

Supplementary Materials

Fig. S1. Improvement of locomotor symptoms in *Pla2g6*^{-/-} mice with weekly Semaglutide treatment.

Fig. S2. H&E staining of brain (A) and visceral organs (B) sections.

Fig. S3. Ct Gapdh Values for qPCR.

Fig. S4. P-GSK3 β Y216 Western blot and quantification.

Fig. S5. Full length Western blots of RIP, RIP3 and β -actin.

Table S1. Primers sequence table for qPCR.

Table S2. Summary table of antibodies used for the ICH and western blot.

Table S3. Forward and Reverse Primers sequences table for genotyping.

Table S4. *P* values for Fig 1.

Table S5. *P* values for Fig 2.

Table S6. *P* values for Fig 3.

Table S7. *P* values for Fig 4.

Table S8. *P* values for Fig 5.

Table S9. *P* values for Fig 6.

Table S10. *P* values for Fig S1.

Table S11. *P* values for Fig S3.

Fig. S1. Improvement of locomotor symptoms in Pla2g6^{-/-} mice with weekly Semaglutide treatment.

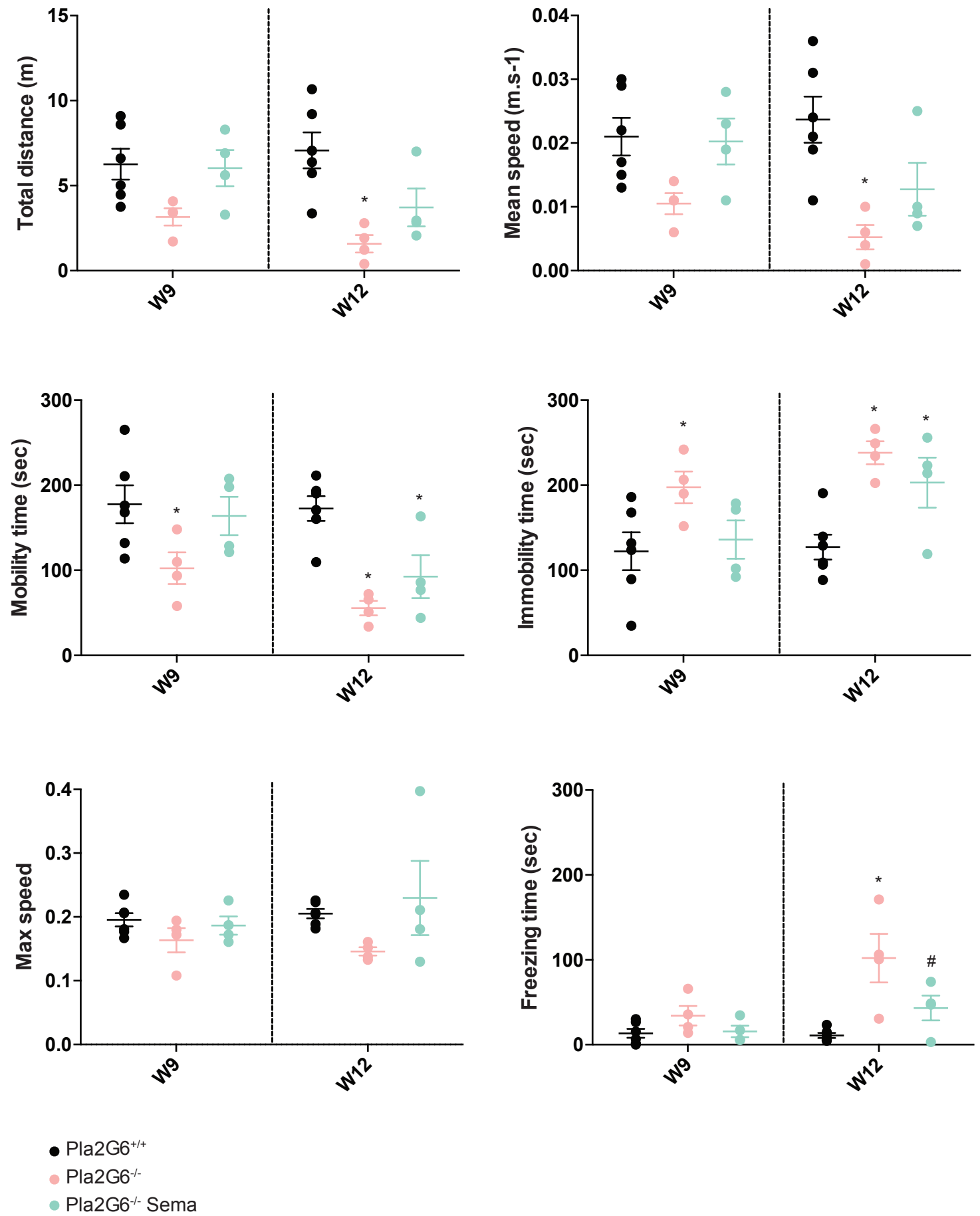
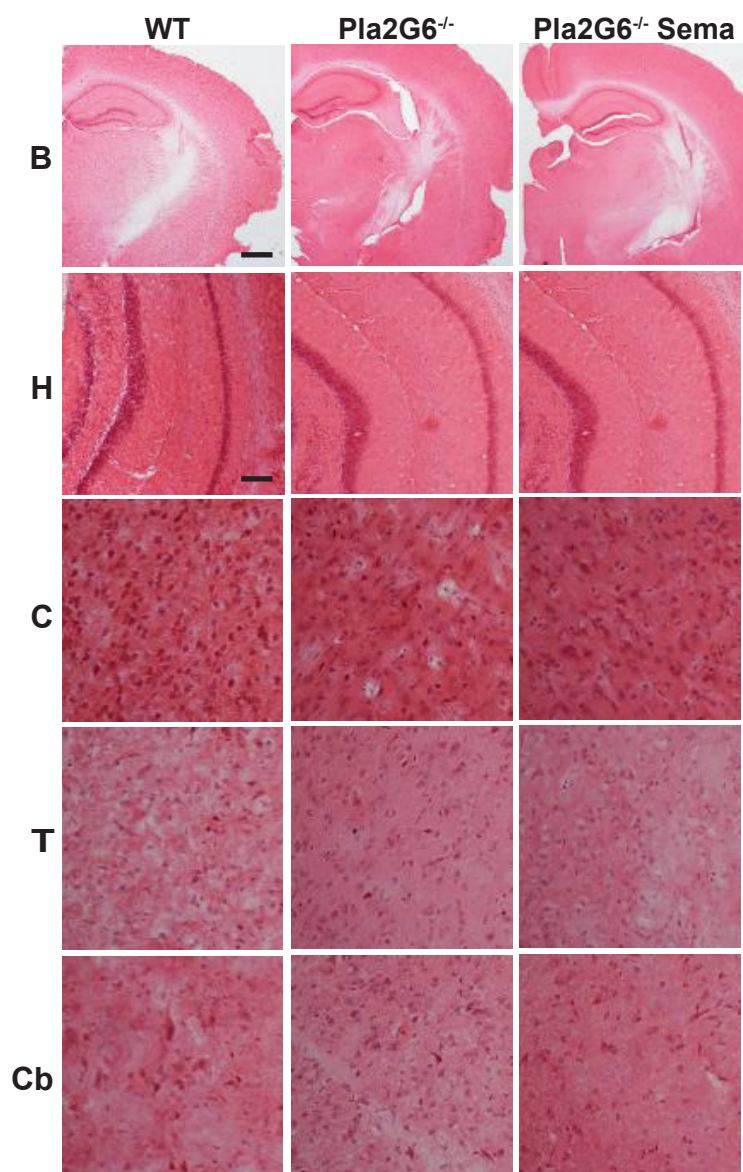


Fig. S2. H&E staining of brain (A) and visceral organs (B) sections.

