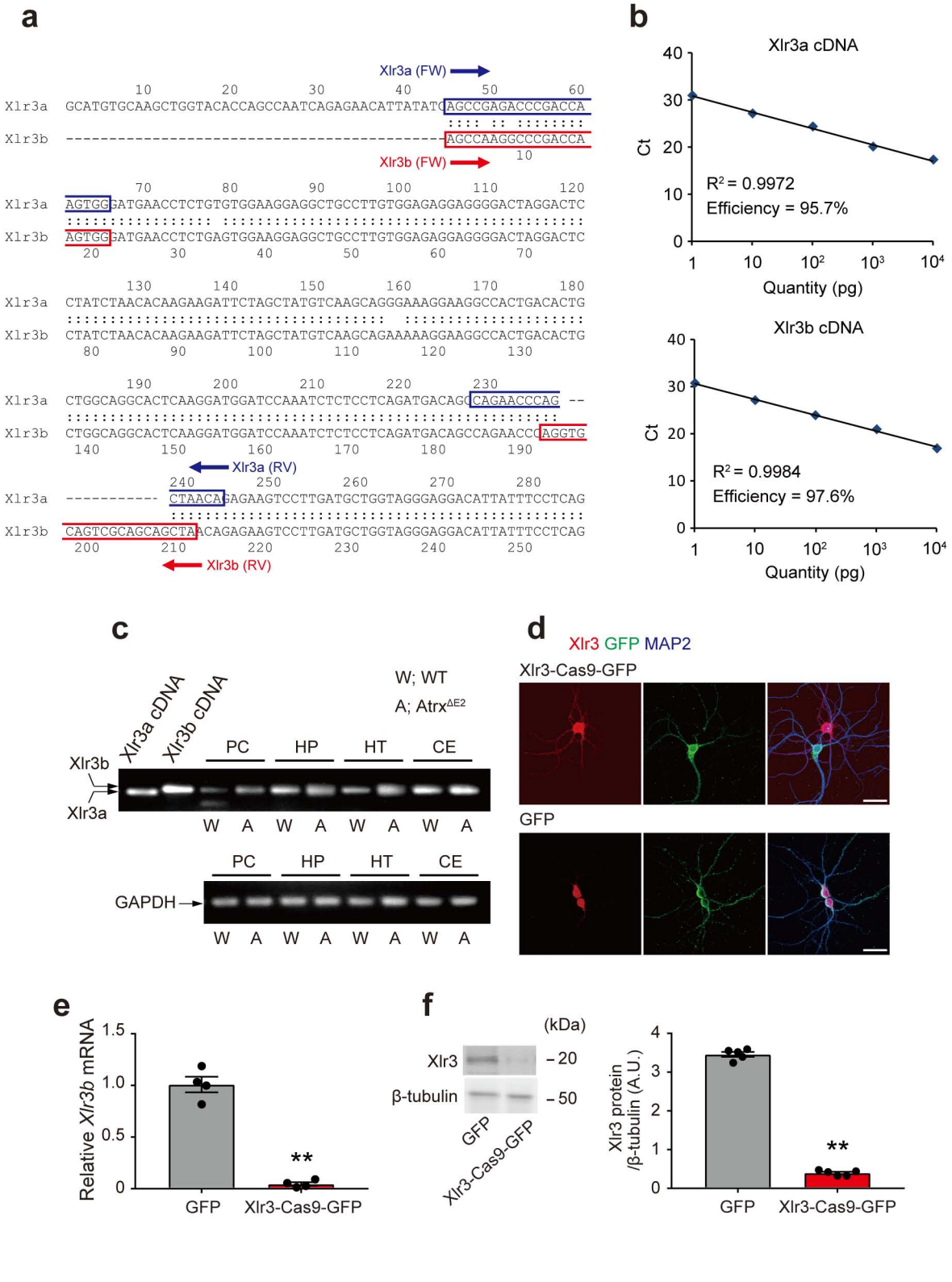
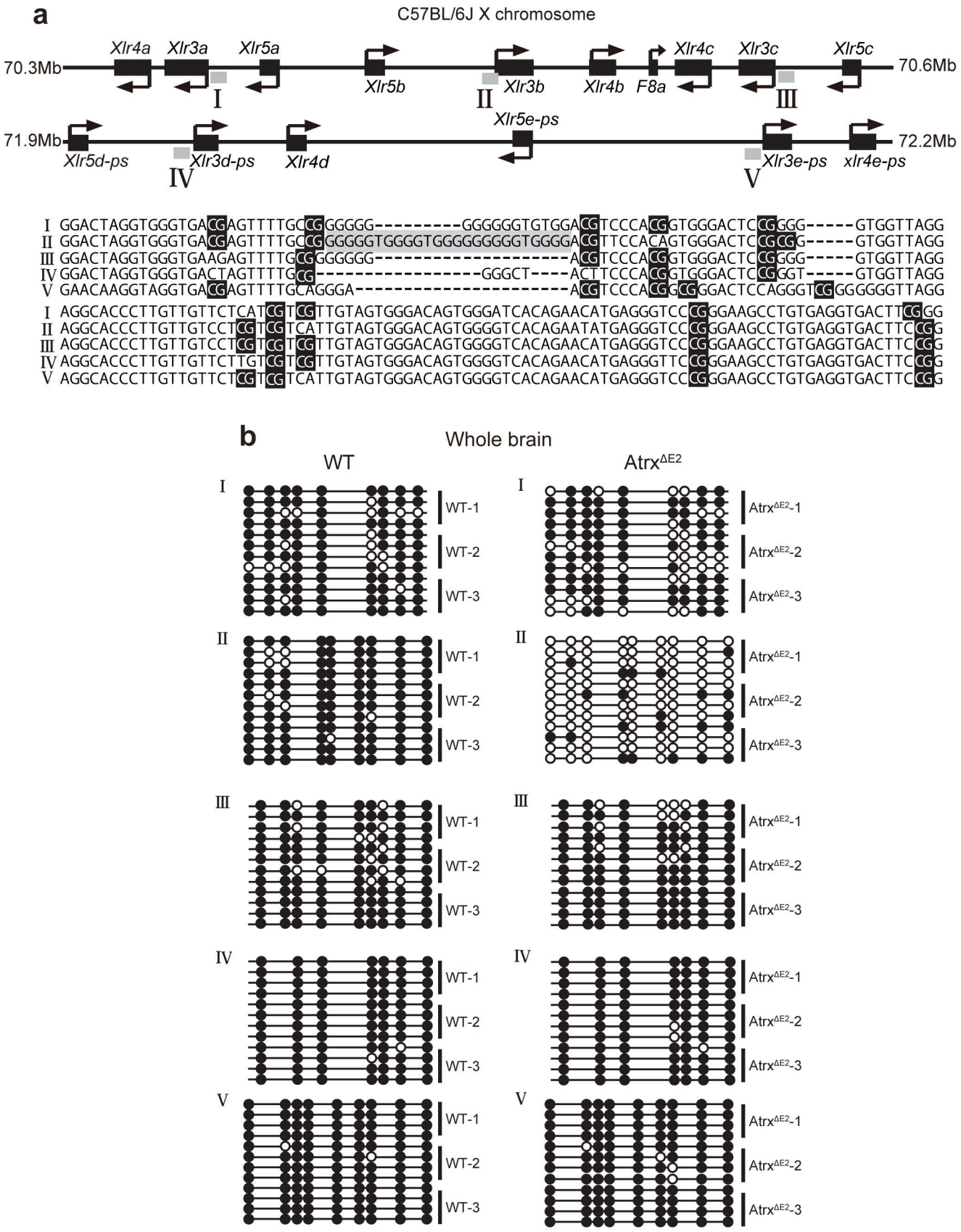
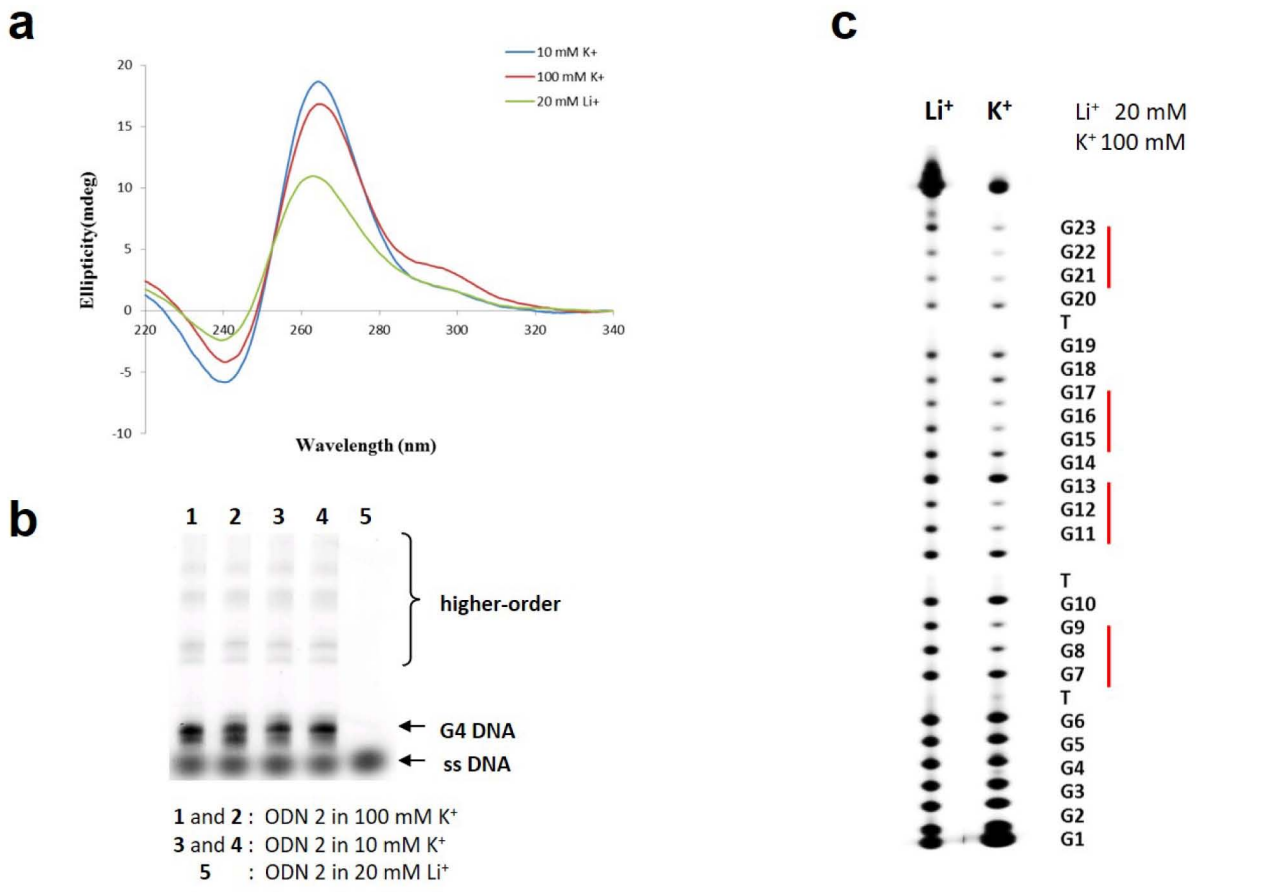


Supplementary Fig. 1. Identification of Xlr3b in mouse brain. a, Sequence of *Xlr3a/Xlr3b* mRNA and position of PCR primers. **b**, *Xlr3a* and *Xlr3b* primer specificity was confirmed by amplifying respective cDNAs. Serial dilutions of cDNA were prepared and Q -PCR performed. A negative correlation was found between increasing concentrations of cDNA and Ct. The R squared value (coefficient of determination, R^2) was used to determine amplification efficiency. The experiments were repeated twice with similar results. **c,** *Xlr3a* and *Xlr3b* mRNA levels in mouse brain tissue as determined by RT-PCR. Xlr3a (lane 1) and Xlr3b (lane 2) cDNAs served as positive controls. W, wild-type mice; A, $Atrx^{\Delta E2}$ mice; PC, prefrontal cortex; HP, hippocampus; HT, hypothalamus; CE, cerebellum.**d,** Cultured hippocampal neurons were transduced with U6gRNA-Cas9-2A-GFP plus guide Xlr3 sgRNA (Xlr3 -Cas9-GFP) lentivirus (top) or control lentivirus expressing GFP (bottom) and immunostained 21 days later. Confocal images revealed loss of Xlr3 (red) immunoreactivity in MAP2-positive (blue) neurons infected with Xlr3-Cas9-GFP but not control GFP virus. In **c** and **d**, the experiments were repeated three times with similar results. **e**, Quantitative real-time RT-PCR showing *Xlr3b* mRNA expression in cells shown in **d**. $^{**}P < 0.01$ by two-sided unpaired t-test. n = 4 biologically independent samples. **f,** Immunoblot (left) and corresponding quantitative (right) analysis of Xlr3 protein in cells shown in **d**. Densitometric analysis of Xlr3 normalized to β-tubulin (arbitrary units, A.U.). $^{**}P < 0.01$ by two-sided unpaired t-test. n = 5 biologically independent samples.

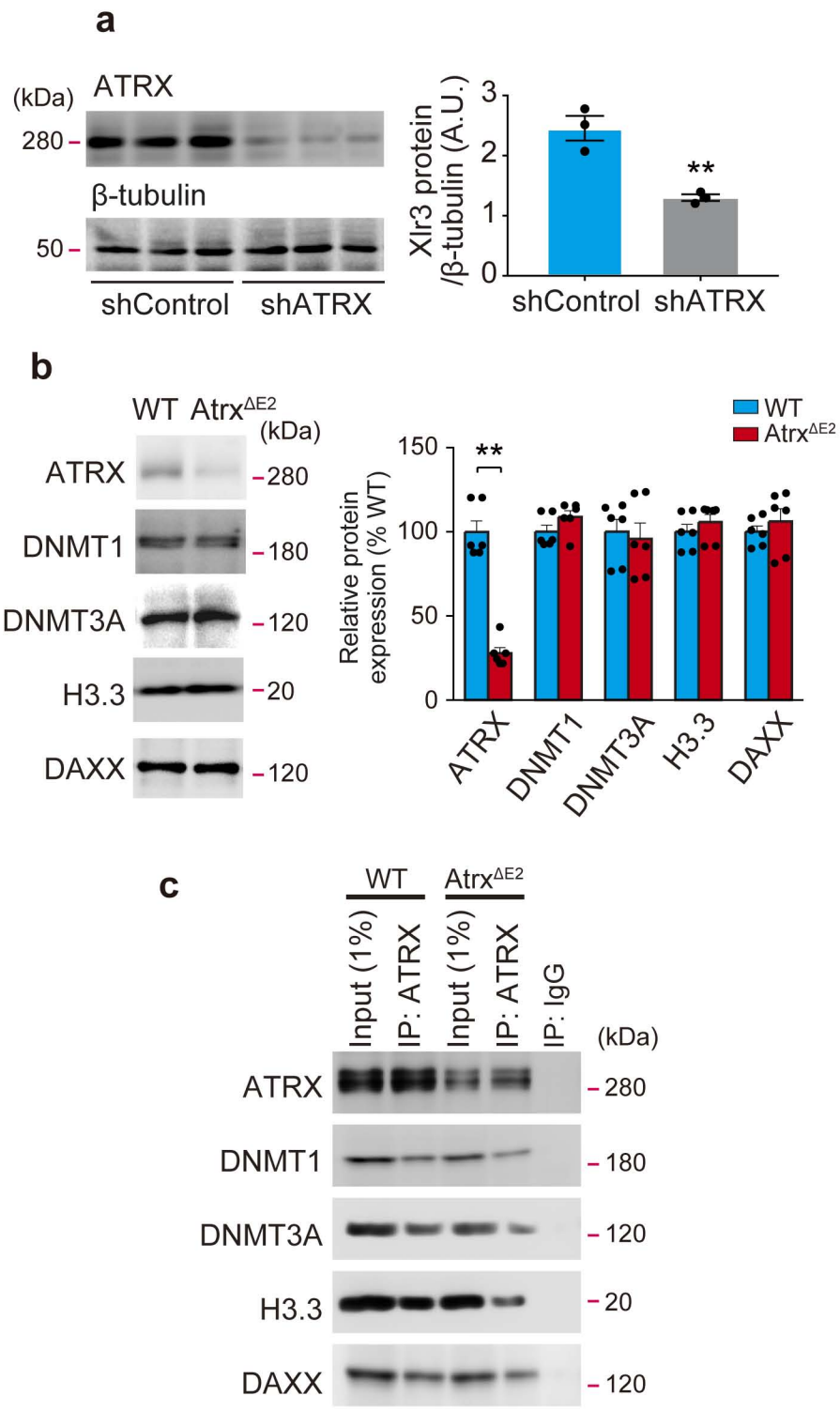


Supplementary Fig. 2. Bisulfite sequencing evaluation of *Xlr3* CGI methylation in Atrx$^{\Delta E2}$ mouse brain lysates. a, (top) Schematic showing clusters of Xlr genes on the C57BL/6J X chromosome. See also Raefski and O'Neill, (2005) [23]. (bottom) Location of Xlr3 CpG sites analyzed. Sequences potentially forming G-quadruplex is shaded in gray. **b,** Methylation status of Xlr3 CpG sites. Open circles, unmethylated CpGs; closed circles, methylated CpGs. Male P90 mice were used. n = 3 mice each. 4 independent clones of each sample were sequenced. Roman numerals correspond to those of the CpG sites shown in **a** and **b**.

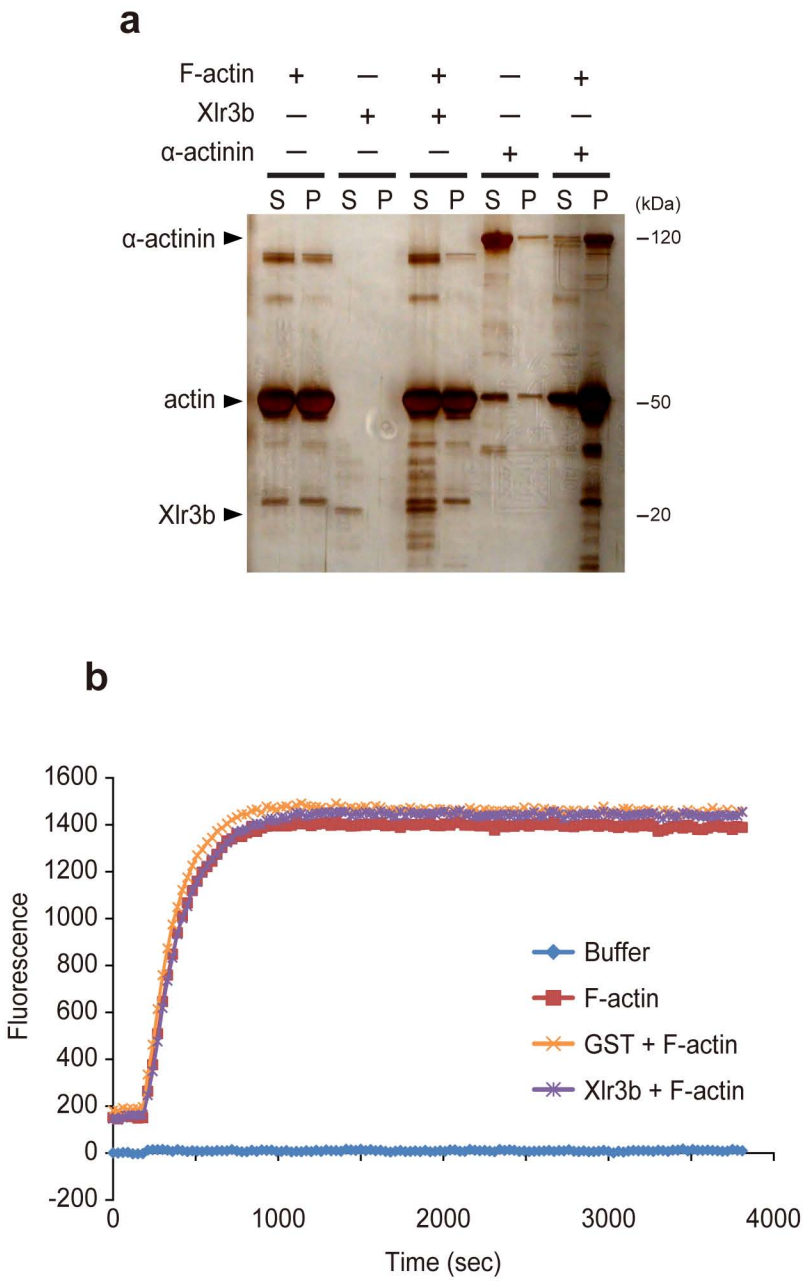


ODN 2 5'-Texas Red-TTTTTGCCGGGGGGTGGGGTGGGGGGGGGGTGGGG-3'

