	21.9	13.5	19.7	19.7	
ASO negative neuron mean	3.3	2.8	6.3	5.3	2.8	3.5	3.5	4.8	2.8	2.8	
ASO negative neuron s.e.m.	1.8	1.5	1.1	0.5	0.8	1.0	1.8	1.2	0.8	0.8	
<b>Thalamus</b>											% ASO positive neurons
Cell count mean	130.3	122.8	83.0	98.8	101.5	84.5					98.0 ± 0.3
Cell count s.e.m.	31.7	24.1	8.9	6.0	9.9	12.8					
ASO negative neuron mean	3.0	3.5	3.5	2.0	0.0	0.8					
ASO negative neuron s.e.m.	2.1	0.8	0.4	0.4	0.0	0.6					
<b>Piriform Cortex</b>											% ASO positive neurons
Cell count mean	123.5	113.8	111.8	109.3	107.5	113.8	122.5	112.0	99.0	99.0	97.7 ± 0.3
Cell count s.e.m.	6.0	2.7	18.0	2.7	13.3	3.8	8.7	5.5	10.8	10.8	
ASO negative neuron mean	3.0	2.8	4.5	3.3	1.3	1.8	1.5	3.0	2.0	2.0	
ASO negative neuron s.e.m.	0.9	0.9	0.8	0.2	1.1	0.9	0.6	0.9	0.6	0.6	

Supplementary table 1 (continued)

ROI	Subregions									% ASO positive neurons	
	1	2	3	4	5	6	7	8	9		
<b>Hippocampus (CA1, Rad, DG)</b>											
Cell count mean	79.8	82.5	80.0	69.8	73.8	48.0	80.5	57.0	68.3	95.9 ± 0.4	
Cell count s.e.m.	14.4	13.8	13.4	12.4	10.4	9.4	5.3	6.3	10.5		
ASO negative neuron mean	3.5	3.3	2.5	2.3	1.3	1.5	4.5	3.8	3.8		
ASO negative neuron s.e.m.	1.3	1.3	1.1	1.2	1.1	0.8	0.3	0.4	0.6		
<b>Subiculum</b>	1	2	3	4	5	6				% ASO positive neurons	
Cell count mean	102.3	101.3	124.3	127.8	102.0	128.8				97.5 ± 0.3	
Cell count s.e.m.	9.3	17.9	14.0	10.8	3.9	7.3					
ASO negative neuron mean	1.5	2.0	4.5	4.0	2.8	2.5					
ASO negative neuron s.e.m.	0.6	1.0	0.6	0.6	0.8	0.9					
<b>Entorhinal cortex</b>	1	2	3	4	5	6	7	8	9	% ASO positive neurons	
Cell count mean	76.3	93.3	78.5	104.5	87.8	89.8	80.3	82.0	95.3	97.4 ± 0.3	
Cell count s.e.m.	6.9	8.3	7.1	13.7	7.2	4.9	9.5	7.1	2.9		
ASO negative neuron mean	2.8	4.0	1.5	1.8	2.8	3.0	1.5	2.0	1.8		
ASO negative neuron s.e.m.	0.8	0.6	0.6	0.9	0.9	0.5	0.6	0.6	0.4		
<b>Visual cortex</b>	1	2	3	4	5	6				% ASO positive neurons	
Cell count mean	127.8	135.0	144.8	145.8	127.5	145.5				97.6 ± 0.4	
Cell count s.e.m.	13.4	11.9	4.7	1.9	13.3	12.0					
ASO negative neuron mean	2.0	4.0	3.8	3.0	3.3	3.8					
ASO negative neuron s.e.m.	1.1	0.4	0.6	1.3	1.0	0.4					
<b>Cerebellum</b>	1	2	3							% ASO positive neurons	
Cell count mean	22.0	22.8	30.8							98.9 ± 0.6	
Cell count s.e.m.	4.1	4.6	6.2								
ASO negative neuron mean	0.0	0.0	1.0								
ASO negative neuron s.e.m.	0.0	0.0	0.5								
<b>Brain stem</b>	1	2	3							% ASO positive neurons	
Cell count mean	123.0	107.8	76.0							98.1 ± 0.6	
Cell count s.e.m.	11.8	9.1	15.5								
ASO negative neuron mean	2.5	2.3	1.5								
ASO negative neuron s.e.m.	1.3	0.2	0.6								

**Supplementary table 2 TaqMan probes used for RT-qPCR**

<b>Gene</b>	<b>Exon boundary</b>	<b>Probe ID and Chemistry</b>
<i>Scn1a</i>	18/19	Mm00450580_m1 (FAM-MGB)
<i>Scn2a</i>	22/23	Mm01270367_m1 (FAM-MGB)
<i>Scn3a</i>	16/17	Mm00658167_m1 (FAM-MGB)
<i>Scn8a</i>	25/26	Mm00488123_m1 (FAM-MGB)
<i>Scn9a</i>	25/26	Mm07294340_m1 (FAM-MGB)
<i>Scn10a</i>	24/25	Mm01342493_m1 (FAM-MGB)
<i>Gusb</i>	10/11	Mm01197698_m1 (VIC-MGB)