A



B

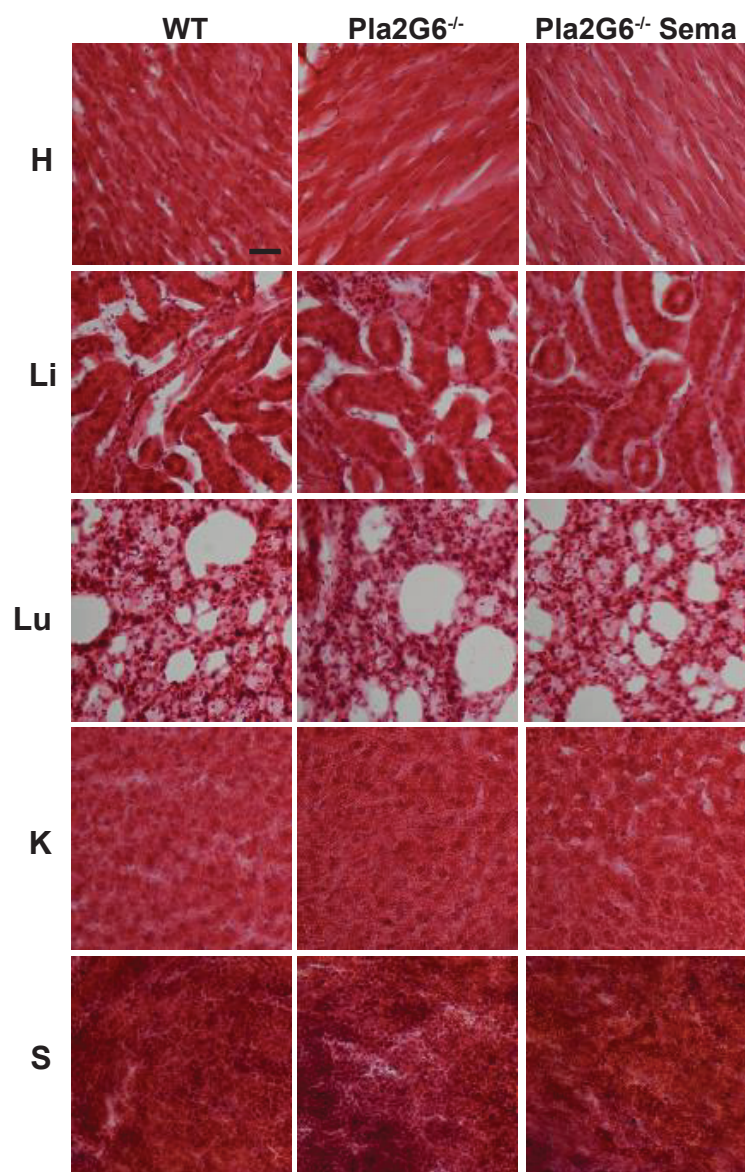


Fig. S3. Ct Gapdh Values for qPCR.