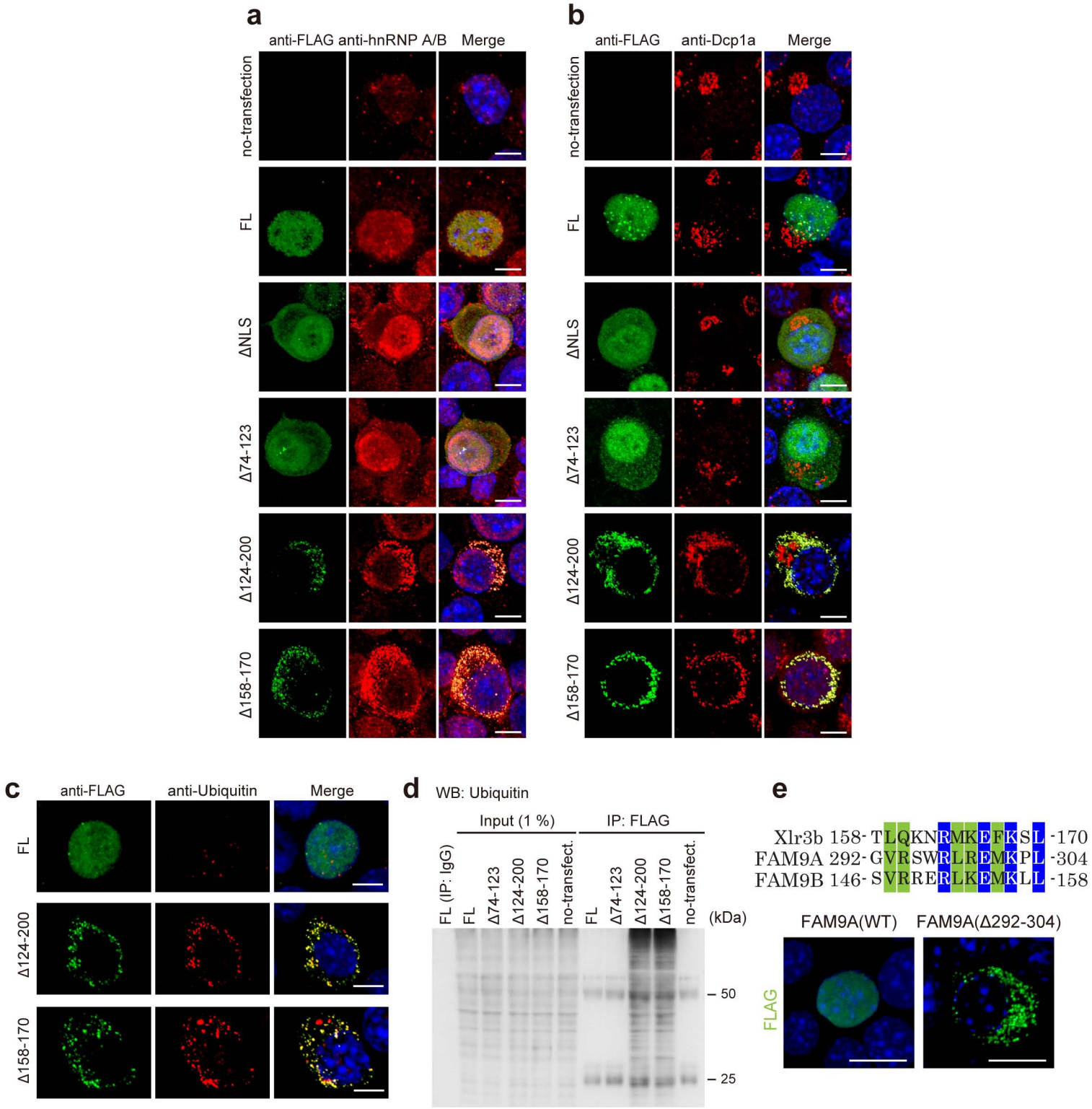
Supplementary Fig. 3. **G-quadruplex formation by sequences of *Xlr3b* CGI (Xlr3b-ODN). a,** CD spectra of Xlr3b-ODN in Li^+ or K^+ solutions. **b,** Xlr3b-ODN primarily formed intramolecular, parallel G-quadruplexes based on native gel electrophoresis. **c,** DMS footprinting of G-quadruplexes formed on Xlr3b-ODN in the Li^+ or K^+ solutions. In **a-c**, the experiments were repeated twice with similar results.



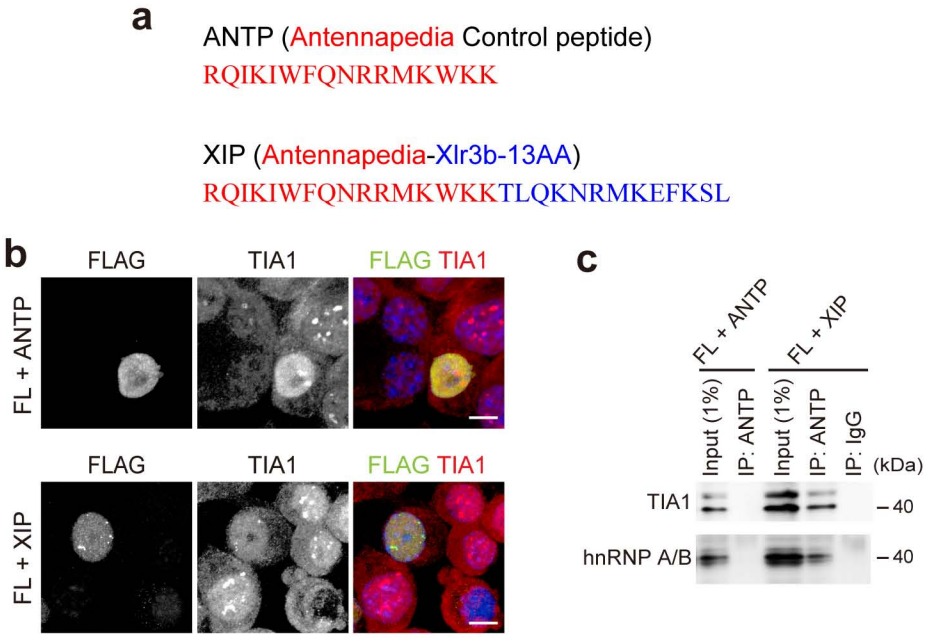
Supplementary Fig. 4. **ATRX interacts with DAXX, DNMT1, DNMT3A and H3.3 in mouse hippocampus. a,** Effect of ATRX shRNA in Neuro-2a cells. Immunoblot analysis (left) and densitometric quantification (right) of protein expression. Densitometric analysis of ATRX normalized to β-tubulin (arbitrary units, A.U.). $^{**}P < 0.01$ by two-sided unpaired t-test. n = 3 biologically independent samples . **b**, (left) Representative immunoblot of P90 mouse hippocampal lysates probed with indicated antibodies, (right) Quantitative densitometry analyses. $^{**}P < 0.01$ by two-sided unpaired t-test. n = 6 mice each. **c,** ATRX was immunoprecipitated (IP'd) from P90 WT and Atrx$^{\Delta E2}$ hippocampal extracts, and western blot analysis performed for indicated proteins. Control reactions were performed with IgG. Extracts were assessed as 1% input. The experiments were repeated three times with similar results.



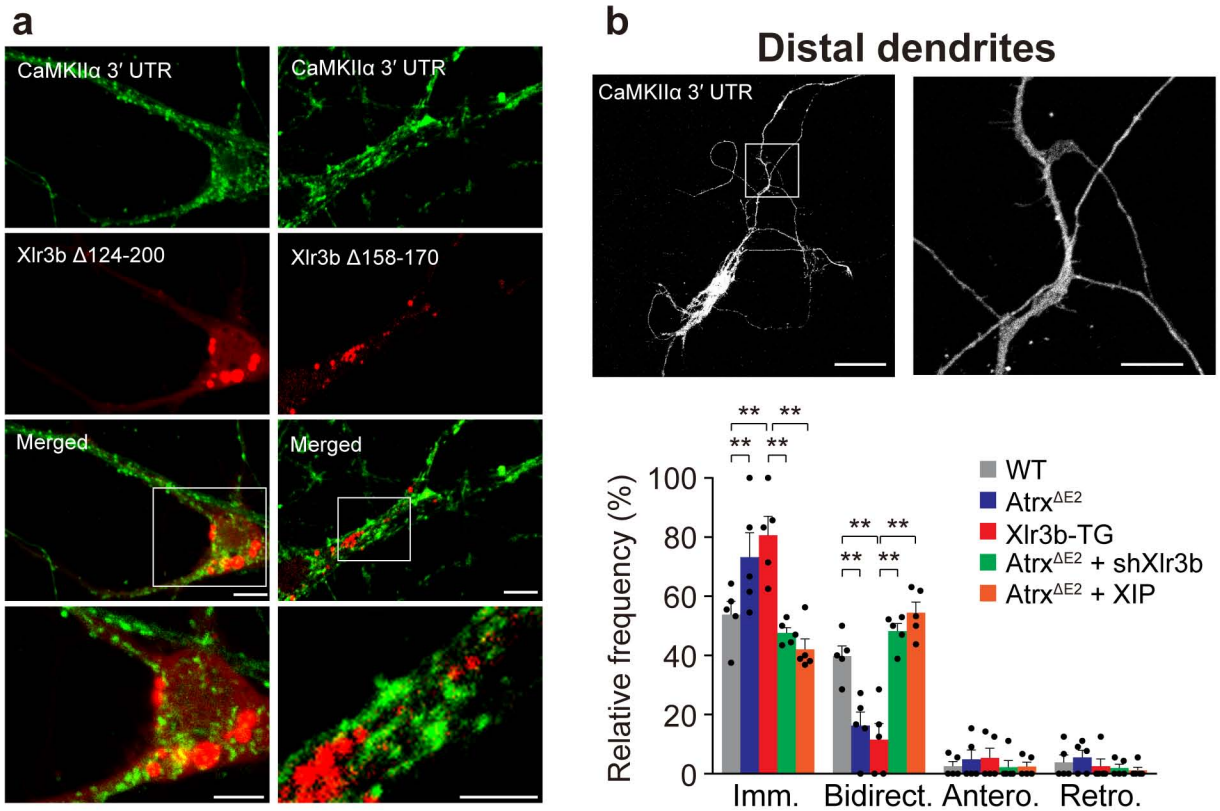
Supplementary Fig. 5. **Purified Xlr3b protein does not bind F-actin or alter actin polymerization. a,** F-actin binding assay. Supernatant (S) and pellet (P) fractions were collected and samples separated on a SDS-gel subsequently stained using a Silver Stain Kit. Reactions were set up as indicated at top. Most α-actinin was found in pellet in the presence of F-actin filaments (lanes 9 and 10), while Xlr3b remained in the supernatant in presence of F-actin filaments (lanes 5 and 6). **b,** Actin polymerization as measured by enhanced fluorescence of pyrene-conjugated actin. Xlr3b addition to purified actin did not alter polymerization. In **a** and **b**, the experiments were repeated twice with similar results.



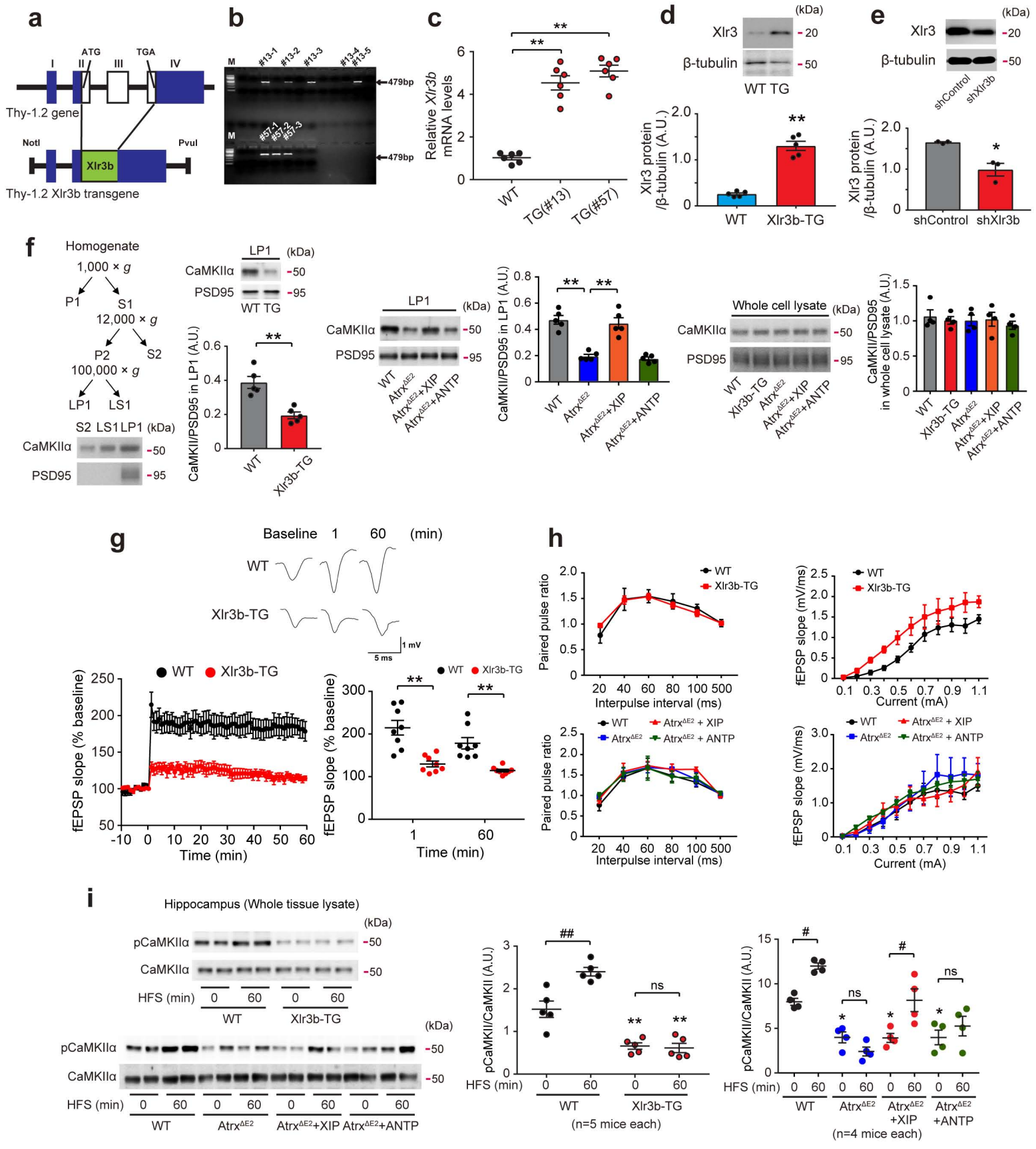
Supplementary Fig. 6 . Xlr3b co -localizes with hnRNP A/B. a-c, Confocal images show ing co-localization of FLAG -tagged Xlr3b constructs with hnRNP A/B **(a)**, Dcp1a **(b)** and ubiquitin **(c)** in Neuro-2a cells. Nuclear DNA is labeled with DAPI (blue). Scale bars, 10μm. **d**, Neuro-2a cells were transfected with FLAG-tagged Xlr3b constructs, cell lysates were immunoprecipitated (IP) with anti-FLAG antibody, and western blot (WB) was probed with ubiquitin antibody. **e**, (top) Sequence comparison of Xlr3b residues 158 -170 and com parable sequences from the Xlr human orthlogs FAM9A and FAM9B. Identical AAs are in blue and similar in light green. (bottom) Confocal images show localization of FLAG-tagged FAM9A constructs (green) in Neuro-2a cells. Nuclear DNA is labeled with DAPI (blue). Scale bars, 10μm. In **a-e**, the experiments were repeated three times with similar results.



Supplementary Fig. 7 . Interaction of Xlr3b AA 158-170 and RBPs. a, Diagram of permeabilization control peptide (antennapedia homeodomain (ANTP)) and Xlr3b inhibitory peptide (XIP). The latter is a 29-AA peptide that contains Xlr3b AA 158-170 plus ANTP. **b,** FL-Xlr3b-transfected cells were treated with XIP (1μM for 4h) and immunostained for TIA1. Scale bars, 20μm. **c,** Pull-down assays with an ANTP antibody assessing TIA1 and hnRNP A/B in P90 mouse brain lysates. Eluted proteins and inputs were immunoblotted with indicated antibodies. Extract samples served as 1% input. IP, immunoprecipitation. In **b** and **c**, the experiments were repeated three times with similar results.



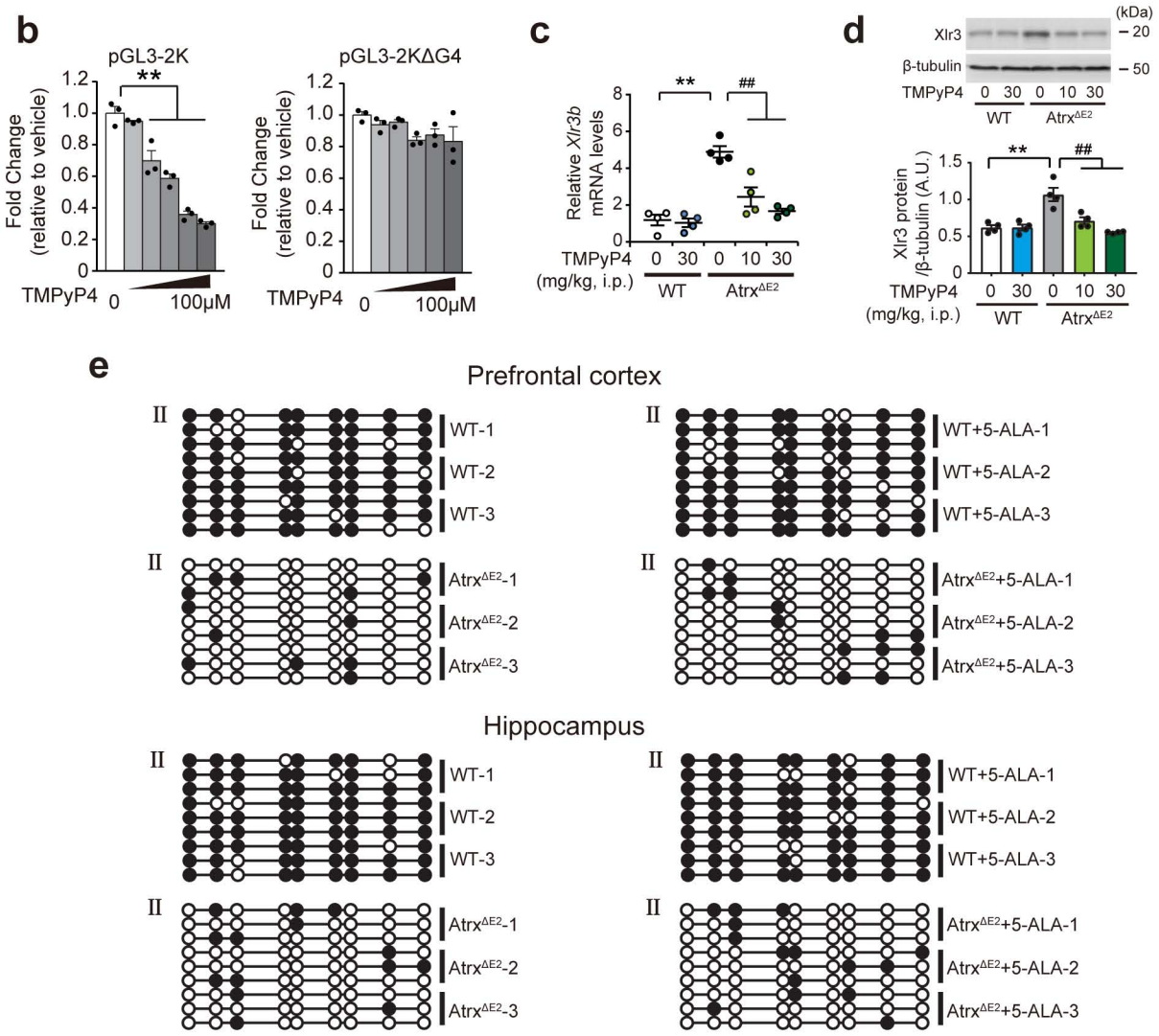
Supplementary Fig. 8. Dynamics of CaMKIIα mRNA transport in distal dendrites. a, Confocal images of mCherry-Xlr3b Δ124-200 or Δ158-170 (red) and GFP-CaMKIIα 3′ UTR (green) in cultured neurons at day 21 *in vitro*. Scale bars, 10μm. The experiments were repeated three times with similar results. **b,** (top, left) A confocal image of GFP-CaMKIIα 3′ UTR in primary mouse cultured neurons at day 21 *in vitro*. Scale bar, 50μm. Images at right is enlarged from corresponding boxed area. Scale bar, 10μm. See also **Supplementary Video 2**. (bottom) Relative frequency of movement of GFP-CaMKIIα 3′ UTR granules. $^{**}P < 0.01$ by two-way ANOVA with Bonferroni's post hoc test; n= 5 neurons each, a distal dendrite (100-200μm away from the cell body) per neuron to measure relative frequencies. Cells were treated with XIP (1μM) 4 h before imaging. Imm., immobile; Bidirect., bidirectional movement; Antero., anterograde movement; and Retro., retrograde movement.