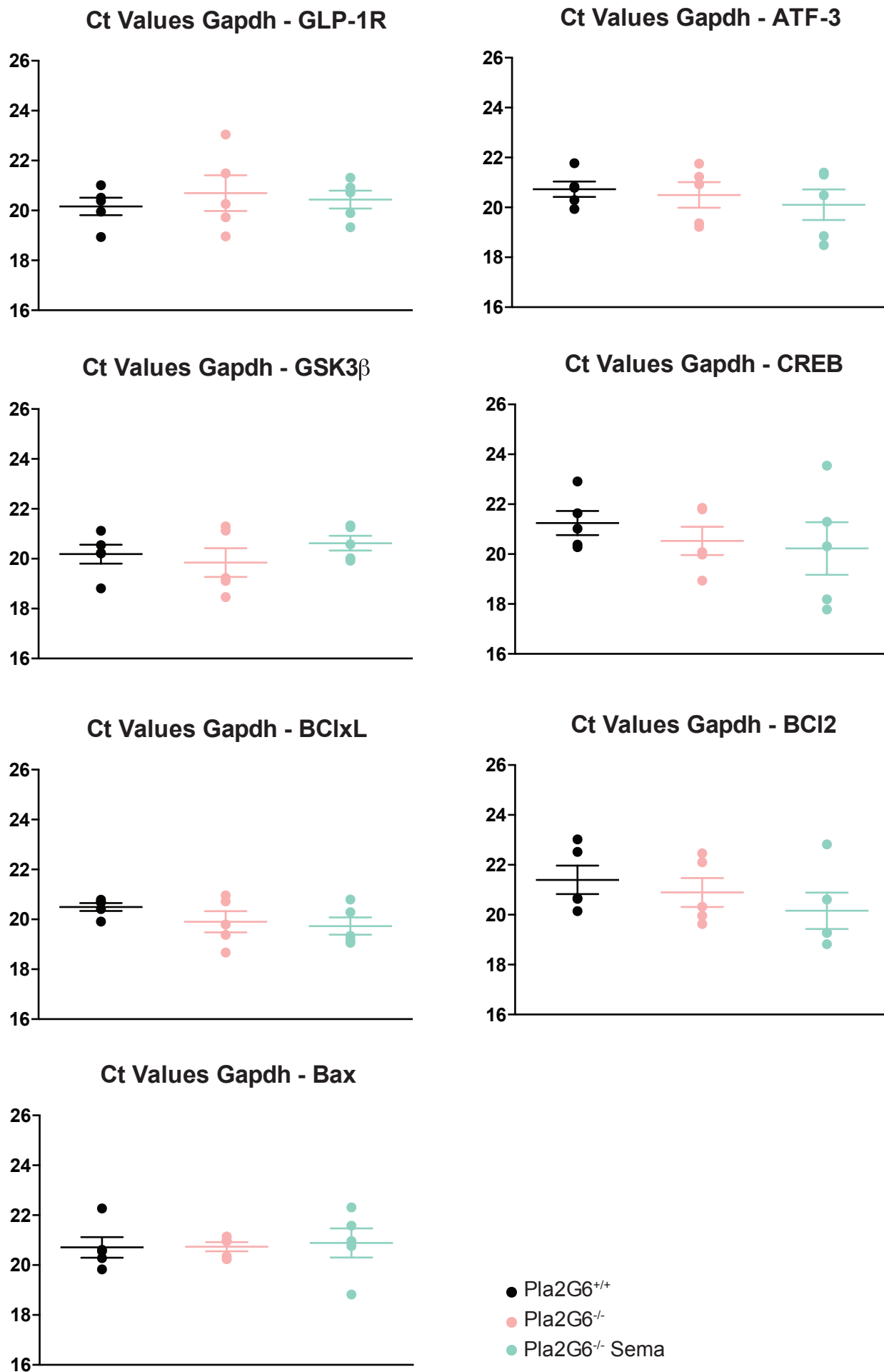
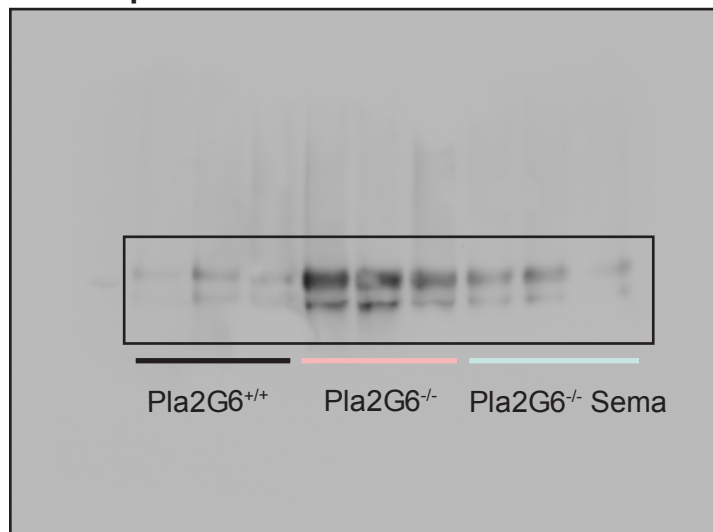


Fig. S4. P-GSK3 β Y216 full-length blot.