a
ATG
TGA
I
II
III
IV
Thy-1.2 gene
NotI
PvuI
Xlr3b
Thy-1.2 Xlr3b transgene
b
M
#13-1
#13-2
#13-3
#13-4
#13-5
479bp
#57-1
#57-2
#57-3
c
Relative Xlr3b mRNA levels
WT
TG(#13)
TG(#57)
d
Xlr3
β-tubulin
(kDa)
20
50
WT TG
Xlr3 protein /β-tubulin (A.U.)
WT
Xlr3b-TG
e
shControl
shXlr3b
f
Homogenate
1,000 × g
P1
S1
12,000 × g
P2
S2
100,000 × g
LP1
LS1
S2 LS1 LP1 (kDa)
CaMKIIα
PSD95
CaMKII/PSD95 in LP1 (A.U.)
Atrx^ΔE2
Atrx^ΔE2+XIP
Atrx^ΔE2+ANTP
Whole cell lysate
CaMKII/PSD95 in whole cell lysate (A.U.)
g
Baseline
1
60
(min)
1 mV
5 ms
fEPSP slope (% baseline)
Time (min)
h
Paired pulse ratio
Interpulse interval (ms)
fEPSP slope (mV/ms)
Current (mA)
i
Hippocampus (Whole tissue lysate)
pCaMKIIα
HFS (min)
(n=5 mice each)
(n=4 mice each)
j
NOR test
Discrimination index
k
PA test
Latency (seconds)
l
Y-maze test
Alternations (%)

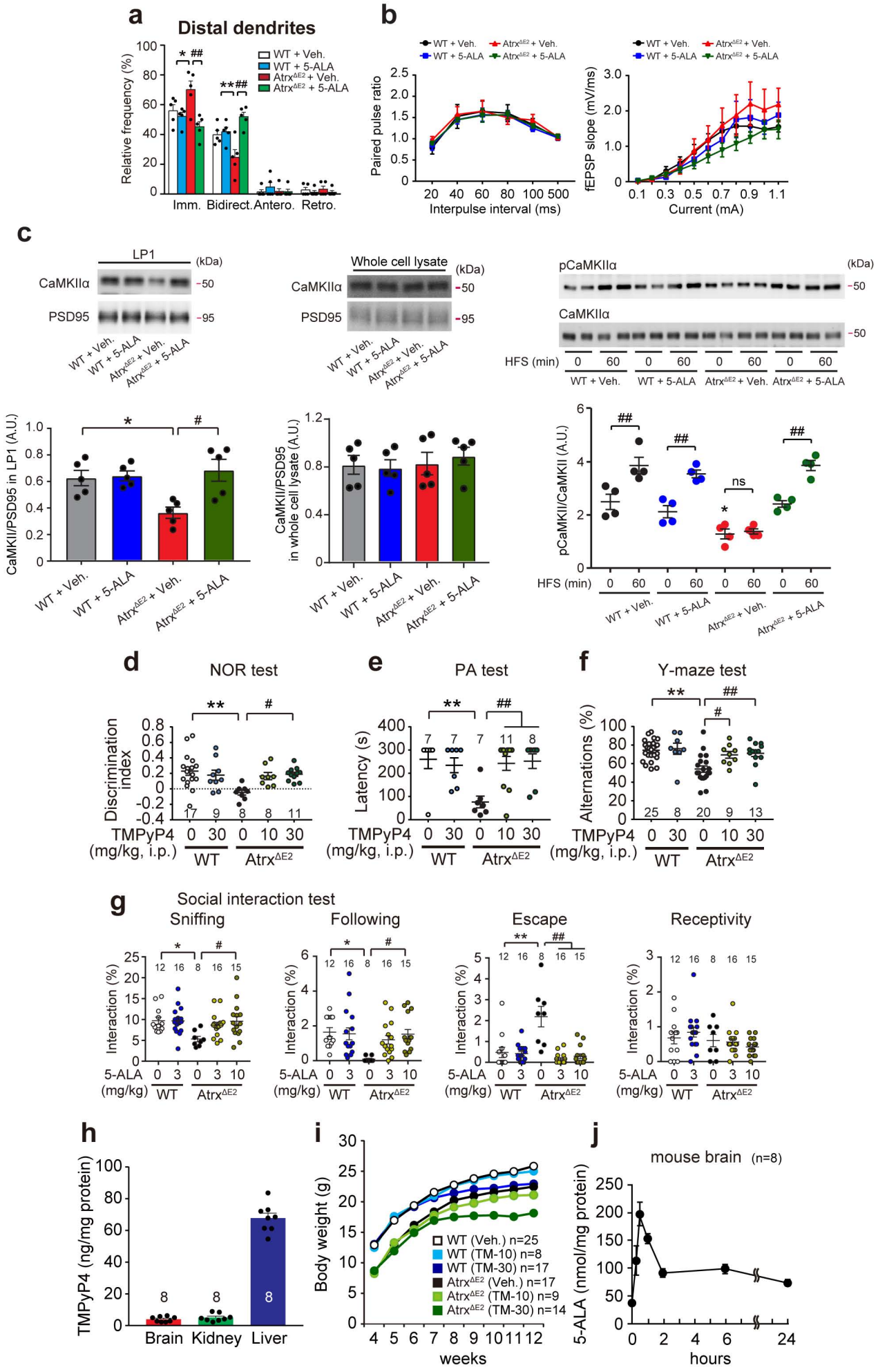
Supplementary Fig. 9 . Generation of Thy1 -Xlr3b transgenic mice. a, Genomic organization of Thy1 gene (top) and the transgenic construct (bottom). The Xlr3b cDNA was subcloned into a XhoI site of the Thy1.2 expression cassette. Blue boxes, untranslated exons. **b,** Representative PCR genotyping using tail DNA of transgenic founders (#13 and #57). M, size marker. **c**, Quantitative real-time RT-PCR showing *Xlr3b* mRNA expression in P90 mouse hippocampal lysates. $^{**}P < 0.01$ by one-way ANOVA with Bonferroni's post hoc test;n = 6 mice each. TG, Xlr3b transgenic mouse. **d**, (top) Representative immunoblot of mouse hippocampal lysates probed with Xlr3 and β-tubulin antibodies, (bottom) Densitometric analysis of Xlr3 normalized to β-tubulin (arbitrary units, A.U.). $^{**}P < 0.01$ by two-sided unpaired t-test; n = 5 mice each. **e,** Effect of Xlr3b shRNA in cultured neurons. Immunoblot analysis (top) and densitometric quantification (bottom) of protein expression. Densitometric analysis of Xlr3 normalized to β-tubulin (arbitrary units, A.U.). $^{*}P < 0.05$ by two-sided unpaired t-test; n = 3 biologically independent samples. **f,** (left) Method for isolation of synaptosomal membrane fractions from cultured neurons. The procedure for the subcellular fractionation is described in Methods. P1, nucleus/cell debris; S1, postnuclear supernatant; S2, cytosol fraction; P2, crude synaptosomal fraction; LS1, synaptosomal cytosol fraction; LP1, synaptosomal membrane fraction. Immunoblot showing CaMKIIα and postsynaptic marker, PSD95 between S2, LS1, and LP1 in cultured neurons from WT mice . (middle and right) Immunoblot and corresponding quantitative analysis of CaMKIIα and PSD95 proteins at LP1 and whole cell lysates in cultured neurons. Densitometric analyses of CaMKIIα normalized to PSD95 (arbitrary units, A.U.). $^{**}P < 0.01$ by one-way ANOVA with Bonferroni's post hoc test. (In WT vs. Xlr3b-TG, $^{**}P < 0.01$ by two-sided unpaired t-test.) LP1, n = 5 biologically independent samples; whole cell lysates, n = 4 biologically independent samples. **g,** (top) Representative field excitatory post-synaptic potentials (fEPSPs) were recorded from the hippocampal CA1 region of mice. (left), Changes in fEPSP slope following high frequency stimulation (HFS) were attenuated in Xlr3b-TG mice in hippocampal CA1. (right), Changes in fEPSP slope following HFS at 1 or 60 min. $^{**}P < 0.01$ by two-way ANOVA with Bonferroni's post hoc test;n = 8 mice each. **h**, Paired pulse facilitation (left) and input-output relationship (right) were recorded. n = 5 mice each. There were no significant changes between the groups. **i**, LTP-induced CaMKIIα phosphorylation in the hippocampus. (left) Representative images of immunoblots using antibodies against phosphorylated CaMKIIα (pCaMKIIα) and total CaMKIIα. (right) Densitometric analysis of pCaMKIIα normalized to total CaMKIIα (arbitrary units, A.U.). $^{**}P < 0.01$, $^{*}P < 0.05$, vs. WT mice before high-frequency stimulation (HFS), $^{\#\#}P < 0.01$, $^{\#}P < 0.05$, before HFS vs. after HFS in each group by two-way ANOVA with Bonferroni's post hoc test Respective sample sizes are indicated. **j-l,** Xlr3b-TG mice show memory deficits. Novel-object recognition (NOR) test **(j)**, Latency time in retention trials in a passive avoidance (PA) test **(k),** Alternations in a Y-maze test **(l)** are shown. $^{**}P < 0.01$, $^{*}P < 0.05$ by two-sided unpaired t-test. Respective sample sizes are indicated.

a

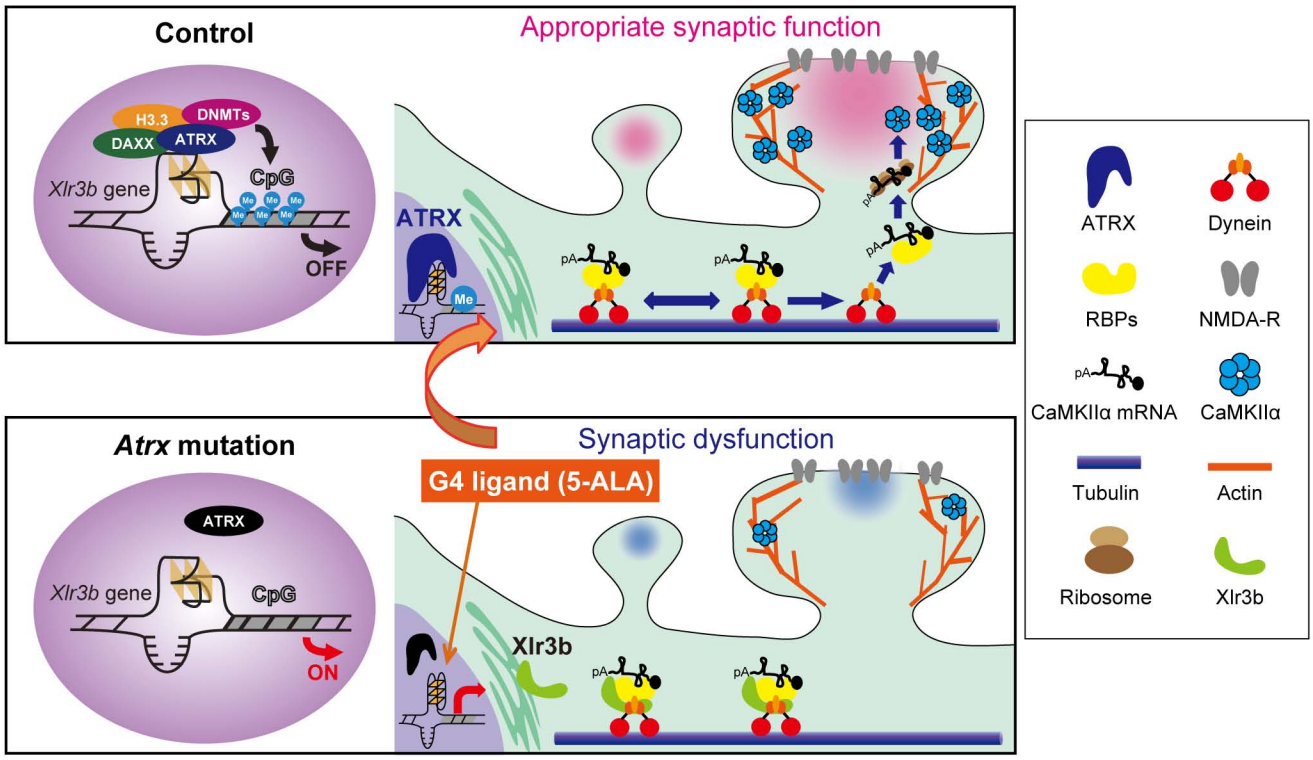
Samples	Xlr3b-ODN	Xlr3b-ODN +PpIX	Xlr3b-ODN +hemin	Xlr3b-ODN +TMPyP4
Tm (°C)	70.1	72.1	72.4	75.3
Δ*Tm* (°C)	0	2.0	2.3	4.2



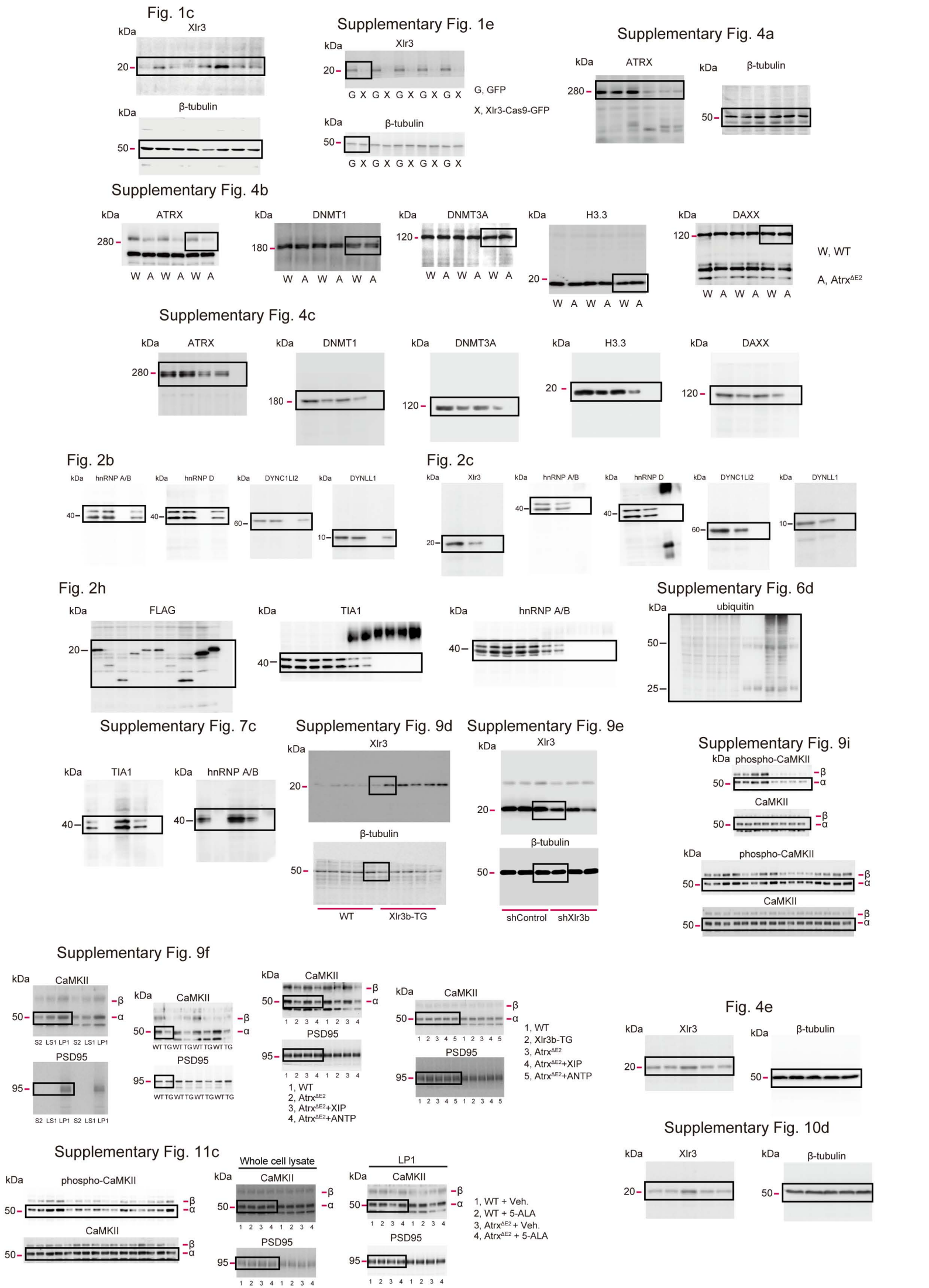
Supplementary Fig. 10. TMPyP4 treatment inhibits Xlr3b expression. a, The binding effect of P rotoporphyrin IX (PpIX), hemin and TMPyP4 on G-quadruplexes formed by Xlr3b-ODN based on a UV melting experiment. **b,** Luciferase activity of Neuro-2a cells transfected with pGL3-2K or pGL3-2KΔG4 and treated with TMPyP4 (1, 3, 10, 30 and 100μM) for 48 h. Luciferase activity is shown relative to activity in vehicle-treated cells. $^{**}P < 0.01$ by one-way ANOVA with Bonferroni's post hoc test;n = 3 biological replicates. **c,** Quantitative real-time RT-PCR showing *Xlr3b* mRNA expression in mouse hippocampal lysates. $^{**}P < 0.01$ vs. vehicle-treated WT mice, $^{\#\#}P < 0.01$ vs. vehicle-treated $Atrx^{\Delta E2}$ mice by one-way ANOVA with Bonferroni's post hoc test ; n = 4 mice each. **d**, (top) Representative immunoblot of mouse hippocampal lysates probed with Xlr3 and β-tubulin antibodies, (bottom) Densitometric analysis of Xlr3 normalized to β-tubulin (arbitrary units, A.U.). $^{**}P < 0.01$ vs. vehicle-treated WT mice, $^{\#\#}P < 0.01$ vs. vehicle-treated $Atrx^{\Delta E2}$ mice by one-way ANOVA with Bonferroni's post hoc test; n = 4 mice each. **e**, Methylation status of Xlr3b CpG sites. Open circles, unmethylated CpGs; closed circles, methylated CpGs. Male P90 mice were used. n = 3 mice each. three independent clones of each sample were sequenced.


a
Distal dendrites
Relative frequency (%)
WT + Veh.
WT + 5-ALA
Atrx$^{\Delta E2}$ + Veh.
Atrx$^{\Delta E2}$ + 5-ALA
Imm. Bidirect. Antero. Retro.
b
Paired pulse ratio
Interpulse interval (ms)
fEPSP slope (mV/ms)
Current (mA)
c
LP1
Whole cell lysate
CaMKIIα
PSD95
pCaMKIIα
(kDa)
HFS (min)
CaMKII/PSD95 in LP1 (A.U.)
CaMKII/PSD95 in whole cell lysate (A.U.)
pCaMKII/CaMKII (A.U.)
d
NOR test
Discrimination index
TMPyP4 (mg/kg, i.p.)
WT
Atrx$^{\Delta E2}$
e
PA test
Latency (s)
f
Y-maze test
Alternations (%)
g
Social interaction test
Sniffing
Following
Escape
Receptivity
Interaction (%)
5-ALA (mg/kg)
h
TMPyP4 (ng/mg protein)
Brain
Kidney
Liver
i
Body weight (g)
WT (Veh.) n=25
WT (TM-10) n=8
WT (TM-30) n=17
Atrx$^{\Delta E2}$ (Veh.) n=17
Atrx$^{\Delta E2}$ (TM-10) n=9
Atrx$^{\Delta E2}$ (TM-30) n=14
weeks
j
mouse brain (n=8)
5-ALA (nmol/mg protein)
hours

Supplementary Fig. 11. TMPyP4 treatment rescues cognitive deficits seen in Atrx$^{\Delta E2}$ mice. a, Relative frequency of movement of GFP-CaMKIIα 3′ UTR granules in distal dendrites. Cells were treated with 5-ALA (1μM) for 7 days before imaging. $^{**}P < 0.01$, $^{*}P < 0.05$ vs. vehicle-treated WT neurons, $^{\#\#}P < 0.01$ vs. vehicle-treated Atrx$^{\Delta E2}$ neurons by two-way ANOVA with Bonferroni's post hoc test; n = 5 neurons each, a distal dendrite (100-200μm away from the cell body) per neuron to measure relative frequencies. Imm., immobile; Bidirect., bidirectional movement; Antero., anterograde movement; and Retro., retrograde movement. **b**, Paired pulse facilitation (left) and input-output relationship (right) were recorded. n = 5 mice each. There were no significant changes between the groups. **c**, (left) Immunoblot and corresponding quantitative analyses of CaMKIIα and PSD95 proteins at LP1 (synaptosomal membrane fractions) and whole cell lysates in cultured neurons. Densitometric analyses of CaMKIIα normalized to PSD95 (arbitrary units, A.U.). $^{*}P < 0.05$ vs. vehicle-treated WT neurons, $^{\#}P < 0.05$ vs. vehicle-treated Atrx$^{\Delta E2}$ neurons by one-way ANOVA with Bonferroni's post hoc test; n = 5 biologically independent samples. (right) LTP-induced CaMKIIα phosphorylation in the hippocampus. Representative images of immunoblots using antibodies against phosphorylated CaMKIIα (pCaMKIIα) and CaMKIIα. Densitometric analysis of pCaMKIIα normalized to total CaMKIIα (arbitrary units, A.U.). $^{*}P < 0.05$, vs. WT mice before high-frequency stimulation (HFS), $^{\#\#}P < 0.01$, before HFS vs. after HFS in each group by two-way ANOVA with Bonferroni's post hoc test; n 4 mice each. **d-f,** TMPyP4 treatment rescued cognitive deficits in Atrx$^{\Delta E2}$ mice based on memory-related behavioral tests. Novel-object recognition (NOR) test **(d)**, latency time in retention trials in a passive avoidance (PA) test **(e),** alternations in a Y-maze test **(f)** are shown. $^{**}P < 0.01$ vs. vehicle-treated WT mice, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. vehicle-treated Atrx$^{\Delta E2}$ mice by one-way ANOVA with Bonferroni's post hoc test; Respective sample sizes are indicated. **g,** Atrx$^{\Delta E2}$ mice show withdrawal in social interactions with WT mice. Atrx$^{\Delta E2}$ mice showed enhanced passivity, higher escape duration and decreased social activity, such as following and sniffing behaviors, in social interactions with WT mice. These behaviors are dramatically improved by 5-ALA treatment. $^{**}P < 0.01$, $^{*}P < 0.05$ vs. vehicle-treated WT mice, $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ vs. vehicle-treated Atrx$^{\Delta E2}$ mice by one-way ANOVA with Bonferroni's post hoc test; Respective sample sizes are indicated. **h**, Measurements of TMPyP4 fluorescence levels. Chronic intraperitoneal injection of TMPyP4 in P90 mice increased fluorescence levels in some tissues, including brain. Respective sample sizes are indicated. **i,** Measurements of body weight following chronic TMPyP4 administration on day 60 (i.p. twice weekly from P30 to P90). Respective sample sizes are indicated. **j,** Measurements of 5-ALA levels in P90 mouse brain after oral administration (3mg/kg, p.o.). Respective sample sizes are indicated



Supplementary Fig. 12. Schematic showing outcomes following *Atrx* mutation. ATRX binds to parallel G-quadruplexes in *Xlr3b* CGIs along with DNMTs, DAXX and H3.3, regulating *Xlr3b* gene expression through DNA methylation in cooperation with DMNTs. CaMKIIα mRNA locates in neuronal dendrites, and its transport is dynamically regulated by the motor protein, dynein. CaMKII α translation enhances synaptic efficacy postsynaptically, which is critical for learning and memory. In control neurons, ATRX binds G-quadruplex-forming DNA in *Xlr3b* CGIs, inhibiting *Xlr3b* expression through DNA methylation. In *Atrx* mutant neurons, aberrant expression of Xlr3b protein occurs through DNA de-methylation at the site. Xlr3b protein has RNA binding capacity and cooperates with RNA binding proteins (RBPs) , and inhibits dendritic transport of CaMKIIα mRNA, resulting synaptic dysfunction. Treatment with G-quadruplex (G4) ligand 5-ALA represses *Xlr3b* transcription, antagonizing both synaptic dysfunction and cognitive deficits in *Atrx* mutant mice.



Supplementary Fig. 13. Full-size scans of western blots shown in figures.

List of genes with an FDR < 0.05 and a log2 fold change of > 0.5 or <0.5 (WT vs. Atrx ΔE2)

	Log2 global normalization														FDR	Difference
symbol	WT-1	WT-2	WT-3	WT-4	WT-5	WT-6	WT-7	$Atrx^{\Delta E2}$-1	$Atrx^{\Delta E2}$-2	$Atrx^{\Delta E2}$-3	$Atrx^{\Delta E2}$-4	$Atrx^{\Delta E2}$-5	$Atrx^{\Delta E2}$-6	$Atrx^{\Delta E2}$-7	WT vs $Atrx^{\Delta E2}$	$Atrx^{\Delta E2}$ – WT
Xlr3b	5.0	5.6	4.8	3.9	4.0	4.9	5.1	7.3	5.9	5.6	6.4	6.7	6.0	6.3	0.00392	1.553
Cap1	8.2	6.0	5.9	6.5	6.1	6.2	6.3	8.3	8.9	6.2	7.8	7.9	8.1	7.9	0.01751	1.403
Xlr3a	4.1	4.2	3.9	2.9	3.3	4.0	4.2	6.3	5.0	4.9	5.1	5.1	5.0	4.8	0.00116	1.392
S100a4	4.2	4.1	4.5	4.3	4.6	4.7	4.7	5.2	5.0	4.8	5.4	5.4	4.9	5.1	0.00044	0.639
Fbxo39	5.4	6.2	5.6	5.5	5.6	5.5	5.9	6.4	6.3	5.4	6.6	6.6	6.4	6.2	0.00604	0.611
Prdm16	4.5	4.3	4.4	5.0	5.0	5.2	4.9	5.1	4.8	4.6	6.1	5.8	5.4	5.5	0.03460	0.554
M6prbp1	6.6	6.9	6.8	7.4	7.3	7.3	7.5	7.5	7.4	7.1	7.9	8.0	7.8	8.1	0.03433	0.539
D030013I16Rik	6.9	7.1	6.9	6.9	6.7	6.6	6.8	7.8	7.6	7.5	7.1	7.2	7.2	7.3	0.00951	0.527
Rora	7.0	6.9	7.0	7.5	7.2	7.0	7.1	7.3	7.3	7.1	6.2	6.3	6.1	6.0	0.04791	−0.515
Cpne9	6.9	7.1	6.8	6.5	6.5	6.4	6.7	6.8	6.8	6.6	5.6	5.5	5.8	6.0	0.03830	−0.533
Plcb4	7.1	6.9	7.1	7.4	7.5	7.2	7.3	6.8	6.9	7.0	6.7	6.6	6.4	6.4	0.00210	−0.536
F2r	5.5	6.1	5.5	6.5	6.5	6.2	6.3	5.8	5.4	5.6	5.8	5.9	5.2	5.1	0.04965	−0.541
4921511K06Rik	8.8	8.7	8.6	8.9	8.9	8.5	8.8	8.3	8.8	8.5	8.2	8.0	7.6	7.7	0.03422	−0.567
Atp7a	5.4	5.5	5.5	5.9	5.8	5.8	5.9	4.9	4.8	4.7	5.5	5.4	5.2	5.4	0.00456	−0.576
Zic1	6.4	6.4	7.0	7.9	8.0	7.6	7.8	6.7	6.3	6.7	6.7	6.6	6.6	6.5	0.03200	−0.693
ENSMUSG00000056615	6.0	6.4	6.0	6.3	6.1	5.3	5.4	6.4	6.3	5.5	4.5	4.5	4.6	4.7	0.04991	−0.73
Inpp4b	3.2	3.5	4.1	5.0	4.9	4.7	4.9	3.4	3.6	4.0	4.1	3.8	3.1	3.0	0.04544	−0.749
Vash2	4.2	4.5	5.4	5.5	5.4	4.9	5.1	4.6	4.2	5.5	4.3	4.2	3.5	3.4	0.04181	−0.754
Klhdc8a	5.9	5.5	5.6	5.9	6.1	5.6	5.8	5.7	5.0	5.8	4.5	4.3	4.7	4.8	0.00763	−0.771
Arsj	4.6	4.7	4.8	4.6	4.7	4.5	4.3	4.3	4.4	4.2	4.1	4.1	2.5	2.8	0.02578	−0.833
Tmie	4.6	4.6	4.8	5.3	5.5	5.5	5.4	4.3	4.6	4.8	4.1	4.2	3.9	3.8	0.00179	−0.87
Atrx	5.1	5.5	5.6	4.5	4.0	4.3	4.5	4.5	4.0	4.4	2.9	3.8	3.6	0.0	0.04837	−0.92
Rgs16	5.1	5.4	5.4	7.3	7.4	6.8	7.1	5.5	5.3	5.1	6.1	6.1	4.7	5.0	0.04499	−0.949
Agxt2l1	5.9	6.7	5.9	6.5	6.6	6.4	6.4	5.5	5.4	5.0	5.4	5.8	5.3	5.3	0.00022	−0.953
Zic2	4.1	4.5	5.1	5.8	5.8	5.5	5.6	5.0	3.9	5.0	4.0	4.0	3.8	3.8	0.01841	−0.97
Mrvi1	3.7	4.4	3.9	5.4	5.5	4.8	5.0	3.6	3.5	3.8	4.1	4.3	2.9	3.4	0.01339	−0.994
Ramp3	8.6	8.2	8.3	8.7	8.7	8.4	8.7	8.3	8.2	8.2	7.0	7.0	6.5	6.3	0.01383	−1.144
Cbln1	6.4	6.2	7.4	6.5	6.4	6.6	6.8	6.2	6.2	7.4	4.0	4.3	5.1	4.9	0.03435	−1.187
Tac2	6.6	7.0	7.0	5.1	5.3	7.9	7.8	6.6	6.7	6.6	4.3	4.4	4.6	4.9	0.04419	−1.237
Slc17a6	5.2	5.2	5.9	8.2	8.3	8.0	8.0	5.2	5.2	5.8	5.8	6.2	4.9	5.1	0.02692	−1.517
Spry2	6.1	4.7	5.9	5.4	5.4	5.6	5.6	3.2	2.5	6.2	2.3	2.1	2.8	2.5	0.00349	−2.449

	Difference_Log2 global normalization													
symbol	WT-1	WT-2	WT-3	WT-4	WT-5	WT-6	WT-7	$Atrx^{\Delta E2}$-1	$Atrx^{\Delta E2}$-2	$Atrx^{\Delta E2}$-3	$Atrx^{\Delta E2}$-4	$Atrx^{\Delta E2}$-5	$Atrx^{\Delta E2}$-6	$Atrx^{\Delta E2}$-7
Xlr3b	−0.5	0.0	−0.8	−1.6	−1.6	−0.6	−0.4	1.8	0.3	0.0	0.8	1.2	0.5	0.8
Cap1	1.0	−1.2	−1.2	−0.7	−1.1	−0.9	−0.8	1.1	1.8	−1.0	0.6	0.7	1.0	0.8
Xlr3a	−0.4	−0.3	−0.6	−1.6	−1.2	−0.5	−0.3	1.9	0.5	0.4	0.6	0.7	0.6	0.3
S100a4	−0.5	−0.7	−0.2	−0.4	−0.2	−0.1	−0.1	0.4	0.2	0.0	0.6	0.6	0.1	0.3
Fbxo39	−0.6	0.2	−0.4	−0.5	−0.4	−0.4	−0.1	0.4	0.3	−0.5	0.7	0.6	0.4	0.2
Prdm16	−0.5	−0.7	−0.6	−0.1	0.0	0.2	−0.1	0.0	−0.2	−0.4	1.0	0.7	0.4	0.4
M6prbp1	−0.8	−0.5	−0.6	0.0	−0.1	−0.1	0.1	0.1	0.0	−0.3	0.5	0.6	0.4	0.7
D030013I16Rik	−0.2	0.0	−0.3	−0.2	−0.4	−0.5	−0.3	0.7	0.5	0.3	−0.1	0.0	0.1	0.2
Rora	0.2	0.1	0.2	0.6	0.3	0.2	0.3	0.4	0.5	0.2	−0.7	−0.6	−0.7	−0.9
Cpne9	0.5	0.7	0.3	0.1	0.0	0.0	0.2	0.4	0.4	0.2	−0.9	−0.9	−0.6	−0.4
Plcb4	0.2	−0.1	0.2	0.4	0.6	0.3	0.4	−0.1	−0.1	0.1	−0.3	−0.3	−0.6	−0.5
F2r	−0.3	0.3	−0.3	0.6	0.7	0.4	0.5	0.0	−0.5	−0.2	0.0	0.1	−0.6	−0.7
4921511K06Rik	0.4	0.2	0.2	0.5	0.4	0.0	0.3	−0.1	0.4	0.1	−0.3	−0.5	−0.9	−0.7
Atp7a	0.0	0.1	0.1	0.5	0.4	0.4	0.5	−0.5	−0.6	−0.7	0.1	0.0	−0.2	0.0
Zic1	−0.6	−0.5	0.1	0.9	1.0	0.7	0.8	−0.2	−0.6	−0.2	−0.2	−0.3	−0.4	−0.5
ENSMUSG00000056615	0.4	0.9	0.5	0.7	0.5	−0.2	−0.2	0.8	0.7	−0.1	−1.0	−1.1	−1.0	−0.9
Inpp4b	−0.7	−0.5	0.1	1.1	1.0	0.7	0.9	−0.5	−0.3	0.0	0.2	−0.2	−0.8	−1.0
Vash2	−0.5	−0.1	0.8	0.8	0.8	0.3	0.5	0.0	−0.4	0.8	−0.3	−0.4	−1.1	−1.2
Klhdc8a	0.5	0.1	0.2	0.5	0.7	0.2	0.4	0.3	−0.3	0.4	−0.8	−1.0	−0.7	−0.5
Arsj	0.4	0.5	0.7	0.4	0.5	0.3	0.1	0.1	0.2	0.0	−0.1	−0.1	−1.7	−1.4
Tmie	−0.1	−0.1	0.1	0.7	0.8	0.9	0.7	−0.3	−0.1	0.1	−0.6	−0.5	−0.8	−0.9
Atrx	1.1	1.5	1.5	0.5	0.0	0.3	0.4	0.4	0.0	0.3	−1.1	−0.2	−0.5	−4.1
Rgs16	−0.8	−0.4	−0.5	1.5	1.5	0.9	1.2	−0.4	−0.6	−0.8	0.2	0.2	−1.1	−0.9
Agxt2l1	0.1	0.8	0.0	0.6	0.8	0.6	0.5	−0.3	−0.5	−0.8	−0.5	−0.1	−0.5	−0.6
Zic2	−0.6	−0.2	0.4	1.1	1.1	0.8	0.9	0.3	−0.8	0.3	−0.7	−0.7	−0.9	−0.9
Mrvi1	−0.5	0.2	−0.2	1.2	1.3	0.6	0.8	−0.5	−0.6	−0.4	0.0	0.1	−1.2	−0.8
Ramp3	0.6	0.2	0.4	0.7	0.8	0.5	0.8	0.4	0.3	0.3	−0.9	−0.9	−1.5	−1.6
Cbln1	0.3	0.2	1.4	0.4	0.4	0.6	0.8	0.2	0.2	1.4	−2.0	−1.7	−0.9	−1.2
Tac2	0.6	0.9	0.9	−1.0	−0.8	1.9	1.8	0.5	0.6	0.5	−1.7	−1.6	−1.4	−1.2
Slc17a6	−1.0	−1.0	−0.3	2.0	2.1	1.8	1.7	−1.0	−1.0	−0.4	−0.4	−0.1	−1.3	−1.1
Spry2	1.8	0.4	1.6	1.1	1.1	1.3	1.3	−1.1	−1.8	1.9	−2.0	−2.2	−1.5	−1.8

Supplementary Table 1. List of genes exhibiting differential expression in hippocampus of P90 WT and $Atrx^{\Delta E2}$ mice.

Accession Number	Gene Symbol	Protein name	Group
gi|597955343	Dynlrb1	DYNLRB1, dynein light chain roadblock-type 1 isoform a	Dynein
gi|31543851	Dynlt3	DYNLT3, dynein light chain Tctex-type 3	Dynein
gi|568966877	Myl6	MYL6, PREDICTED: myosin light polypeptide 6 isoform X1	Actin/Myosin
gi|148709713	Dynll1	DYNLL1, mCG13330, dynein light chain 1, cytoplasmic	Dynein
gi|211826253	Hnrnpd	HNRNPD, Hnrnpd protein, partial	Ribosome/RNA binding
gi|576795839	Rufy3	RUFY3, RUN and FYVE domain containing 3	Actin/Myosin
gi|1903236	Capzb	CAPZB, capping protein beta 3 subunit, partial	Actin/Myosin
gi|148676482	Sptan1	SPECTAN1, mCG18286, spectrin alpha chain, non-erythrocytic 1 isoform X6	Actin/Myosin
gi|569001405	Rps10	RPS10, PREDICTED: 40S ribosomal protein S10 isoform X1	Ribosome/RNA binding
gi|6680924	Cfl1	CFL1, cofilin-1	Actin/Myosin
gi|148678220	Pcdhb4	PCDHB4, protocadherin beta 4	Other
gi|6755911	Txn1	TXN1, thioredoxin	Other
gi|6754222	Hnrnpab	HNRNPAB, heterogeneous nuclear ribonucleoprotein A/B isoform 2	Ribosome/RNA binding
gi|21594641	Dlat	DLAT, Dihydrolipoamide S-acetyltransferase	Other
gi|6678047	Snca	SNCA, alpha-synuclein	Other
gi|148681931	Capza2	CAPZA2, capping protein (actin filament) muscle Z-line, alpha 2, isoform CRA_a	Actin/Myosin
gi|568899179	Gm6988	RPS25, PREDICTED: 40S ribosomal protein S25-like	Ribosome/RNA binding
gi|35193080	Dync1li2	DYNC1LI2, Dynein, cytoplasmic 1 light intermediate chain 2	Dynein

Supplementary Table 2. Xlr3 interaction partners identified in proteomic screen using LC-MS/MS analysis.