P-GSK3 β Y216 blot



Actin blot

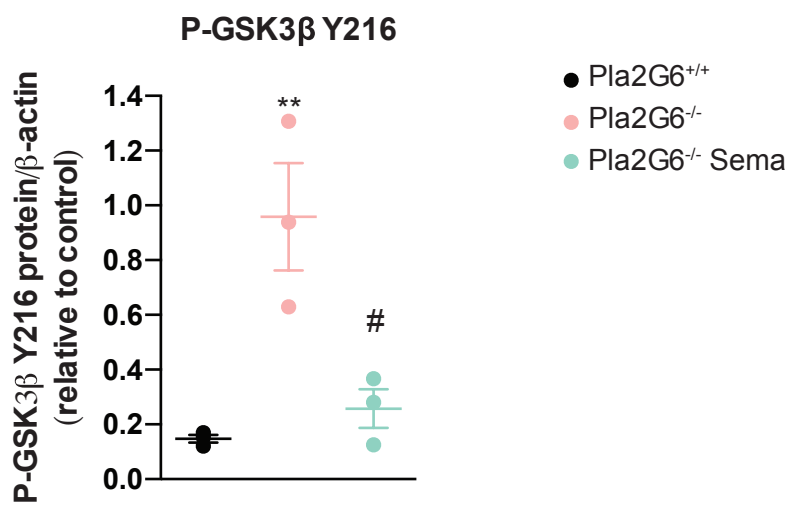
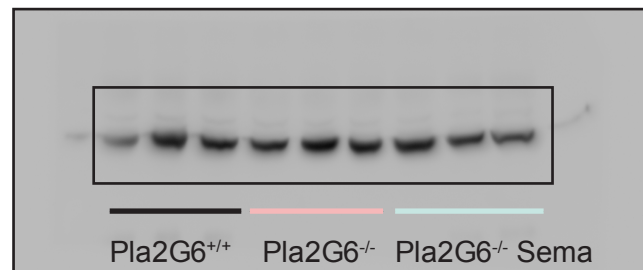
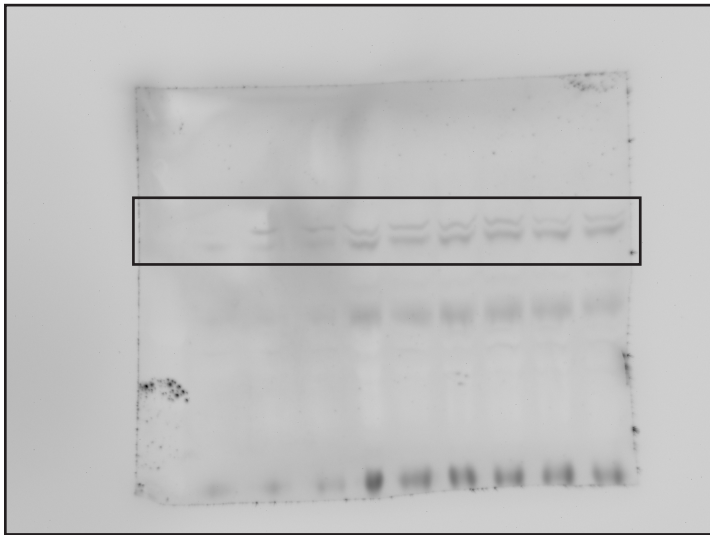