	Log2 global normalization																			Average				variation within a subgroup			variation between subgroups	F-value	p-value	Bonferroni p<0.05	t-test		Difference between the average value in Log2 global normalization				FDR
symbol	WT-1	WT-2	WT-3	WT-4	WT-5	WT-6	WT-7	Atrx$^{\Delta E2}$-1	Atrx$^{\Delta E2}$-2	Atrx$^{\Delta E2}$-3	Atrx$^{\Delta E2}$-4	Atrx$^{\Delta E2}$-5	Atrx$^{\Delta E2}$-6	Atrx$^{\Delta E2}$-7	Atrx$^{\Delta E2}$+5-ALA-1	Atrx$^{\Delta E2}$+5-ALA-2	Atrx$^{\Delta E2}$+5-ALA-3	Atrx$^{\Delta E2}$+5-ALA-4	All	WT	Atrx	Atrx+ALA	WT	Atrx	Atrx+ALA					WT vs Atrx	Atrx vs Atrx+ALA	(Atrx)−(WT)	(Atrx+ALA)−(Atrx)	UP	DOWN	WT vs Atrx
Xlr3b	5.0	5.6	4.8	3.9	4.0	4.9	5.1	7.3	5.9	5.6	6.4	6.7	6.0	6.3	4.4	4.3	4.0	3.8	5.2	4.8	6.3	4.1	2.188	1.937	0.208	14.625	25.314	0.000	¥	0.000	0.000	1.553	-2.189	*		0.0039183
Cap1	8.2	6.0	5.9	6.5	6.1	6.2	6.3	8.3	8.9	6.2	7.8	7.9	8.1	7.9	5.8	5.7	6.1	5.9	6.9	6.5	7.9	5.9	3.633	4.305	0.074	12.011	11.243	0.001	¥	0.007	0.001	1.403	-1.985	*		0.0175131
Xlr3a	4.1	4.2	3.9	2.9	3.3	4.0	4.2	6.3	5.0	4.9	5.1	5.1	5.0	4.8	3.2	3.0	3.0	3.1	4.2	3.8	5.2	3.1	1.457	1.658	0.012	12.815	30.738	0.000	¥	0.000	0.000	1.392	-2.089	*		0.0011574
S100a4	4.2	4.1	4.5	4.3	4.6	4.7	4.7	5.2	5.0	4.8	5.4	5.4	4.9	5.1	4.9	4.6	4.4	4.6	4.7	4.5	5.1	4.6	0.329	0.315	0.129	1.513	14.667	0.000	¥	0.000	0.000	0.639	-0.482	*		0.0004448
Fbxo39	5.4	6.2	5.6	5.5	5.6	5.5	5.9	6.4	6.3	5.4	6.6	6.6	6.4	6.2	5.3	5.1	5.1	4.9	5.8	5.7	6.3	5.1	0.491	0.977	0.094	3.585	17.221	0.000	¥	0.008	0.000	0.611	-1.161	*		0.0060373
Prdm16	4.5	4.3	4.4	5.0	5.0	5.2	4.9	5.1	4.8	4.6	6.1	5.8	5.4	5.5	5.8	5.4	5.2	5.4	5.1	4.8	5.3	5.5	0.681	1.654	0.192	1.601	4.746	0.025		0.040	0.586	0.554	0.133			0.0345954
M6prbp1	6.6	6.9	6.8	7.4	7.3	7.3	7.5	7.5	7.4	7.1	7.9	8.0	7.8	8.1	7.9	7.8	7.7	7.6	7.5	7.1	7.7	7.8	0.731	0.794	0.047	1.459	6.965	0.007	¥	0.015	0.493	0.539	0.100			0.0343348
D030013I16Rik	6.9	7.1	6.9	6.9	6.7	6.6	6.8	7.8	7.6	7.5	7.1	7.2	7.2	7.3	6.6	6.5	6.7	6.5	7.0	6.9	7.4	6.6	0.156	0.431	0.035	1.842	22.210	0.000	¥	0.001	0.000	0.527	-0.793	*		0.0095063
Rora	7.0	6.9	7.0	7.5	7.2	7.0	7.1	7.3	7.3	7.1	6.2	6.3	6.1	6.0	5.9	5.9	6.5	6.1	6.7	7.1	6.6	6.1	0.194	2.176	0.241	2.765	7.941	0.004	¥	0.066	0.090	-0.515	-0.511			0.0479101
Cpne9	6.9	7.1	6.8	6.5	6.5	6.4	6.7	6.8	6.8	6.6	5.6	5.5	5.8	6.0	6.1	6.0	5.6	5.4	6.3	6.7	6.2	5.8	0.380	1.948	0.348	2.375	6.657	0.009	¥	0.052	0.180	-0.533	-0.400			0.0383024
Plcb4	7.1	6.9	7.1	7.4	7.5	7.2	7.3	6.8	6.9	7.0	6.7	6.6	6.4	6.4	7.3	7.3	6.6	6.9	7.0	7.2	6.7	7.0	0.238	0.332	0.358	1.022	8.255	0.004	¥	0.001	0.144	-0.536	0.342		*	0.002096
F2r	5.5	6.1	5.5	6.5	6.5	6.2	6.3	5.8	5.4	5.6	5.8	5.9	5.2	5.1	6.1	5.9	5.6	5.6	5.8	6.1	5.6	5.8	1.092	0.634	0.208	1.030	3.995	0.041		0.022	0.242	-0.541	0.229		*	0.0496517
4921511K06Rik	8.8	8.7	8.6	8.9	8.9	8.5	8.8	8.3	8.8	8.5	8.2	8.0	7.6	7.7	8.5	8.4	7.9	7.8	8.4	8.7	8.2	8.1	0.142	1.163	0.435	1.412	6.089	0.012	¥	0.013	0.941	-0.567	-0.019			0.0342211
Atp7a	5.4	5.5	5.5	5.9	5.8	5.8	5.9	4.9	4.8	4.7	5.5	5.4	5.2	5.4	5.6	5.5	5.5	5.5	5.4	5.7	5.1	5.5	0.283	0.623	0.010	1.193	9.761	0.002	¥	0.003	0.019	-0.576	0.387		*	0.0045611
Zic1	6.4	6.4	7.0	7.9	8.0	7.6	7.8	6.7	6.3	6.7	6.7	6.6	6.6	6.5	7.0	6.8	6.9	7.1	6.9	7.3	6.6	6.9	2.718	0.135	0.036	1.680	4.359	0.032		0.034	0.003	-0.693	0.334		*	0.0319954
ENSMUSG00000056615	6.0	6.4	6.0	6.3	6.1	5.3	5.4	6.4	6.3	5.5	4.5	4.5	4.6	4.7	6.6	6.4	5.8	5.8	5.7	5.9	5.2	6.1	1.019	4.184	0.555	2.878	3.749	0.048		0.069	0.037	-0.730	0.935		*	0.0499101
Inpp4b	3.2	3.5	4.1	5.0	4.9	4.7	4.9	3.4	3.6	4.0	4.1	3.8	3.1	3.0	4.3	4.3	4.2	4.3	4.0	4.3	3.6	4.3	3.242	1.056	0.010	2.302	4.008	0.040		0.042	0.004	-0.749	0.704		*	0.0454361
Vash2	4.2	4.5	5.4	5.5	5.4	4.9	5.1	4.6	4.2	5.5	4.3	4.2	3.5	3.4	4.7	4.7	4.0	4.1	4.6	5.0	4.2	4.4	1.496	2.890	0.446	2.185	3.391	0.061		0.040	0.707	-0.754	0.120		*	0.041813
Klhdc8a	5.9	5.5	5.6	5.9	6.1	5.6	5.8	5.7	5.0	5.8	4.5	4.3	4.7	4.8	4.7	4.6	5.2	5.0	5.3	5.8	5.0	4.9	0.272	1.892	0.248	2.860	8.894	0.003	¥	0.010	0.664	-0.771	-0.115			0.0076294
Arsj	4.6	4.7	4.8	4.6	4.7	4.5	4.3	4.3	4.4	4.2	4.1	4.1	2.5	2.8	5.0	5.0	3.7	3.6	4.2	4.6	3.8	4.3	0.179	3.526	1.813	2.488	3.382	0.061		0.028	0.295	-0.833	0.554		*	0.0257788
Tmie	4.6	4.6	4.8	5.3	5.5	5.5	5.4	4.3	4.6	4.8	4.1	4.2	3.9	3.8	4.8	4.3	4.4	4.6	4.6	5.1	4.2	4.5	1.068	0.814	0.159	2.705	9.937	0.002	¥	0.002	0.132	-0.870	0.393		*	0.0017917
Atrx	5.1	5.5	5.6	4.5	4.0	4.3	4.5	4.5	4.0	4.4	2.9	3.8	3.6	0.0	2.7	2.5	3.5	3.3	4.0	4.8	3.9	3.0	2.311	1.659	0.676	8.676	14.008	0.000	¥	0.018	0.029	-0.920	-0.896			0.0483708
Rgs16	5.1	5.4	5.4	7.3	7.4	6.8	7.1	5.5	5.3	5.1	6.1	6.1	4.7	5.0	7.0	6.8	6.2	5.9	6.0	6.3	5.4	6.5	6.164	1.684	0.884	4.273	3.670	0.050		0.056	0.018	-0.949	1.074		*	0.0449912
Agxt2l1	5.9	6.7	5.9	6.5	6.6	6.4	6.4	5.5	5.4	5.0	5.4	5.8	5.3	5.3	6.4	6.3	5.7	6.0	5.9	6.3	5.4	6.1	0.606	0.321	0.259	3.368	21.315	0.000	¥	0.000	0.008	-0.953	0.720		*	0.000218
Zic2	4.1	4.5	5.1	5.8	5.8	5.5	5.6	5.0	3.9	5.0	4.0	4.0	3.8	3.8	5.1	4.9	4.6	4.2	4.7	5.2	4.2	4.7	2.753	1.622	0.392	3.293	5.180	0.019		0.012	0.110	-0.970	0.477		*	0.0184097
Mrvi1	3.7	4.4	3.9	5.4	5.5	4.8	5.0	3.6	3.5	3.8	4.1	4.3	2.9	3.4	5.1	4.9	4.1	3.8	4.2	4.7	3.7	4.5	2.892	1.304	1.159	3.779	5.293	0.018		0.010	0.071	-0.994	0.816		*	0.0133851
Ramp3	8.6	8.2	8.3	8.7	8.7	8.4	8.7	8.3	8.2	8.2	7.0	7.0	6.5	6.3	8.1	7.8	7.6	7.3	7.9	8.5	7.4	7.7	0.270	4.386	0.301	4.783	7.236	0.006	¥	0.012	0.407	-1.144	0.315		*	0.0138331
Cbln1	6.4	6.2	7.4	6.5	6.4	6.6	6.8	6.2	6.2	7.4	4.0	4.3	5.1	4.9	4.8	4.5	6.1	6.0	5.9	6.6	5.4	5.4	1.013	8.848	1.880	6.315	4.034	0.040		0.043	0.906	-1.187	-0.074			0.0343525
Tac2	6.6	7.0	7.0	5.1	5.3	7.9	7.8	6.6	6.7	6.6	4.3	4.4	4.6	4.9	4.5	4.5	5.1	5.1	5.8	6.7	5.5	4.8	7.527	7.335	0.360	10.259	5.054	0.021		0.060	0.198	-1.237	-0.623			0.04419
Slc17a6	5.2	5.2	5.9	8.2	8.3	8.0	8.0	5.2	5.2	5.8	5.8	6.2	4.9	5.1	7.2	6.9	6.5	6.0	6.3	7.0	5.5	6.6	12.582	1.331	0.900	8.636	4.373	0.032		0.033	0.012	-1.517	1.189		*	0.0269155
Spry2	6.1	4.7	5.9	5.4	5.4	5.6	5.6	3.2	2.5	6.2	2.3	2.1	2.8	2.5	4.4	4.5	4.5	4.0	4.3	5.5	3.1	4.3	1.159	11.859	0.121	20.990	11.981	0.001	¥	0.003	0.056	-2.449	1.297		*	0.0034932

	Difference_Log2 global normalization																	
symbol	WT-1	WT-2	WT-3	WT-4	WT-5	WT-6	WT-7	Atrx$^{\Delta E2}$-1	Atrx$^{\Delta E2}$-2	Atrx$^{\Delta E2}$-3	Atrx$^{\Delta E2}$-4	Atrx$^{\Delta E2}$-5	Atrx$^{\Delta E2}$-6	Atrx$^{\Delta E2}$-7	Atrx$^{\Delta E2}$+5-ALA-1	Atrx$^{\Delta E2}$+5-ALA-2	Atrx$^{\Delta E2}$+5-ALA-3	Atrx$^{\Delta E2}$+5-ALA-4
Xlr3b	−0.2	0.4	−0.4	−1.3	−1.2	−0.3	−0.1	2.1	0.6	0.4	1.1	1.5	0.8	1.1	−0.8	−0.9	−1.2	−1.4
Cap1	1.3	−0.9	−1.0	−0.4	−0.8	−0.6	−0.5	1.4	2.0	−0.7	0.9	1.0	1.2	1.0	−1.1	−1.1	−0.8	−1.0
Xlr3a	0.0	0.0	−0.3	−1.3	−0.8	−0.2	0.0	2.2	0.8	0.7	0.9	1.0	0.9	0.6	−1.0	−1.1	−1.1	−1.0
S100a4	−0.5	−0.7	−0.2	−0.4	−0.1	−0.1	0.0	0.4	0.3	0.0	0.6	0.6	0.2	0.3	0.2	−0.1	−0.3	−0.2
Fbxo39	−0.4	0.4	−0.2	−0.3	−0.2	−0.2	0.1	0.6	0.5	−0.3	0.9	0.8	0.6	0.4	−0.4	−0.7	−0.7	−0.8
Prdm16	−0.6	−0.8	−0.7	−0.2	−0.1	0.1	−0.2	−0.1	−0.3	−0.5	0.9	0.7	0.3	0.3	0.7	0.3	0.1	0.2
M6prbp1	−0.9	−0.6	−0.7	−0.1	−0.2	−0.2	0.1	0.0	−0.1	−0.4	0.4	0.5	0.3	0.6	0.4	0.3	0.3	0.1
D030013I16Rik	−0.1	0.1	−0.1	−0.1	−0.3	−0.4	−0.2	0.8	0.6	0.5	0.1	0.2	0.2	0.3	−0.4	−0.5	−0.3	−0.5
Rora	0.4	0.2	0.3	0.8	0.5	0.3	0.4	0.6	0.6	0.4	−0.5	−0.4	−0.6	−0.7	−0.8	−0.8	−0.2	−0.6
Cpne9	0.6	0.8	0.5	0.3	0.2	0.1	0.4	0.5	0.5	0.4	−0.7	−0.7	−0.5	−0.3	−0.2	−0.3	−0.7	−0.9
Plcb4	0.2	−0.1	0.2	0.4	0.5	0.3	0.3	−0.1	−0.1	0.0	−0.3	−0.3	−0.6	−0.5	0.3	0.3	−0.4	0.0
F2r	−0.3	0.3	−0.3	0.6	0.7	0.4	0.5	0.0	−0.5	−0.2	0.0	0.1	−0.6	−0.7	0.3	0.1	−0.3	−0.2
4921511K06Rik	0.4	0.3	0.3	0.5	0.5	0.1	0.4	−0.1	0.4	0.2	−0.2	−0.4	−0.8	−0.7	0.1	0.1	−0.5	−0.6
Atp7a	0.0	0.1	0.0	0.5	0.4	0.4	0.5	−0.5	−0.7	−0.7	0.0	0.0	−0.2	−0.1	0.2	0.0	0.0	0.1
Zic1	−0.6	−0.5	0.1	0.9	1.0	0.7	0.8	−0.2	−0.6	−0.2	−0.2	−0.3	−0.4	−0.5	0.0	−0.2	0.0	0.1
ENSMUSG00000056615	0.3	0.7	0.3	0.6	0.4	−0.4	−0.3	0.7	0.6	−0.2	−1.2	−1.2	−1.1	−1.0	0.9	0.7	0.1	0.1
Inpp4b	−0.8	−0.5	0.0	1.0	0.9	0.6	0.8	−0.6	−0.4	−0.1	0.1	−0.2	−0.9	−1.0	0.3	0.2	0.2	0.3
Vash2	−0.4	0.0	0.9	0.9	0.8	0.3	0.5	0.1	−0.4	0.9	−0.3	−0.3	−1.1	−1.2	0.2	0.1	−0.6	−0.5
Klhdc8a	0.6	0.2	0.3	0.6	0.8	0.3	0.5	0.4	−0.2	0.5	−0.7	−0.9	−0.6	−0.4	−0.6	−0.7	−0.1	−0.2
Arsj	0.4	0.5	0.6	0.4	0.5	0.3	0.1	0.0	0.2	0.0	−0.1	−0.1	−1.7	−1.4	0.8	0.8	−0.6	−0.6
Tmie	0.0	0.0	0.1	0.7	0.9	0.9	0.7	−0.3	−0.1	0.1	−0.6	−0.4	−0.8	−0.9	0.2	−0.4	−0.2	0.0
Atrx	1.3	1.7	1.8	0.7	0.2	0.5	0.6	0.7	0.2	0.6	−0.9	0.0	−0.2	−3.8	−1.1	−1.4	−0.4	−0.5
Rgs16	−0.9	−0.6	−0.6	1.3	1.4	0.8	1.1	−0.5	−0.7	−0.9	0.1	0.1	−1.3	−1.0	1.0	0.8	0.2	−0.1
Agxt2l1	0.0	0.8	0.0	0.5	0.7	0.5	0.4	−0.4	−0.5	−0.9	−0.5	−0.2	−0.6	−0.7	0.5	0.4	−0.2	0.1
Zic2	−0.6	−0.2	0.4	1.1	1.1	0.8	0.9	0.3	−0.8	0.3	−0.7	−0.7	−0.9	−0.9	0.4	0.2	−0.1	−0.5
Mrvi1	−0.6	0.1	−0.3	1.1	1.2	0.6	0.8	−0.6	−0.7	−0.5	−0.1	0.1	−1.3	−0.9	0.9	0.7	−0.1	−0.4
Ramp3	0.7	0.3	0.5	0.8	0.8	0.5	0.8	0.4	0.3	0.3	−0.9	−0.8	−1.4	−1.6	0.2	−0.1	−0.3	−0.6
Cbln1	0.5	0.3	1.6	0.6	0.5	0.7	1.0	0.3	0.3	1.5	−1.8	−1.6	−0.8	−1.0	−1.0	−1.3	0.2	0.1
Tac2	0.9	1.2	1.2	−0.7	−0.5	2.2	2.0	0.8	0.9	0.8	−1.5	−1.4	−1.2	−0.9	−1.3	−1.3	−0.6	−0.7
Slc17a6	−1.1	−1.1	−0.4	1.9	2.0	1.7	1.7	−1.1	−1.1	−0.5	−0.5	−0.1	−1.4	−1.2	0.9	0.6	0.2	−0.3
Spry2	1.8	0.4	1.6	1.1	1.1	1.3	1.3	−1.1	−1.8	1.9	−2.0	−2.2	−1.5	−1.8	0.1	0.1	0.2	−0.3

Supplementary Table 3. List of genes exhibiting differential expression in P90 WT, Atrx$^{\Delta E2}$ and 5-ALA treated Atrx$^{\Delta E2}$ mouse hippocampus.