Table S12

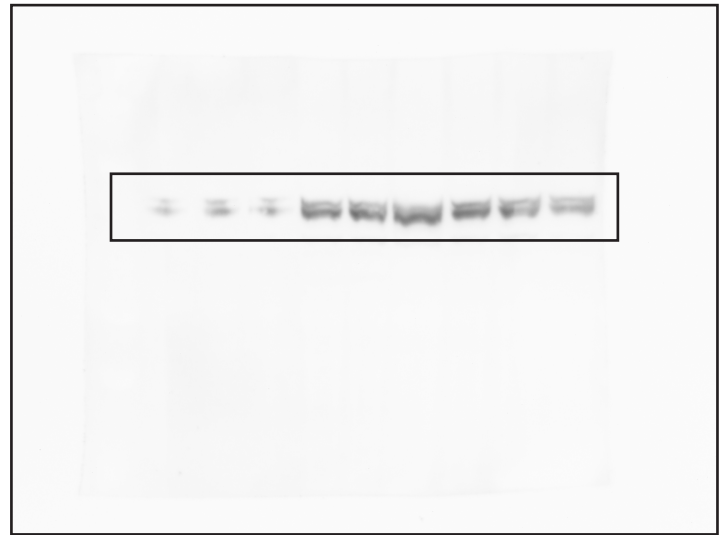
	<i>P</i> value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	0.0075
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.8011
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.0148

Fig. S5. Full-length blots.

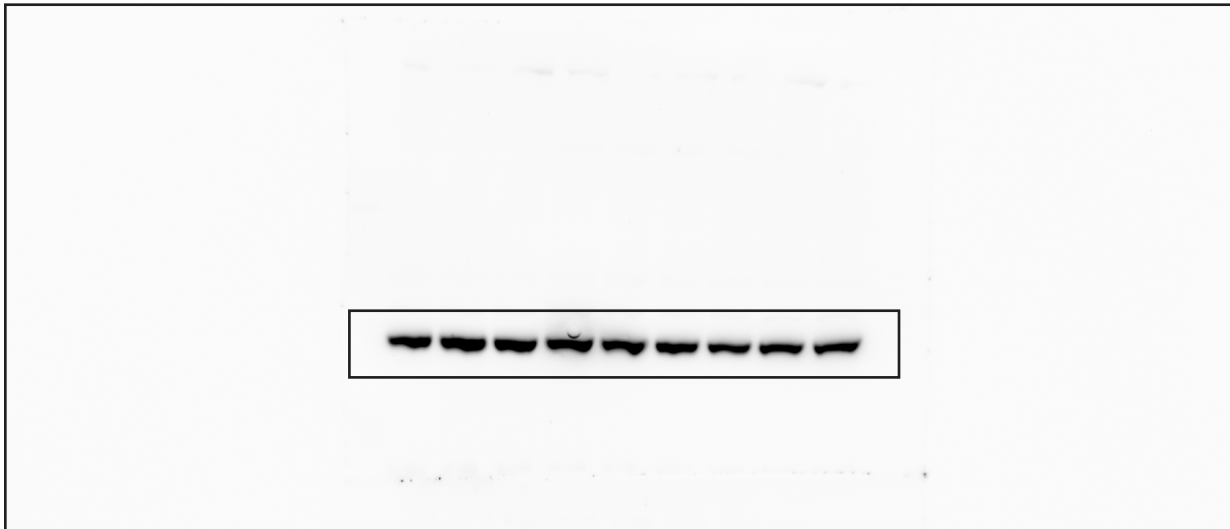
RIP1 blot



RIP3 blot



Actin blot



Supplementary Data Tables

Target Gene	Sequence	Reference
Gapdh	<u>F</u> GTTGCTCCTGCGACTTCA <u>R</u> GGTGGTCCAGGGTTTCTTA	Pick primers
CREB	<u>F</u> CACAGAACCAGTTTCCATCATCCAGT <u>R</u> CATGTTCCAGAGGGTTAGGGAGAGCA	Miller, 2012
GSK3 β	<u>F</u> TTGACAAAGGTCTTCCGGC <u>R</u> AAGAGTGCAGGTGTGTCTCG	Li, 2015
GLP1-R	<u>F</u> AGACGGTGCAGAAATGGAGA <u>R</u> TGCGCTTCCGTGAGG	During, 2003
ATF-3	<u>F</u> TTACCGTCAACAACAGACCC <u>R</u> TCAGCTCAGCATTCACTC	Edagawa, 2014
BCI2	<u>F</u> GTGGTGGAGGAACCTTTCAG <u>R</u> GTTCCACAAAGGCATCCAG	Wenyuan, 2016
BCI _x L	<u>F</u> CGGAGAGCGTTCAGTGATCTA <u>R</u> TTGTCTACGCTTTCACGCA	Pick primers
Bax	<u>F</u> AGCAAAGTGGTGTCAAGGC <u>R</u> CCACAAAGATGGTCACTGTC	Wenyuan, 2016

Antibody	Reference	Dilution	Protocol
CD68	MCA1957	1:2000	ICH
NeuN	MAB377	1:500	ICH
Iba-1	ab5076	1:500	ICH
GFAP	MAB3402	1:2000	ICH
RIP1	ab72139	1:1000	WB
Actin	ab8226	1:5000	WB
P-GSK3 β Y216	ab75745	1:1000	WB

Gene	Sequence	Size
Pla2G6 WT	R: CTCTGCTTGTCTGCTGCTG F: GTCAAAGCCCTCATTGTATTCGG	346 bp
Pla2G6 Mutant	R: GGAGGGTCGGGTCCTATTTA F: GTCAAAGCCCTCATTGTATTCAG	617 bp

	% Survival
Pla2G6^{-/-} vs. Pla2G6^{-/-} Sema 0.5ug/week	<0.001
Pla2G6^{-/-} vs. Pla2G6^{-/-} Sema 0.25ug/week	0.0505
Pla2G6^{-/-} vs. Pla2G6^{-/-} Sema 0.15ug/week	0.5107
Pla2G6^{-/-} Sema 0.25ug/week vs. Pla2G6^{-/-} Sema 0.15ug/week	>0.9999
Pla2G6^{-/-} Sema 0.25ug/week vs. Pla2G6^{-/-} Sema 0.5ug/week	0.7429
Pla2G6^{-/-} Sema 0.15ug/week vs. Pla2G6^{-/-} Sema 0.5ug/week	0.0457

	Age (weeks)									
	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14
Pla2G6^{+/+} vs. Pla2G6^{-/-}	0.7601	0.5981	0.5507	0.448	0.3947	0.0163	0.0003	0.0161	0.0087	0.0058
Pla2G6^{+/+} vs. Pla2G6^{-/-} Sema	0.9996	0.9989	0.9972	0.8484	0.9616	0.9139	0.1149	0.4664	0.3332	0.3469
Pla2G6^{-/-} vs. Pla2G6^{-/-} Sema	0.7818	0.6258	0.6488	0.2473	0.6104	0.0773	0.1475	0.3022	0.314	0.2473

	Age (weeks)									
	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14
Pla2G6^{+/+} vs. Pla2G6^{-/-}	0.4734	> 0.9999	0.9974	0.2104	0.0002	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Pla2G6^{+/+} vs. Pla2G6^{-/-} Sema	0.944	0.9965	0.9275	0.9495	0.9976	0.3005	0.0998	0.0006	0.0001	< 0.0001
Pla2G6^{-/-} vs. Pla2G6^{-/-} Sema	0.7204	0.9964	0.9154	0.4152	0.0008	< 0.0001	< 0.0001	0.0016	0.0033	0.3467

Table S5. P values for Fig. 2.

	GLP1-R mRNA <i>P</i> value	ATF-3 mRNA <i>P</i> value	GSK3 β mRNA <i>P</i> value	CREB mRNA <i>P</i> value	S1BF NeuN <i>P</i> value	VPM/VPL NeuN <i>P</i> value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	0.6872	< 0,0001	0.0001	0.0003	< 0,0001	< 0,0001
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.0003	0.1873	0.9506	0.9617	< 0,0001	< 0,0001
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	< 0,0001	0.0005	< 0,0001	0.0002	0.0006	0.0012

Table S6. P values for Fig. 3.

	BClxl mRNA <i>P</i> value	Bcl2 mRNA <i>P</i> value	Bax mRNA <i>P</i> value	RIP1 protein <i>P</i> value	RIP3 protein <i>P</i> value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	< 0,0001	0.0001	< 0,0001	0.0329	< 0,0001
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.3552	0.1814	0.0115	0.2692	0.0003
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.0002	0.0028	0.015	0.2867	0.0009

Table S7. P values for Fig. 4.