RefSeq_id	symbol	description	Log2Ratio (Atrx vs. WT)	Log2Ratio (Atrx+TMPyP4 vs. WT)	Fold change of Log2 Ratio
NM_011727	Xlr3b	X-linked lymphocyte-regulated 3B [Source:MarkerSymbol;Acc:MGI:109505]	2.47	0.46	2.010333
XM_138959	LOC675151	–	2.23	0.64	1.591672
NM_011728	Xlr3a	X-linked lymphocyte-regulated 3A [Source:MarkerSymbol;Acc:MGI:109506]	1.97	0.34	1.630019
NM_001004189	Q8C1Z1_MOUSE	Colon RCB-0549 Cle-H3 cDNA, RIKEN full-length enriched library, clone:G430046L24 product:hypothetical protein, full in	1.17	-0.03	1.203156
NM_177817	EG328479	predicted gene, EG328479 [Source:MarkerSymbol;Acc:MGI:3644731]	1.13	-0.19	1.319503
NM_173393	Xkr6	X Kell blood group precursor related family member 6 homolog [Source:MarkerSymbol;Acc:MGI:2447765]	1.09	0.00	1.089522
NM_001005856	9930111J21Rik	RIKEN cDNA 9930111J21 gene [Source:MarkerSymbol;Acc:MGI:3041173]	1.07	-0.23	1.303114
–	Zcchc7	zinc finger, CCHC domain containing 7 [Source:MarkerSymbol;Acc:MGI:2442912]	1.04	-0.93	1.967821
NM_177209	B130006D01Rik	RIKEN cDNA B130006D01 gene [Source:MarkerSymbol;Acc:MGI:2444371]	1.00	-0.72	1.724123
NM_009114	S100a9	S100 calcium binding protein A9 (calgranulin B) [Source:MarkerSymbol;Acc:MGI:1338947]	2.02	-1.18	3.201592
–	ENSMUSG00000062319	predicted gene, ENSMUSG00000062319 [Source:MarkerSymbol;Acc:MGI:3641675]	1.53	-1.66	3.183841
–	Ank2	ankyrin 2, brain [Source:MarkerSymbol;Acc:MGI:88025]	1.42	-1.02	2.440133
–	3321401G04Rik	RIKEN cDNA 3321401G04 gene [Source:MarkerSymbol;Acc:MGI:1914665]	1.23	-1.05	2.279265
–	A930011G23Rik	RIKEN cDNA A930011G23 gene [Source:MarkerSymbol;Acc:MGI:2442790]	1.20	-1.08	2.279857
NM_024272	Ssbp2	–	1.18	-1.69	2.869524
NM_175232	5830427D03Rik	–	1.12	-1.21	2.325892
NM_173366	1500010G04Rik	–	1.03	-1.25	2.280221
NM_008067	Gabra3	gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 3 [Source:MarkerSymbol;Acc:MGI:95615]	-1.00	0.23	1.237521
NM_175035	Gimap5	GTPase, IMAP family member 5 [Source:MarkerSymbol;Acc:MGI:2442232]	-1.01	0.53	1.542840
NM_146744	Olfr1362	olfactory receptor 1362 [Source:MarkerSymbol;Acc:MGI:3031196]	-1.02	0.17	1.186697
NM_028829	Paqr8	progestin and adipoQ receptor family member VIII [Source:MarkerSymbol;Acc:MGI:1921479]	-1.02	0.17	1.192346
NM_198653	Iars2	isoleucine-tRNA synthetase 2, mitochondrial [Source:MarkerSymbol;Acc:MGI:1919586]	-1.02	0.36	1.381099
NM_172675	Stx16	syntaxin 16 [Source:MarkerSymbol;Acc:MGI:1923396]	-1.02	0.00	1.027755
NM_176968	Nt5dc1	5'-nucleotidase domain containing 1 [Source:MarkerSymbol;Acc:MGI:2442446]	-1.03	0.46	1.483206
NM_019634	Tspan7	tetraspanin 7 [Source:MarkerSymbol;Acc:MGI:1298407]	-1.04	0.04	1.081032
–	Diras2	DIRAS family, GTP-binding RAS-like 2 [Source:MarkerSymbol;Acc:MGI:1915453]	-1.04	0.25	1.291703
–	Nr3c2	nuclear receptor subfamily 3, group C, member 2 [Source:MarkerSymbol;Acc:MGI:99459]	-1.04	0.10	1.148482
NM_018878	Paxip1	PAX interacting (with transcription-activation domain) protein 1 [Source:MarkerSymbol;Acc:MGI:1890430]	-1.05	0.27	1.316909
XM_146887	Layn	layilin [Source:MarkerSymbol;Acc:MGI:2685357]	-1.05	0.04	1.091993
NM_009964	Cryab	crystallin, alpha B [Source:MarkerSymbol;Acc:MGI:88516]	-1.05	-0.04	1.009206
–	Cdh19	cadherin 19, type 2 [Source:MarkerSymbol;Acc:MGI:3588198]	-1.06	0.19	1.241764
NM_181325	Slc25a15	solute carrier family 25 (mitochondrial carrier ornithine transporter), member 15 [Source:MarkerSymbol;Acc:MGI:1342274]	-1.06	0.39	1.443669
NM_013614	Odc1	ornithine decarboxylase, structural 1 [Source:MarkerSymbol;Acc:MGI:97402]	-1.06	0.18	1.231974
–	Zfp367	zinc finger protein 367 [Source:MarkerSymbol;Acc:MGI:2442266]	-1.06	0.72	1.773871
NM_033561	Eif4h	eukaryotic translation initiation factor 4H [Source:MarkerSymbol;Acc:MGI:1341822]	-1.06	0.14	1.200000
NM_194335	4933440H19Rik	RIKEN cDNA 4933440H19 gene [Source:MarkerSymbol;Acc:MGI:1918504]	-1.06	0.06	1.126024
–	Prkab2	protein kinase, AMP-activated, beta 2 non-catalytic subunit [Source:MarkerSymbol;Acc:MGI:1336185]	-1.07	0.05	1.113586
NM_010501	Ifit3	interferon-induced protein with tetratricopeptide repeats 3 [Source:MarkerSymbol;Acc:MGI:1101055]	-1.07	0.21	1.281597
–	Hnrph2	heterogeneous nuclear ribonucleoprotein H2 [Source:MarkerSymbol;Acc:MGI:1201779]	-1.07	0.50	1.574810
–	P2ry12	purinergic receptor P2Y, G-protein coupled 12 [Source:MarkerSymbol;Acc:MGI:1918089]	-1.07	0.10	1.171684
NM_146549	Olfr786	olfactory receptor 786 [Source:MarkerSymbol;Acc:MGI:3030620]	-1.08	0.36	1.439608
NM_172307	Mbtps2	membrane-bound transcription factor peptidase, site 2 [Source:MarkerSymbol;Acc:MGI:2444506]	-1.08	0.04	1.123502
NM_026556	Dynll2	dynein light chain LC8-type 2 [Source:MarkerSymbol;Acc:MGI:1915347]	-1.09	0.27	1.351974
NM_133967	Zdhhc7	zinc finger, DHHC domain containing 7 [Source:MarkerSymbol;Acc:MGI:2142662]	-1.10	0.44	1.546705
XM_484008	Hspd1	–	-1.12	0.34	1.461368
XM_125902	Xpot	exportin, tRNA (nuclear export receptor for tRNAs) [Source:MarkerSymbol;Acc:MGI:1920442]	-1.13	0.11	1.236408
–	Zfp273	zinc finger protein 273 [Source:MarkerSymbol;Acc:MGI:3036278]	-1.13	0.01	1.137444
NM_145360	Idi1	isopentenyl-diphosphate delta isomerase [Source:MarkerSymbol;Acc:MGI:2442264]	-1.13	0.30	1.432477
NM_198033	Setx	senataxin [Source:MarkerSymbol;Acc:MGI:2443480]	-1.14	0.34	1.478910
XM_354533	3110003A17Rik	RIKEN cDNA 3110003A17 gene [Source:MarkerSymbol;Acc:MGI:1920362]	-1.14	0.04	1.177701
NM_020622	ORF9	open reading frame 9 [Source:MarkerSymbol;Acc:MGI:1270150]	-1.15	0.10	1.254856
NM_010829	Msh3	mutS homolog 3 (E. coli) [Source:MarkerSymbol;Acc:MGI:109519]	-1.17	-0.09	1.074412
NM_028122	Slc14a1	solute carrier family 14 (urea transporter), member 1 [Source:MarkerSymbol;Acc:MGI:1351654]	-1.17	0.03	1.202038
–	Nr1d2	nuclear receptor subfamily 1, group D, member 2 [Source:MarkerSymbol;Acc:MGI:2449205]	-1.17	0.40	1.572532
NM_053185	Col4a6	procollagen, type IV, alpha 6 [Source:MarkerSymbol;Acc:MGI:2152695]	-1.17	0.01	1.178496
NM_026664	Vps53	vacuolar protein sorting 53 (yeast) [Source:MarkerSymbol;Acc:MGI:1915549]	-1.17	0.22	1.397046
NM_009426	Trh	thyrotropin releasing hormone [Source:MarkerSymbol;Acc:MGI:98823]	-1.18	0.18	1.356558
NM_182839	2900041A09Rik	RIKEN cDNA 2900041A09 gene [Source:MarkerSymbol;Acc:MGI:1920198]	-1.19	-0.18	1.013228
NM_020295	Lmbr1	limb region 1 [Source:MarkerSymbol;Acc:MGI:1861746]	-1.19	-0.08	1.118049
NM_024288	Rmnd5a	required for meiotic nuclear division 5 homolog A (S. cerevisiae) [Source:MarkerSymbol;Acc:MGI:1915727]	-1.19	0.20	1.396597
NM_201531	Kcnf1	potassium voltage-gated channel, subfamily F, member 1 [Source:MarkerSymbol;Acc:MGI:2687399]	-1.20	-0.02	1.184722
–	Tfb2m	transcription factor B2, mitochondrial [Source:MarkerSymbol;Acc:MGI:107937]	-1.21	0.21	1.412245
XM_358307	Dock4	dedicator of cytokinesis 4 [Source:MarkerSymbol;Acc:MGI:1918006]	-1.22	0.13	1.345407
XM_284491	Ppp2r1b	protein phosphatase 2 (formerly 2A), regulatory subunit A (PR 65), beta isoform [Source:MarkerSymbol;Acc:MGI:1920949]	-1.22	0.27	1.498374
NM_018780	Sfrp5	secreted frizzled-related sequence protein 5 [Source:MarkerSymbol;Acc:MGI:1860298]	-1.23	-0.08	1.145663
–	Krt12	keratin 12 [Source:MarkerSymbol;Acc:MGI:96687]	-1.23	0.66	1.891645
NM_009170	Shh	sonic hedgehog [Source:MarkerSymbol;Acc:MGI:98297]	-1.24	0.64	1.879827
NM_033552	Slc4a10	solute carrier family 4, sodium bicarbonate cotransporter-like, member 10 [Source:MarkerSymbol;Acc:MGI:2150150]	-1.25	-0.02	1.229069
NM_146249	BC031441	cDNA sequence BC031441 [Source:MarkerSymbol;Acc:MGI:2385323]	-1.26	0.67	1.927299
–	Cdc7	cell division cycle 7 (S. cerevisiae) [Source:MarkerSymbol;Acc:MGI:1309511]	-1.26	-0.14	1.120414
NM_080454	Gja12	gap junction membrane channel protein alpha 12 [Source:MarkerSymbol;Acc:MGI:2153060]	-1.27	-0.25	1.019467
NM_147026	Olfr532	olfactory receptor 532 [Source:MarkerSymbol;Acc:MGI:3030366]	-1.31	-0.04	1.273267
NM_001004359	Gprasp1	G protein-coupled receptor associated sorting protein 1 [Source:MarkerSymbol;Acc:MGI:1917418]	-1.31	0.00	1.316550
NM_170599	NP_733548.2	immunoglobulin superfamily, member 11 [Source:RefSeq_peptide;Acc:NP_733548]	-1.33	-0.20	1.124560
NM_008070	Gabrb2	gamma-aminobutyric acid (GABA-A) receptor, subunit beta 2 [Source:MarkerSymbol;Acc:MGI:95620]	-1.35	0.51	1.856034
NM_177145	Pde4dip	phosphodiesterase 4D interacting protein (myomegalin) [Source:MarkerSymbol;Acc:MGI:1891434]	-1.37	0.47	1.838309
NM_172877	4732496O08Rik	RIKEN cDNA 4732496O08 gene [Source:MarkerSymbol;Acc:MGI:2140473]	-1.37	0.08	1.449849
NM_174848	BC043118	cDNA sequence BC043118 [Source:MarkerSymbol;Acc:MGI:2676311]	-1.39	-0.18	1.207100
NM_015822	Fbxl3	F-box and leucine-rich repeat protein 3 [Source:MarkerSymbol;Acc:MGI:1354702]	-1.39	0.15	1.539873
NM_001001176	Taf9b	TAF9B RNA polymerase II, TATA box binding protein (TBP)-associated factor [Source:MarkerSymbol;Acc:MGI:3039562]	-1.41	0.31	1.722699
XM_139711	Arid1b	AT rich interactive domain 1B (Swi1 like) [Source:MarkerSymbol;Acc:MGI:1926129]	-1.43	0.31	1.730451
NM_007685	Cfc1	cripto, FRL-1, cryptic family 1 [Source:MarkerSymbol;Acc:MGI:109448]	-1.43	-0.28	1.143741
NM_011177	Klk6	kallikrein related-peptidase 6 [Source:MarkerSymbol;Acc:MGI:1343166]	-1.46	-0.19	1.264705
–	Cldn22	claudin 22 [Source:MarkerSymbol;Acc:MGI:1922927]	-1.46	0.19	1.645775
NM_008105	Gcnt2	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme [Source:MarkerSymbol;Acc:MGI:1100870]	-1.50	0.26	1.762353
NM_139149	Fus	fusion, derived from t(12;16) malignant liposarcoma (human) [Source:MarkerSymbol;Acc:MGI:1353633]	-1.55	-0.10	1.458135
NM_010127	Pou6f1	POU domain, class 6, transcription factor 1 [Source:MarkerSymbol;Acc:MGI:102935]	-1.59	0.16	1.745119
NM_181424	Gtpbp5	GTP binding protein 5 [Source:MarkerSymbol;Acc:MGI:106565]	-1.64	-0.21	1.427462
XM_195728	4833427B12Rik	RIKEN cDNA 4833427B12 gene [Source:MarkerSymbol;Acc:MGI:1921019]	-1.67	-0.22	1.443435
NM_138948	Cabp7	calcium binding protein 7 [Source:MarkerSymbol;Acc:MGI:2183437]	-1.74	-0.61	1.133338
NM_178672	Scfd2	sec1 family domain containing 2 [Source:MarkerSymbol;Acc:MGI:2443446]	-1.79	-0.02	1.772730
NM_145942	Hmgcs1	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1 [Source:MarkerSymbol;Acc:MGI:107592]	-1.83	-0.29	1.532335

Supplementary Table 4. List of genes exhibiting differential expression in P90 WT, Atrx$^{\Delta E2}$ and TMPyP4 treated Atrx$^{\Delta E2}$ mouse hippocampus.

Supplementary Table 5. Summary of all statistical data

Fig. 1b

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	genotype × tissue	F (7, 153) = 8.025	P <0.0001
	genotype	F (1, 153) = 25.7	P <0.0001
	tissue	F (7, 153) = 39.07	P <0.0001

tissue	**t**	**DF**	**P value (WT vs Atrx$^{\Delta E2}$)**
PC	4.47	153	0.0001
HP	3.929	153	0.001
HT	5.024	153	<0.0001
CE	2.781	153	0.0489
Lung	1.537	153	>0.9999
Heart	1.258	153	>0.9999
Liver	0.1321	153	>0.9999
Kidney	0.5894	153	>0.9999

Fig. 1c

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	genotype × tissue	F (3, 24) = 3.389	P =0.0344
	genotype	F (1, 24) = 58.74	P <0.0001
	tissue	F (3, 24) = 20.94	P <0.0001

tissue	**t**	**DF**	**P value (WT vs Atrx$^{\Delta E2}$)**
PC	2.795	24	0.0402
HP	6.591	24	<0.0001
HT	2.978	24	0.0261
CE	2.965	24	0.027

Fig. 1d

Statistical analysis		Two-sided unpaired t test	
Amplicon	**t**	**DF**	**P value (WT vs Atrx$^{\Delta E2}$)**
Xlr3a	1.705	22	0.1024
Xlr3b	11.48	22	<0.0001
Xlr3c	0.1669	22	0.869
Xlr3d	0.4838	22	0.6333

Xlr3e	0.9199	22	0.3676

Fig. 1f

Reporter plasmid		2K	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 100.2	P <0.0001
Comparison	**t**	**DF**	**P value**
Mock vs ATRX	5.874	20	<0.0001
Mock vs shControl	0.6575	20	>0.9999
Mock vs shATRX	11.14	20	<0.0001
ATRX vs shControl	6.532	20	<0.0001
ATRX vs shATRX	17.01	20	<0.0001
shControl vs shATRX	10.48	20	<0.0001

Reporter plasmid		2KΔG4	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 0.04775	P =0.9858
Comparison	**t**	**DF**	**P value**
Mock vs ATRX	0.2003	20	>0.9999
Mock vs shControl	0.0445	20	>0.9999
Mock vs shATRX	0.2759	20	>0.9999
ATRX vs shControl	0.2448	20	>0.9999
ATRX vs shATRX	0.07566	20	>0.9999
shControl vs shATRX	0.3204	20	>0.9999

Reporter plasmid		1KΔCGI	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 0.1926	P =0.9002
Comparison	**t**	**DF**	**P value**
Mock vs ATRX	0.6854	20	>0.9999

Mock vs shControl	0.4161	20	>0.9999
Mock vs shATRX	0.6266	20	>0.9999
ATRX vs shControl	0.2693	20	>0.9999
ATRX vs shATRX	0.05875	20	>0.9999
shControl vs shATRX	0.2105	20	>0.9999

Fig. 1g

Reporter plasmid		2K	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (5, 30) = 45.82	P <0.0001
Comparison	**t**	**DF**	**P value**
Mock vs DNMT1	9.067	30	<0.0001
Mock vs DNMT3A	9.69	30	<0.0001
Mock vs M. SssI	12.05	30	<0.0001
Mock vs H3.3	2.79	30	0.1362
Mock vs DAXX	3.061	30	0.0694

Reporter plasmid		2KΔG4	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (5, 30) = 25.3	P <0.0001
Comparison	**t**	**DF**	**P value**
Mock vs DNMT1	2.294	30	0.4346
Mock vs DNMT3A	2.709	30	0.1658
Mock vs M. SssI	9.135	30	<0.0001
Mock vs H3.3	0.9359	30	>0.9999
Mock vs DAXX	0.745	30	>0.9999

Reporter plasmid		1KΔCGI	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (5, 30) = 1.049	P =0.4076
Comparison	**t**	**DF**	**P value**

Mock vs DNMT1	1.392	30	>0.9999
Mock vs DNMT3A	0.535	30	>0.9999
Mock vs SssI	1.389	30	>0.9999
Mock vs H3.3	0.387	30	>0.9999
Mock vs DAXX	0.3794	30	>0.9999

Fig. 1h

Amplicon		R1	
Statistical analysis		Two-sided unpaired t test	
Antibody	**t**	**DF**	**P value (WT vs Atrx$^{\Delta E2}$)**
ATRX	t=9.903	10	<0.0001
DNMT1	t=14.79	10	<0.0001
DNMT3A	t=4.772	10	0.0008
H3.3	t=4.186	10	0.0019
DAXX	t=4.67	10	0.0009
Negative control IgG	t=1.12	10	0.2889

Amplicon		R2	
Statistical analysis		Two-sided unpaired t test	
Antibody	**t**	**DF**	**P value (WT vs Atrx$^{\Delta E2}$)**
ATRX	t=2.59	10	0.027
DNMT1	t=1.284	10	0.2281
DNMT3A	t=0.9472	10	0.3658
H3.3	t=1.125	10	0.2868
DAXX	t=1.125	10	0.2868
Negative control IgG	t=0.06366	10	0.9505

Fig. 3a

Amplicon		CaMKIIα mRNA	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 16) = 70.66	P <0.0001
Comparison	**t**	**DF**	**P value**
no-treatment vs ANTP	0.4224	16	>0.9999
no-treatment vs XIP	5.386	16	0.0004

no-treatment vs IgG	12.77	16	<0.0001
ANTP vs XIP	4.963	16	0.0008
ANTP vs IgG	12.35	16	<0.0001
XIP vs IgG	7.386	16	<0.0001

Amplicon		Arc mRNA	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 16) = 35.8	P <0.0001
Comparison	**t**	**DF**	**P value**
no-treatment vs ANTP	0.3551	16	>0.9999
no-treatment vs XIP	5.907	16	0.0001
no-treatment vs IgG	8.594	16	<0.0001
ANTP vs XIP	5.552	16	0.0003
ANTP vs IgG	8.239	16	<0.0001
XIP vs IgG	2.687	16	0.0971

Amplicon		BDNF mRNA	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 16) = 85.14	P <0.0001
Comparison	**t**	**DF**	**P value**
no-treatment vs ANTP	0.7309	16	>0.9999
no-treatment vs XIP	5.476	16	0.0003
no-treatment vs IgG	14.18	16	<0.0001
ANTP vs XIP	4.745	16	0.0013
ANTP vs IgG	13.45	16	<0.0001
XIP vs IgG	8.705	16	<0.0001

Fig. 3c

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	group × mobility	F (12, 80) = 17.95	P <0.0001
	group	F (4, 80) = 0	P >0.9999
	mobility	F (3, 80) = 245.9	P <0.0001
Mobility		Immobile	

Comparison	t	DF	P value
WT vs Atrx$^{\Delta E2}$	4.751	80	<0.0001
WT vs Xlr3b-TG	5.275	80	<0.0001
WT vs Atrx$^{\Delta E2}$ + shXlr3b	1.799	80	0.7574
WT vs Atrx$^{\Delta E2}$ + XIP	1.721	80	0.8908
Atrx$^{\Delta E2}$ vs Xlr3b-TG	0.5248	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + shXlr3b	6.55	80	<0.0001
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	6.472	80	<0.0001
Xlr3b-TG vs Atrx$^{\Delta E2}$ + shXlr3b	7.075	80	<0.0001
Xlr3b-TG vs Atrx$^{\Delta E2}$ + XIP	6.997	80	<0.0001
Atrx$^{\Delta E2}$ + shXlr3b vs Atrx$^{\Delta E2}$ + XIP	0.07811	80	>0.9999
Mobility		Bidirectional	
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	4.575	80	0.0002
WT vs Xlr3b-TG	5.291	80	<0.0001
WT vs Atrx$^{\Delta E2}$ + shXlr3b	2.866	80	0.0531
WT vs Atrx$^{\Delta E2}$ + XIP	2.386	80	0.1941
Atrx$^{\Delta E2}$ vs Xlr3b-TG	0.7166	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + shXlr3b	7.441	80	<0.0001
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	6.96	80	<0.0001
Xlr3b-TG vs Atrx$^{\Delta E2}$ + shXlr3b	8.157	80	<0.0001
Xlr3b-TG vs Atrx$^{\Delta E2}$ + XIP	7.677	80	<0.0001
Atrx$^{\Delta E2}$ + shXlr3b vs Atrx$^{\Delta E2}$ + XIP	0.4803	80	>0.9999

Mobility		Anterograde	
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.6821	80	>0.9999
WT vs Xlr3b-TG	0.4907	80	>0.9999
WT vs Atrx$^{\Delta E2}$ + shXlr3b	1.186	80	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.884	80	>0.9999
Atrx$^{\Delta E2}$ vs Xlr3b-TG	0.1914	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + shXlr3b	0.5041	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.2019	80	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$ + shXlr3b	0.6955	80	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$ + XIP	0.3933	80	>0.9999
Atrx$^{\Delta E2}$ + shXlr3b vs Atrx$^{\Delta E2}$ + XIP	0.3022	80	>0.9999
Mobility		Retrograde	
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.5061	80	>0.9999
WT vs Xlr3b-TG	0.5065	80	>0.9999
WT vs Atrx$^{\Delta E2}$ + shXlr3b	0.1194	80	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.2194	80	>0.9999
Atrx$^{\Delta E2}$ vs Xlr3b-TG	0.0003858	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + shXlr3b	0.3866	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.2867	80	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$ + shXlr3b	0.387	80	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$ + XIP	0.2871	80	>0.9999
Atrx$^{\Delta E2}$ + shXlr3b	0.09998	80	>0.9999

vs Atrx$^{\Delta E2}$ + XIP			

Fig. 3d

Positive puncta		PSD95	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (4, 95) = 1.396	P =0.2412
Comparison	**t**	**DF**	**P value**
WT vs Xlr3b-TG	0.2089	95	>0.9999
WT vs Atrx$^{\Delta E2}$	0.9747	95	>0.9999
WT vs Xlr3b-TG+shXlr3b	1.671	95	0.9802
WT vs Xlr3b-TG+XIP	1.392	95	>0.9999
Atrx$^{\Delta E2}$ vs Xlr3b-TG	1.184	95	>0.9999
Atrx$^{\Delta E2}$ vs Xlr3b-TG+shXlr3b	1.88	95	0.632
Atrx$^{\Delta E2}$ vs Xlr3b-TG+XIP	1.601	95	>0.9999
Xlr3b-TG vs Xlr3b-TG+shXlr3b	0.6962	95	>0.9999
Xlr3b-TG vs Xlr3b-TG+XIP	0.4177	95	>0.9999
Xlr3b-TG+shXlr3b vs Xlr3b-TG+XIP	0.2785	95	>0.9999

Positive puncta		PSD95 and CaMKIIα mRNA	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (4, 95) = 15.5	P <0.0001
Comparison	**t**	**DF**	**P value**
WT vs Xlr3b-TG	6.362	95	<0.0001
WT vs Atrx$^{\Delta E2}$	4.439	95	0.0002
WT vs Xlr3b-TG+shXlr3b	0.5178	95	>0.9999

WT vs Xlr3b-TG+XIP	1.036	95	>0.9999
Atrx$^{\Delta E2}$ vs Xlr3b-TG	1.923	95	0.5743
Atrx$^{\Delta E2}$ vs Xlr3b-TG+shXlr3b	5.844	95	<0.0001
Atrx$^{\Delta E2}$ vs Xlr3b-TG+XIP	5.326	95	<0.0001
Xlr3b-TG vs Xlr3b-TG+shXlr3b	3.921	95	0.0017
Xlr3b-TG vs Xlr3b-TG+XIP	3.403	95	0.0098
Xlr3b-TG+shXlr3b vs Xlr3b-TG+XIP	0.5178	95	>0.9999

Fig. 3e

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	group × time	F (3, 52) = 0.3463	P =0.7920
	group	F (3, 52) = 18.8	P <0.0001
	time	F (1, 52) = 7.878	P =0.0070
Time	1min after HFS		
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	4.261	52	0.0005
WT vs Atrx$^{\Delta E2}$ + XIP	0.5489	52	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	4.723	52	0.0001
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	3.712	52	0.003
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.7787	52	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	4.215	52	0.0006
Time	60min after HFS		
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	3.445	52	0.0068
WT vs Atrx$^{\Delta E2}$ + XIP	0.4974	52	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	3.513	52	0.0056
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	2.947	52	0.0287
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.324	52	>0.9999