	Iba-1			
	Cortex <i>P</i> value	Hippocampus <i>P</i> value	Thalamus <i>P</i> value	Cerebellum <i>P</i> value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	0.0002	0.0072	0.0002	0.0122
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.2666	0.7235	0.2666	0.3026
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.0057	0.043	0.0057	0.2176

	CD68			
	Cortex <i>P</i> value	Hippocampus <i>P</i> value	Thalamus <i>P</i> value	Cerebellum <i>P</i> value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	0.0059	> 0,9999	< 0,0001	< 0,0001
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.832	0.0648	0.982	0.9761
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.0043	0.0641	< 0,0001	< 0,0001

	GFAP			
	Cortex <i>P</i> value	Hippocampus <i>P</i> value	Thalamus <i>P</i> value	Cerebellum <i>P</i> value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	0.8969	< 0,0001	0.0028	0.0015
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.3454	0.9847	0.3357	0.006
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.6355	0.0001	0.0539	0.6126

Table S8. P values for Fig 5.

	Vacuoles <i>P</i> value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	0.0001
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.0375
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.0047

	Spheroids			
	Cortex <i>P</i> value	Hippocampus <i>P</i> value	Thalamus <i>P</i> value	Cerebellum <i>P</i> value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	< 0,0001	< 0,0001	0.014	0.0003
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.0001	0.0001	0.0025	0.0008
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.2637	0.2068	0.4889	0.7448

Table S9. P values for Fig. 6.

	CD68					
	Brain P value	Heart P value	Kidney P value	Lung P value	Liver P value	Spleen P value
Pla2G6 ^{+/+} vs. Pla2G6 ^{+/+} 1/10 dose	> 0,9999	> 0,9999	> 0,9999	> 0,9999	> 0,9999	> 0,9999
Pla2G6 ^{+/+} vs. Pla2G6 ^{+/+} 1/2 dose	0.339	> 0,9999	> 0,9999	0.2685	0.639	> 0,9999
Pla2G6 ^{+/+} vs. Pla2G6 ^{+/+} Full-dose	> 0,9999	> 0,9999	> 0,9999	> 0,9999	0.9247	0.339

	Total WBC P value	Neutrophils P value	Lymphocytes P value	Monocytes P value	Eosinophils P value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.1143	0.4857	0.6571	0.0286	0.3429

	Basophils P value	Haematocrit P value	Platelets P value	Red blood cells P value	Haemoglobin P value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.3429	0.0286	0.6571	0.0286	0.0286

Table S10. P values for Fig. S1.

	Total distance (m)		Immobility time (s)	
	W9 P value	W12 P value	W9 P value	W12 P value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	0.0843	0.0013	0.0485	0.0027
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.9975	0.0563	0.9529	0.0463
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.1721	0.3991	0.1845	0.6291

	Mean speed (m.s-1)		Max speed	
	W9 P value	W12 P value	W9 P value	W12 P value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	0.0895	0.0016	0.6881	0.2067
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.9978	0.074	0.9891	0.8286
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.1779	0.3783	0.8845	0.0707

	Mobility time (s)		W14	
	W9 P value	W12 P value	W9 P value	W14 P value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	0.0366	0.001	0.5659	< 0,0001
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.9462	0.0245	0.9988	0.2048
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.1544	0.5521	0.7142	0.0151

Table S11. P values for Fig. S3.

	Ct Values GAPDH						
	GLP1-R P value	ATF-3 P value	GSK3β P value	CREB P value	BC1xL P value	Bcl2 P value	Bax P value
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-}	0.7375	0.9426	0.7581	0.78	0.264	0.841	0.999
Pla2G6 ^{+/+} vs. Pla2G6 ^{-/-} Sema	0.9221	0.658	0.8479	0.6105	0.4353	0.3789	0.9543
Pla2G6 ^{-/-} vs. Pla2G6 ^{-/-} Sema	0.9284	0.8438	0.4383	0.9554	0.9261	0.6981	0.9665