$Atrx^{\Delta E2}$ +XIP vs $Atrx^{\Delta E2}$ + ANTP	3.053	52	0.0214

Fig. 4b

Reporter plasmid		2K	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (5, 12) = 59.67	P <0.0001
Comparison	**t**	**DF**	**P value**
Vehicle vs 100nM 5-ALA	2.171	12	0.7602
Vehicle vs 300nM 5-ALA	5.18	12	0.0034
Vehicle vs 1μM 5-ALA	10.05	12	<0.0001
Vehicle vs 3μM 5-ALA	12.57	12	<0.0001
Vehicle vs 10μM 5-ALA	12.77	12	<0.0001

Reporter plasmid		2KΔG4	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (5, 12) = 1.472	P =0.2693
Comparison	**t**	**DF**	**P value**
Vehicle vs 100nM 5-ALA	0.6311	12	>0.9999
Vehicle vs 300nM 5-ALA	1.206	12	>0.9999
Vehicle vs 1μM 5-ALA	1.564	12	>0.9999
Vehicle vs 3μM 5-ALA	0.6031	12	>0.9999
Vehicle vs 10μM 5-ALA	2.435	12	0.4717

Fig. 4c

Reporter plasmid		2K	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (5, 12) = 22.64	P <0.0001
Comparison	**t**	**DF**	**P value**
10μM 5-ALA vs 10μM 5-ALA + 1μM Succinylacetone	0.5653	12	>0.9999
10μM 5-ALA vs 10μM 5-ALA	2.669	12	0.3065

+ 10μM Succinylacetone.			
10μM 5-ALA vs 10μM 5-ALA + 100μM Succinylacetone	5.988	12	0.0009
10μM 5-ALA vs 10μM 5-ALA + 1mM Succinylacetone	7.019	12	0.0002

Reporter plasmid		2KΔG4	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (5, 12) = 0.2803	P =0.9151
Comparison	**t**	**DF**	**P value**
10μM 5-ALA vs 10μM 5-ALA + 1μM Succinylacetone	0.2476	12	>0.9999
10μM 5-ALA vs 10μM 5-ALA + 10μM Succinylacetone.	0.6308	12	>0.9999
10μM 5-ALA vs 10μM 5-ALA + 100μM Succinylacetone	0.3411	12	>0.9999
10μM 5-ALA vs 10μM 5-ALA + 1mM Succinylacetone	0.4673	12	>0.9999

Fig. 4d

Statistical analysis	**F (DFn, DFd)**		**P value**
One-way ANOVA with Bonferroni's post hoc test	F (4, 25) = 28.79		P <0.0001
Comparison	**t**	**DF**	**P value**
WT vs WT+5-ALA	0.3074	25	>0.9999
WT vs $Atrx^{\Delta E2}$	8.939	25	<0.0001
WT vs $Atrx^{\Delta E2}$+5-ALA 3mg/kg	1.086	25	>0.9999
WT vs $Atrx^{\Delta E2}$+5-ALA 10mg/kg	0.6135	25	>0.9999
WT+5-ALA vs $Atrx^{\Delta E2}$	8.631	25	<0.0001
WT+5-ALA vs $Atrx^{\Delta E2}$+5-ALA 3mg/kg	0.7781	25	>0.9999
WT+5-ALA vs $Atrx^{\Delta E2}$+5-ALA 10mg/kg	0.3061	25	>0.9999
$Atrx^{\Delta E2}$ vs $Atrx^{\Delta E2}$+5-ALA 3mg/kg	7.853	25	<0.0001
$Atrx^{\Delta E2}$ vs $Atrx^{\Delta E2}$+5-ALA 10mg/kg	8.325	25	<0.0001
$Atrx^{\Delta E2}$+5-ALA 3mg/kg vs	0.4721	25	>0.9999

Atrx$^{\Delta E2}$+5-ALA 10mg/kg			

Fig. 4e

Statistical analysis	F (DFn, DFd)		P value
One-way ANOVA with Bonferroni's post hoc test	F (4, 15) = 47.62		P <0.0001
Comparison	**t**	**DF**	**P value**
WT vs WT+5-ALA	0.7762	15	>0.9999
WT vs Atrx$^{\Delta E2}$	11.5	15	<0.0001
WT vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	1.665	15	>0.9999
WT vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	0.2904	15	>0.9999
WT+5-ALA vs Atrx$^{\Delta E2}$	10.73	15	<0.0001
WT+5-ALA vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	0.8891	15	>0.9999
WT+5-ALA vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	0.4858	15	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	9.837	15	<0.0001
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	11.21	15	<0.0001
Atrx$^{\Delta E2}$+5-ALA 3mg/kg vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	1.375	15	>0.9999

Fig. 4f

Statistical analysis	Interaction	F (DFn, DFd)	P value
Two-way ANOVA with Bonferroni's post hoc test	group × tissue	F (3, 64) = 0.04741	P =0.9862
	group	F (3, 64) = 302.8	P <0.0001
	tissue	F (1, 64) = 1.138	P =0.2901
tissue		PC	
Comparison	**t**	**DF**	**P value**
WT+Veh. vs WT+5-ALA	0	64	>0.9999
WT+Veh. vs Atrx$^{\Delta E2}$+Veh.	15.2	64	<0.0001
WT+Veh. vs Atrx$^{\Delta E2}$+5-ALA	14.93	64	<0.0001
WT+5-ALA vs Atrx$^{\Delta E2}$+Veh.	15.2	64	<0.0001
WT+5-ALA vs Atrx$^{\Delta E2}$+5-ALA	14.93	64	<0.0001
Atrx$^{\Delta E2}$+Veh. vs Atrx$^{\Delta E2}$+5-ALA	0.2667	64	>0.9999
tissue		HP	
Comparison	**t**	**DF**	**P value**

WT+Veh. vs WT+5-ALA	0.5333	64	>0.9999
WT+Veh. vs Atrx$^{\Delta E2}$+Veh.	15.47	64	<0.0001
WT+Veh. vs Atrx$^{\Delta E2}$+5-ALA	15.2	64	<0.0001
WT+5-ALA vs Atrx$^{\Delta E2}$+Veh.	14.93	64	<0.0001
WT+5-ALA vs Atrx$^{\Delta E2}$+5-ALA	14.67	64	<0.0001
Atrx$^{\Delta E2}$+Veh. vs Atrx$^{\Delta E2}$+5-ALA	0.2667	64	>0.9999

Fig. 4g

Amplicon		No. 1	
Antibody		ATRX	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 157.5	P <0.0001
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.4336	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	15.38	20	<0.0001
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	14.92	20	<0.0001
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	15.81	20	<0.0001
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	15.35	20	<0.0001
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4596	20	>0.9999

Amplicon		No. 1	
Antibody		RNA polymerase II	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 10.72	P =0.0002
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.09304	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	4.886	20	0.0005
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.872	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	4.793	20	0.0007
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.7789	20	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	4.014	20	0.0041

Amplicon	No. 1

Antibody		Negative control IgG	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 1.337	P =0.2904
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	1.276	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	1.821	20	0.5019
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.62	20	0.7253
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.5449	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.3442	20	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.2007	20	>0.9999

Amplicon		No. 2	
Antibody		ATRX	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 10.31	P =0.0003
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.2742	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	3.979	20	0.0044
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	4.149	20	0.003
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	3.704	20	0.0084
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	3.875	20	0.0057
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.1704	20	>0.9999

Amplicon		No. 2	
Antibody		RNA polymerase II	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 7.003	P =0.0021
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.09865	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	3.881	20	0.0056
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.742	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	3.98	20	0.0044

WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.8407	20	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	3.139	20	0.031

Amplicon		No. 2	
Antibody		Negative control IgG	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 0.504	P =0.6839
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.03382	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.465	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.077	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.4312	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	1.043	20	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.6117	20	>0.9999

Amplicon		No. 3	
Antibody		ATRX	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 19.74	P <0.0001
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.2287	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	5.355	20	0.0002
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	5.738	20	<0.0001
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	5.126	20	0.0003
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	5.509	20	0.0001
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.3829	20	>0.9999

Amplicon		No. 3	
Antibody		RNA polymerase II	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 10.61	P =0.0002
Comparison	**t**	**DF**	**P value**

WT + Veh. vs WT + 5-ALA	0.255	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	4.847	20	0.0006
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.5272	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	4.592	20	0.0011
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.2722	20	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	4.319	20	0.002

Amplicon		No. 3	
Antibody		Negative control IgG	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 1.033	P =0.3993
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	1.388	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.6372	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.558	20	0.8101
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.7505	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.1699	20	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.9204	20	>0.9999

Amplicon		No. 4	
Antibody		ATRX	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 1.652	P =0.2092
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.1399	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	1.654	20	0.6819
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.31	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	1.794	20	0.5273
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	1.45	20	0.975
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.3441	20	>0.9999

Amplicon	No. 4
Antibody	RNA polymerase II

Statistical analysis		F (DFn, DFd)	P value
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 4.815	P =0.0111
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.069	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	3.249	20	0.0241
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4398	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	3.18	20	0.0283
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.3708	20	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	2.809	20	0.065

Amplicon		No. 4	
Antibody		Negative control IgG	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 20) = 0.2594	P =0.8537
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.7389	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.7721	20	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4002	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.03321	20	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.3387	20	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.3719	20	>0.9999

Fig.5a

Statistical analysis	Interaction	F (DFn, DFd)	P value
Two-way ANOVA with Bonferroni's post hoc test	group × mobility	F (9, 64) = 5.424	P <0.0001
	group	F (3, 64) = 0	P >0.9999
	mobility	F (3, 64) = 110.4	P <0.0001
Mobility		Immobile	
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	1.194	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	2.823	64	0.038
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.51	64	0.8161

WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	4.018	64	0.0009
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.3156	64	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	4.333	64	0.0003
Mobility		Bidirectional	
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.7657	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	3.058	64	0.0195
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.504	64	0.8257
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	3.823	64	0.0018
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.7378	64	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	4.561	64	0.0001
Mobility		Anterograde	
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.4594	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.4078	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.184	64	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.8672	64	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.6433	64	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.2239	64	>0.9999
Mobility		Retrograde	
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.03086	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.6421	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.1902	64	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.673	64	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.2211	64	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4519	64	>0.9999

Fig. 5b

Positive puncta		PSD95	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 76) = 1.995	P =0.1219
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.8687	76	>0.9999

WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	1.537	76	0.7708
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4009	76	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	2.406	76	0.1115

Positive puncta		PSD95 and CaMKIIα mRNA	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 76) = 20.12	P <0.0001
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	1.373	76	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	5.86	76	<0.0001
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.5494	76	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	7.233	76	<0.0001
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	1.923	76	0.3496
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	5.31	76	<0.0001

Fig. 5c

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	group × time	F (3, 52) = 0.4314	P =0.7314
	group	F (3, 52) = 13.24	P <0.0001
	time	F (1, 52) = 15.16	P =0.0003
Time	1min after HFS		
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.05821	52	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	4.26	52	0.0005
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.03372	52	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	4.002	52	0.0012
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.02699	52	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	4.294	52	0.0005
Time	60min after HFS		
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.3582	52	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	3.045	52	0.0219
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.2709	52	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	3.177	52	0.015

WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.609	52	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	2.774	52	0.0461

Fig.5d

Behavior test		NOR test	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (4, 74) = 9.979	P <0.0001
Comparison	**t**	**DF**	**P value**
WT +Veh. vs WT+5-ALA 3mg/kg	0.09928	74	>0.9999
WT +Veh. vs Atrx$^{\Delta E2}$ +Veh.	5.506	74	<0.0001
WT +Veh. vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	0.283	74	>0.9999
WT +Veh. vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	1.089	74	>0.9999
WT +5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ +Veh.	4.87	74	<0.0001
WT+5-ALA 3mg/kg vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	0.1764	74	>0.9999
WT+5-ALA 3mg/kg vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	0.9434	74	>0.9999
Atrx$^{\Delta E2}$ +Veh. vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	4.361	74	0.0004
Atrx$^{\Delta E2}$ +Veh. vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	3.134	74	0.0247
Atrx$^{\Delta E2}$+5-ALA 3mg/kg vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	0.7471	74	>0.9999

Fig.5e

Behavior test		PA test	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (4, 60) = 4.524	P =0.0029
Comparison	**t**	**DF**	**P value**
WT +Veh. vs WT+5-ALA 3mg/kg	0.8638	60	>0.9999

WT +Veh. vs Atrx$^{\Delta E2}$ +Veh.	4.061	60	0.0014
WT +Veh. vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	0.3092	60	>0.9999
WT +Veh. vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	0.594	60	>0.9999
WT +5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ +Veh.	3.473	60	0.0096
WT+5-ALA 3mg/kg vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	0.4453	60	>0.9999
WT+5-ALA 3mg/kg vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	0.1544	60	>0.9999
Atrx$^{\Delta E2}$ +Veh. vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	3.525	60	0.0082
Atrx$^{\Delta E2}$ +Veh. vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	3.297	60	0.0165
Atrx$^{\Delta E2}$+5-ALA 3mg/kg vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	0.2584	60	>0.9999

Fig.5f

Behavior test		Y-maze test	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (4, 68) = 7.764	P <0.0001
Comparison	**t**	**DF**	**P value**
WT +Veh. vs WT+5-ALA 3mg/kg	1.208	68	>0.9999
WT +Veh. vs Atrx$^{\Delta E2}$ +Veh.	3.557	68	0.0069
WT +Veh. vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	0.1765	68	>0.9999
WT +Veh. vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	0.2823	68	>0.9999
WT +5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ +Veh.	5.321	68	<0.0001
WT+5-ALA 3mg/kg vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	1.167	68	>0.9999
WT+5-ALA 3mg/kg	0.9505	68	>0.9999

vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg			
Atrx$^{\Delta E2}$ +Veh. vs Atrx$^{\Delta E2}$+5-ALA 3mg/kg	4.141	68	0.001
Atrx$^{\Delta E2}$ +Veh. vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	4.01	68	0.0015
Atrx$^{\Delta E2}$+5-ALA 3mg/kg vs Atrx$^{\Delta E2}$+5-ALA 10mg/kg	0.1286	68	>0.9999

Supplementary Fig. 1e

Statistical analysis		Two-sided unpaired t test	
mRNA	**t**	**DF**	**P value (GFP vs Xlr3-Cas9-GFP)**
Xlr3b	12.34	6	<0.0001

Supplementary Fig. 1f

Statistical analysis		Two-sided unpaired t test	
Protein	**t**	**DF**	**P value (GFP vs Xlr3-Cas9-GFP)**
Xlr3	11.59	8	<0.0001

Supplementary Fig.4a

Statistical analysis		Two-sided unpaired t test	
Protein	**t**	**DF**	**P value (WT vs Atrx$^{\Delta E2}$)**
ATRX	5.44	4	0.0055

Supplementary Fig. 4b

Statistical analysis		Two-sided unpaired t test	
Protein	**t**	**DF**	**P value (WT vs Atrx$^{\Delta E2}$)**
ATRX	9.927	10	<0.0001
DMNT1	1.629	10	0.1345
DNMT3A	0.3493	10	0.7341
DAXX	0.907	10	0.3857
H3.3	0.7412	10	0.4756

Supplementary Fig. 8b

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with	group × mobility	F (12, 80) = 15.64	P <0.0001

Bonferroni's post hoc test	group	F (4, 80) = 2.621e-014	P >0.9999
	mobility	F (3, 80) = 266	P <0.0001
Mobility		Immobile	
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	4.198	80	0.0041
WT vs Xlr3b-TG	5.546	80	<0.0001
WT vs Atrx$^{\Delta E2}$ + shXlr3b	1.287	80	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	2.44	80	0.2807
Atrx$^{\Delta E2}$ vs Xlr3b-TG	1.347	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + shXlr3b	5.485	80	<0.0001
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	6.638	80	<0.0001
Xlr3b-TG vs Atrx$^{\Delta E2}$ + shXlr3b	6.833	80	<0.0001
Xlr3b-TG vs Atrx$^{\Delta E2}$ + XIP	7.985	80	<0.0001
Atrx$^{\Delta E2}$ + shXlr3b vs Atrx$^{\Delta E2}$ + XIP	1.153	80	>0.9999
Mobility		Bidirectional	
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	5.18	80	0.0003
WT vs Xlr3b-TG	5.853	80	<0.0001
WT vs Atrx$^{\Delta E2}$ + shXlr3b	1.736	80	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	3.023	80	0.0693
Atrx$^{\Delta E2}$ vs Xlr3b-TG	0.673	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + shXlr3b	6.916	80	<0.0001
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	8.203	80	<0.0001
Xlr3b-TG vs Atrx$^{\Delta E2}$ + shXlr3b	7.589	80	<0.0001
Xlr3b-TG vs Atrx$^{\Delta E2}$ + XIP	8.876	80	<0.0001
Atrx$^{\Delta E2}$ + shXlr3b vs Atrx$^{\Delta E2}$ + XIP	1.287	80	>0.9999
Mobility		Anterograde	
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.5252	80	>0.9999
WT vs Xlr3b-TG	0.5832	80	>0.9999
WT vs Atrx$^{\Delta E2}$ + shXlr3b	0.06571	80	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.01971	80	>0.9999
Atrx$^{\Delta E2}$ vs Xlr3b-TG	0.058	80	>0.9999

Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + shXlr3b	0.5909	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.5449	80	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$ + shXlr3b	0.6489	80	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$ + XIP	0.6029	80	>0.9999
Atrx$^{\Delta E2}$ + shXlr3b vs Atrx$^{\Delta E2}$ + XIP	0.046	80	>0.9999
Mobility		Retrograde	
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.4564	80	>0.9999
WT vs Xlr3b-TG	0.276	80	>0.9999
WT vs Atrx$^{\Delta E2}$ + shXlr3b	0.3835	80	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.5635	80	>0.9999
Atrx$^{\Delta E2}$ vs Xlr3b-TG	0.7324	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + shXlr3b	0.8399	80	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	1.02	80	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$ + shXlr3b	0.1075	80	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$ + XIP	0.2875	80	>0.9999
Atrx$^{\Delta E2}$ + shXlr3b vs Atrx$^{\Delta E2}$ + XIP	0.18	80	>0.9999

Supplementary Fig. 9c

Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (2, 15) = 74.04	P <0.0001
Comparison	**t**	**DF**	**P value**
WT vs Xlr3b TG(#13)	9.694	15	<0.0001
WT vs Xlr3b TG(#57)	11.22	15	<0.0001
Xlr3b TG(#13) vs Xlr3b TG(#57)	1.523	15	0.4454

Supplementary Fig. 9d

Statistical analysis		Two-sided unpaired t test	
Protein	**t**	**DF**	**P value (WT vs Xlr3b TG)**
Xlr3	10.16	8	<0.0001

Supplementary Fig. 9e

Statistical analysis		Two-sided unpaired t test	
Protein	**t**	**DF**	**P value (shControl vs shXlr3b)**
Xlr3	4.278	4	0.0129

Supplementary Fig. 9f (WT and Xlr3b-TG in LP1 fraction)

Statistical analysis		Two-sided unpaired t test	
Protein	**t**	**DF**	**P value (WT vs Xlr3b-TG)**
CaMKIIα	4.809	8	0.0013

Supplementary Fig. 9f (WT, Atrx$^{\Delta E2}$, Atrx$^{\Delta E2}$+XIP, and Atrx$^{\Delta E2}$+ANTP in LP1 fraction)

Statistical analysis		F (DFn, DFd)	P value
One-way ANOVA with Bonferroni's post hoc test		F (3, 16) = 31.21	P <0.0001
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	6.909	16	<0.0001
WT vs Atrx$^{\Delta E2}$ + XIP	0.6621	16	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	7.39	16	<0.0001
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	6.247	16	<0.0001
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.4806	16	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	6.727	16	<0.0001

Supplementary Fig. 9f (WT, Atrx$^{\Delta E2}$, Atrx$^{\Delta E2}$+XIP, and Atrx$^{\Delta E2}$+ANTP in whole cell lysate)

Statistical analysis		F (DFn, DFd)	P value
One-way ANOVA with Bonferroni's post hoc test		F (4, 15) = 0.3603	P = 0.833
Comparison	**t**	**DF**	**P value**
WT vs Xlr3b-TG	0.5339	15	>0.9999
WT vs Atrx$^{\Delta E2}$	0.5414	15	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.3861	15	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	1.177	15	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$	0.007513	15	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$ + XIP	0.1478	15	>0.9999
Xlr3b-TG vs Atrx$^{\Delta E2}$ + ANTP	0.6433	15	>0.9999

$Atrx^{\Delta E2}$ vs $Atrx^{\Delta E2}$ + XIP	0.1553	15	>0.9999
$Atrx^{\Delta E2}$ vs $Atrx^{\Delta E2}$ + ANTP	0.6358	15	>0.9999
$Atrx^{\Delta E2}$ + XIP vs $Atrx^{\Delta E2}$ + ANTP	0.7911	15	>0.9999

Supplementary Fig. 9g

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	genotype × time	F (1, 28) = 0.8316	P =0.3696
	genotype	F (1, 28) = 41.85	P <0.0001
	time	F (1, 28) = 5.031	P =0.0330
Time	1min after HFS		
Comparison	**t**	**DF**	**P value**
WT vs Xlr3b-TG	5.219	28	<0.0001
Time	60min after HFS		
Comparison	**t**	**DF**	**P value**
WT vs Xlr3b-TG	3.929	28	0.003

Supplementary Fig. 9h (WT and Xlr3b-TG in paired pulse ratio of fEPSP)

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	genotype × interpulse interval	F (5, 48) = 0.4486	P =0.8122
	genotype	F (1, 48) = 0.0001278	P =0.9910
	interpulse interval	F (5, 48) = 12.23	P <0.0001
Paired pulse	**t**	**DF**	**P value**
20	1.272	48	>0.9999
40	0.08984	48	>0.9999
60	0.05439	48	>0.9999
80	0.4885	48	>0.9999
100	0.6125	48	>0.9999
500	0.0008888	48	>0.9999

Supplementary Fig. 9h (WT, $Atrx^{\Delta E2}$, $Atrx^{\Delta E2}$ +XIP and $Atrx^{\Delta E2}$+ANTP in paired pulse ratio of fEPSP)

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	group × interpulse interval	F (15, 96) = 0.2757	P =0.9965

	group	F (3, 96) = 0.9092	P =0.4396
	interpulse interval	F (5, 96) = 21.01	P <0.0001
Paired pulse interval 20 ms			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	1.012	96	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.7451	96	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	1.147	96	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.2667	96	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.1351	96	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.4018	96	>0.9999
Paired pulse interval 40 ms			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.4856	96	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.6945	96	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.3677	96	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.2089	96	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.1179	96	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.3268	96	>0.9999
Paired pulse interval 60 ms			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.08869	96	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.3184	96	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.003865	96	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.2297	96	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.08482	96	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.3146	96	>0.9999
Paired pulse interval 80 ms			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.8305	96	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.7554	96	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.1712	96	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.07508	96	>0.9999

$Atrx^{\Delta E2}$ vs $Atrx^{\Delta E2}$ + ANTP	1.002	96	>0.9999
$Atrx^{\Delta E2}$ +XIP vs $Atrx^{\Delta E2}$ + ANTP	0.9266	96	>0.9999
Paired pulse interval 100 ms			
group	**t**	**DF**	**P value**
WT vs $Atrx^{\Delta E2}$	0.391	96	>0.9999
WT vs $Atrx^{\Delta E2}$ + XIP	1.641	96	0.6245
WT vs $Atrx^{\Delta E2}$ + ANTP	0.5213	96	>0.9999
$Atrx^{\Delta E2}$ vs $Atrx^{\Delta E2}$ + XIP	1.25	96	>0.9999
$Atrx^{\Delta E2}$ vs $Atrx^{\Delta E2}$ + ANTP	0.1303	96	>0.9999
$Atrx^{\Delta E2}$ +XIP vs $Atrx^{\Delta E2}$ + ANTP	1.12	96	>0.9999
Paired pulse interval 500 ms			
group	**t**	**DF**	**P value**
WT vs $Atrx^{\Delta E2}$	0.08521	96	>0.9999
WT vs $Atrx^{\Delta E2}$ + XIP	0.2185	96	>0.9999
WT vs $Atrx^{\Delta E2}$ + ANTP	0.07273	96	>0.9999
$Atrx^{\Delta E2}$ vs $Atrx^{\Delta E2}$ + XIP	0.1333	96	>0.9999
$Atrx^{\Delta E2}$ vs $Atrx^{\Delta E2}$ + ANTP	0.1579	96	>0.9999
$Atrx^{\Delta E2}$ +XIP vs $Atrx^{\Delta E2}$ + ANTP	0.2912	96	>0.9999

Supplementary Fig. 9h (input-output relations in WT and Xlr3b-TG)

Statistical analysis	Interaction	F (DFn, DFd)	P value
Two-way ANOVA with Bonferroni's post hoc test	genotype × current	F (10, 88) = 0.5729	P =0.8319
	genotype	F (1, 88) = 31.58	P <0.0001
	current	F (10, 88) = 30.1	P <0.0001
current	**t**	**DF**	**P value**
0.1	0.05794	88	>0.9999
0.2	0.5964	88	>0.9999
0.3	1.356	88	>0.9999
0.4	1.997	88	0.5375
0.5	2.349	88	0.2317
0.6	2.316	88	0.2518

0.7	1.886	88	0.6886
0.8	1.785	88	0.8555
0.9	1.867	88	0.7171
1.0	2.539	88	0.1418
1.1	1.887	88	0.6863

Supplementary Fig. 9h (WT, Atrx$^{\Delta E2}$, Atrx$^{\Delta E2}$ +XIP and Atrx$^{\Delta E2}$+ANTP in input-output relations)

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	group × current	F (30, 176) = 0.3214	P =0.9997
	group	F (3, 176) = 1.502	P =0.2157
	current	F (10, 176) = 23.04	P <0.0001
0.1 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.009243	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.08911	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.03135	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.07986	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.0406	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.1205	176	>0.9999
0.2 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.001158	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.2034	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.5774	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.2045	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.5785	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.374	176	>0.9999
0.3 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.1344	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.2611	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.6994	176	>0.9999

Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.3955	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.8338	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.4383	176	>0.9999
0.4 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.1415	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.8257	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.6249	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.9671	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.7664	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.2008	176	>0.9999
0.5 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.1992	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.3935	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.6752	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.1943	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.476	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.2817	176	>0.9999
0.6 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.3449	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.3377	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.716	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.007245	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.371	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.3783	176	>0.9999
0.7 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.4751	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.395	176	>0.9999

WT vs Atrx$^{\Delta E2}$ + ANTP	0.2397	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.8702	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.2354	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.6348	176	>0.9999
0.8 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	1.268	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.4617	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.3898	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	1.729	176	0.513
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.8779	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.8514	176	>0.9999
0.9 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	1.176	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + XIP	0.01224	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.7582	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	1.189	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.4182	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.7705	176	>0.9999
1.0 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	1.663	176	0.5891
WT vs Atrx$^{\Delta E2}$ + XIP	0.7202	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	1.083	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.9424	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.5801	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.3623	176	>0.9999
1.1 mA			
group	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	0.8828	176	>0.9999

WT vs Atrx$^{\Delta E2}$ + XIP	1.165	176	>0.9999
WT vs Atrx$^{\Delta E2}$ + ANTP	0.5429	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + XIP	0.282	176	>0.9999
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + ANTP	0.3398	176	>0.9999
Atrx$^{\Delta E2}$ +XIP vs Atrx$^{\Delta E2}$ + ANTP	0.6218	176	>0.9999

Supplementary Fig. 9i

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	genotype × time	F (1, 16) = 13.28	P =0.0022
	genotype	F (1, 16) = 108.7	P <0.0001
	time	F (1, 16) = 10.81	P =0.0046
Comparison	**t**	**DF**	**P value**
WT vs WT + HFS	4.901	16	0.001
WT vs Xlr3b-TG	4.797	16	0.0012
Xlr3b-TG vs Xlr3b-TG + HFS	0.2516	16	>0.9999

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	group × time	F (3, 24) = 6.449	P =0.0023
	group	F (3, 24) = 29.44	P <0.0001
	time	F (1, 24) = 13.48	P =0.0012
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	3.695	24	0.0318
WT vs Atrx$^{\Delta E2}$ + XIP	3.759	24	0.0271
WT vs Atrx$^{\Delta E2}$ + ANTP	3.71	24	0.0306
WT vs WT + HFS	3.724	24	0.0295
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + HFS	1.482	24	>0.9999
Atrx$^{\Delta E2}$ + XIP vs Atrx$^{\Delta E2}$ + XIP +HFS	3.92	24	0.018

Supplementary Fig. 9j-9l

Statistical analysis		Two-sided unpaired t test	
Behavior test	**t**	**DF**	**P value (WT vs Xlr3b TG)**
NOR test	t=2.624	12	0.0222

PA test	t=3.084	23	0.0052
Y-maze test	t=5.293	12	0.0002

Supplementary Fig. 10b

Reporter plasmid		2K	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (5, 12) = 69.63	P <0.0001
Comparison	**t**	**DF**	**P value**
Veh.vs 1μM TMPyP4	1.047	12	>0.9999
Veh.vs 3μM TMPyP4	6.098	12	0.0008
Veh.vs 10μM TMPyP4	8.359	12	<0.0001
Veh.vs 30μM TMPyP4	12.98	12	<0.0001
Veh.vs 100μM TMPyP4	14.16	12	<0.0001

Reporter plasmid		2KΔG4	
Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (5, 12) = 2.258	P =0.1151
Comparison	**t**	**DF**	**P value**
Veh.vs 1μM TMPyP4	0.9511	12	>0.9999
Veh.vs 3μM TMPyP4	0.6964	12	>0.9999
Veh.vs 10μM TMPyP4	2.497	12	0.4213
Veh.vs 30μM TMPyP4	1.97	12	>0.9999
Veh.vs 100μM TMPyP4	2.616	12	0.3385

Supplementary Fig. 10c

Statistical analysis	**F (DFn, DFd)**		**P value**
One-way ANOVA with Bonferroni's post hoc test	F (4, 15) = 23.47		P <0.0001
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + TMPyP4 30mg/kg	0.3127	15	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$+ Veh.	8.052	15	<0.0001
WT + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	2.737	15	0.1528
WT + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	1.056	15	>0.9999

WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + Veh.	8.364	15	<0.0001
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	3.05	15	0.0811
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	1.369	15	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	5.315	15	0.0009
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	6.995	15	<0.0001
Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	1.681	15	>0.9999

Supplementary Fig. 10d

Statistical analysis	**F (DFn, DFd)**		**P value**
One-way ANOVA with Bonferroni's post hoc test	F (4, 15) = 16.05		P <0.0001
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + TMPyP4 30mg/kg	0.01972	15	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$+ Veh.	6.198	15	0.0002
WT + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	1.287	15	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.8845	15	>0.9999
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + Veh.	6.179	15	0.0002
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	1.268	15	>0.9999
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.9042	15	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	4.911	15	0.0019
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	7.083	15	<0.0001
Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	2.172	15	0.4631

Supplementary Fig. 11a

Statistical analysis	Interaction	F (DFn, DFd)	P value
Two-way ANOVA with Bonferroni's post hoc test	group × mobility	F (9, 64) = 8.453	P <0.0001
	group	F (3, 64) = 5.086e-014	P >0.9999
	mobility	F (3, 64) = 307.8	P <0.0001

Mobility		Immobile	
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.8468	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	3.278	64	0.0102
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	2.448	64	0.1027
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	4.124	64	0.0007
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	1.601	64	0.6857
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	5.725	64	<0.0001

Mobility		Bidirectional	
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.4507	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	3.498	64	0.0052
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	2.756	64	0.0456
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	3.948	64	0.0012
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	2.306	64	0.1463
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	6.254	64	<0.0001

Mobility		Anterograde	
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.7591	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.0892	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.0545	64	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.6698	64	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.7045	64	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.0347	64	>0.9999

Mobility		Retrograde	
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.363	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.1308	64	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.363	64	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.4939	64	>0.9999

WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0	64	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4939	64	>0.9999

Supplementary Fig. 11b (WT +Veh., WT + 5-ALA, Atrx$^{\Delta E2}$ + Veh., and Atrx$^{\Delta E2}$ + 5-ALA in paired pulse ratio of fEPSP)

Statistical analysis	Interaction	F (DFn, DFd)	P value
Two-way ANOVA with Bonferroni's post hoc test	group × interpulse interval	F (15, 96) = 0.1355	P =0.9965
	group	F (3, 96) = 0.3344	P =0.8005
	interpulse interval	F (5, 96) = 17.26	P <0.0001
Paired pulse interval 20 ms			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.355	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.9063	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4971	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.5513	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.1421	96	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4092	96	>0.9999
Paired pulse interval 40 ms			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.3831	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.2251	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.3954	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.6082	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.01224	96	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.6205	96	>0.9999
Paired pulse interval 60 ms			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.3777	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.03023	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4601	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.4079	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.08243	96	>0.9999

Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4903	96	>0.9999
Paired pulse interval 80 ms			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.2612	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.5308	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.1917	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.2697	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.06949	96	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.3392	96	>0.9999
Paired pulse interval 100 ms			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.4263	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.4972	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.181	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.9235	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.2453	96	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.6782	96	>0.9999
Paired pulse interval 500 ms			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.00744	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.1097	96	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.174	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.1172	96	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.1815	96	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.06429	96	>0.9999

Supplementary Fig. 11b (WT +Veh., WT + 5-ALA, Atrx$^{\Delta E2}$ + Veh., and Atrx$^{\Delta E2}$ + 5-ALA in input-output relations)

Statistical analysis	**Interaction**	**F (DFn, DFd)**	**P value**
Two-way ANOVA with Bonferroni's post hoc test	group × current	F (30, 176) = 0.4079	P =0.9975
	group	F (3, 176) = 4.142	P =0.0072
	current	F (10, 176) = 24.23	P <0.0001
0.1 mA			
group	**t**	**DF**	**P value**

WT + Veh. vs WT + 5-ALA	0.02472	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.01215	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.008427	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.03687	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.03315	176	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.003724	176	>0.9999
0.2 mA			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.007435	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.01346	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.09318	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.006022	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.08575	176	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.07973	176	>0.9999
0.3 mA			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.4304	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.2275	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.2304	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.2029	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.2	176	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.002876	176	>0.9999
0.4 mA			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.2936	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.2483	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.4471	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.04533	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.1535	176	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.1988	176	>0.9999
0.5 mA			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.4945	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.116	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.8497	176	>0.9999

WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.6105	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.3552	176	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.9657	176	>0.9999
0.6 mA			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.5588	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.05057	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.161	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.6093	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.6026	176	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.212	176	>0.9999
0.7 mA			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.6259	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.3894	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.357	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	1.015	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.7315	176	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.747	176	0.4945
0.8 mA			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.4734	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.771	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.25	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.2977	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	1.723	176	0.52
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	2.021	176	0.2691
0.9 mA			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.6175	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	1.604	176	0.6632
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.8023	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.9864	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	1.42	176	0.9446
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	2.406	176	0.1029

1.0 mA			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.5117	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	1.39	176	0.9972
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.04573	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.8786	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.5574	176	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.436	176	0.9166
1.1 mA			
group	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.8399	176	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	1.591	176	0.6808
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.1781	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.7508	176	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	1.018	176	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	1.769	176	0.4719

Supplementary Fig. 11c (WT, WT+Veh., Atrx$^{\Delta E2}$+Veh., and Atrx$^{\Delta E2}$+5-ALA in LP1 fraction)

Statistical analysis		**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test		F (3, 16) = 6.305	P = 0.005
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA	0.1997	16	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	3.193	16	0.034
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.7193	16	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	3.392	16	0.0223
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.5196	16	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	3.912	16	0.0075

Supplementary Fig. 11c (WT, WT+Veh., Atrx$^{\Delta E2}$+Veh., and Atrx$^{\Delta E2}$+5-ALA in whole cell lysate)

Statistical analysis	**F (DFn, DFd)**	**P value**
One-way ANOVA with Bonferroni's post hoc test	F (3, 16) = 0.2801	P = 0.8389

Comparison	t	DF	P value
WT + Veh. vs WT + 5-ALA	0.2352	16	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.09365	16	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.6483	16	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + Veh.	0.3289	16	>0.9999
WT + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA	0.8835	16	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA	0.5546	16	>0.9999

Supplementary Fig. 11c (WT, WT+Veh., Atrx$^{\Delta E2}$+Veh., and Atrx$^{\Delta E2}$+5-ALA in pCaMKIIα/CaMKIIα)

Statistical analysis	Interaction	F (DFn, DFd)	P value
Two-way ANOVA with Bonferroni's post hoc test	group × time	F (3, 24) = 4.391	P =0.0134
	group	F (3, 24) = 39.53	P <0.0001
	time	F (1, 24) = 69.29	P <0.0001
Comparison	**t**	**DF**	**P value**
WT vs Atrx$^{\Delta E2}$	3.867	24	0.0206
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + 5-ALA	4.414	24	0.0052
WT vs WT + HFS	5.258	24	0.0006
WT + 5-ALA vs WT + 5-ALA + HFS	4.798	24	0.0019
Atrx$^{\Delta E2}$ vs Atrx$^{\Delta E2}$ + HFS	1.053	24	>0.9999
Atrx$^{\Delta E2}$ + 5-ALA vs Atrx$^{\Delta E2}$ + 5-ALA + HFS	5.54	24	0.0003

Supplementary Fig. 11d

Behavior test	NOR test		
Statistical analysis	**F (DFn, DFd)**		**P value**
One-way ANOVA with Bonferroni's post hoc test	F (4, 48) = 3.794		P =0.0093
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + TMPyP4 30mg/kg	0.7399	48	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$+ Veh.	3.8	48	0.0041
WT + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	0.8664	48	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.6207	48	>0.9999

WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + Veh.	2.725	48	0.0894
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	0.1367	48	>0.9999
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.1442	48	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	2.516	48	0.1528
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	2.989	48	0.044
Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.2825	48	>0.9999

Supplementary Fig. 11e

Behavior test	PA test		
Statistical analysis	**F (DFn, DFd)**		**P value**
One-way ANOVA with Bonferroni's post hoc test	F (4, 35) = 5.147		P =0.0023
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + TMPyP4 30mg/kg	0.5287	35	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$+ Veh.	3.777	35	0.0059
WT + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	0.3991	35	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.1733	35	>0.9999
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + Veh.	3.248	35	0.0256
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	0.1854	35	>0.9999
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.3727	35	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	3.777	35	0.0059
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	3.728	35	0.0068
Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.2223	35	>0.9999

Supplementary Fig. 11f

Behavior test	Y-maze test		
Statistical analysis	**F (DFn, DFd)**		**P value**
One-way ANOVA with Bonferroni's post hoc test	F (4, 70) = 7.963		P <0.0001
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + TMPyP4 30mg/kg	0.2987	70	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$+ Veh.	5.129	70	<0.0001
WT + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	0.9629	70	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.7307	70	>0.9999
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + Veh.	3.968	70	0.0017
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	1.02	70	>0.9999
WT + TMPyP4 30mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.826	70	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg	2.901	70	0.0497
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	3.617	70	0.0056
Atrx$^{\Delta E2}$ + TMPyP4 10mg/kg vs Atrx$^{\Delta E2}$ + TMPyP4 30mg/kg	0.287	70	>0.9999

Supplementary Fig. 11g

Behavior test	Social interaction test (Sniffing)		
Statistical analysis	**F (DFn, DFd)**		**P value**
One-way ANOVA with Bonferroni's post hoc test	F (4, 62) = 3.032		P =0.0239
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA 3mg/kg	0.02797	62	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	2.958	62	0.0438
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	0.8671	62	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.09708	62	>0.9999
WT + 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ +Veh.	3.093	62	0.0297
WT+ 5-ALA 3mg/kg	0.9063	62	>0.9999

vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg			
WT + 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.07489	62	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	2.353	62	0.218
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	2.998	62	0.0391
Atrx$^{\Delta E 2}$+ 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.8167	62	>0.9999

Behavior test	Social interaction test (Following)		
Statistical analysis	**F (DFn, DFd)**		**P value**
One-way ANOVA with Bonferroni's post hoc test	F (4, 62) = 3.536		P =0.0116
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA 3mg/kg	0.2467	62	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	3.303	62	0.0159
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	1.119	62	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.2919	62	>0.9999
WT + 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ +Veh.	3.264	62	0.0179
WT+ 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	0.9422	62	>0.9999
WT + 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.05243	62	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	2.494	62	0.153
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	3.185	62	0.0227
Atrx$^{\Delta E 2}$+ 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.8744	62	>0.9999

Behavior test	Social interaction test (Escape)	
Statistical analysis	**F (DFn, DFd)**	**P value**

One-way ANOVA with Bonferroni's post hoc test	F (4, 62) = 14.17		P <0.0001
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA 3mg/kg	0.2177	62	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	5.624	62	<0.0001
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	1.238	62	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.7085	62	>0.9999
WT + 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ +Veh.	6.121	62	<0.0001
WT+ 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	1.102	62	>0.9999
WT + 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.5321	62	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	7.021	62	<0.0001
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	6.491	62	<0.0001
Atrx$^{\Delta E 2}$+ 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.5524	62	>0.9999

Behavior test	Social interaction test (Receptivity)		
Statistical analysis	**F (DFn, DFd)**		**P value**
One-way ANOVA with Bonferroni's post hoc test	F (4, 62) = 1.759		P =0.1485
Comparison	**t**	**DF**	**P value**
WT + Veh. vs WT + 5-ALA 3mg/kg	0.9301	62	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + Veh.	0.3642	62	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	0.6728	62	>0.9999
WT + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	1.452	62	>0.9999
WT + 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ +Veh.	1.204	62	>0.9999
WT+ 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	1.731	62	0.8837

WT + 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	2.553	62	0.1317
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 3mg/kg	0.2094	62	>0.9999
Atrx$^{\Delta E2}$ + Veh. vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.9045	62	>0.9999
Atrx$^{\Delta E 2}$+ 5-ALA 3mg/kg vs Atrx$^{\Delta E2}$ + 5-ALA 10mg/kg	0.8495	62	>0.9999