Extended Data Figures and Tables

H3K9me3 inhibition reverses Alzheimer's progression by restoring synaptic and immune proteostasis across the brain–retina axis

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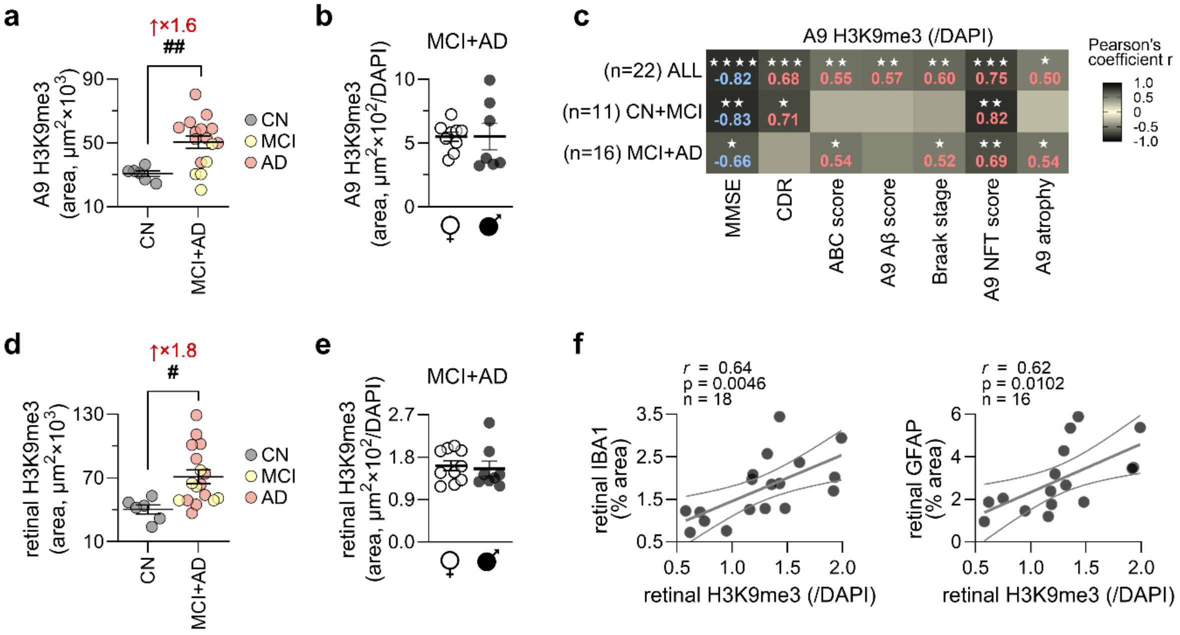
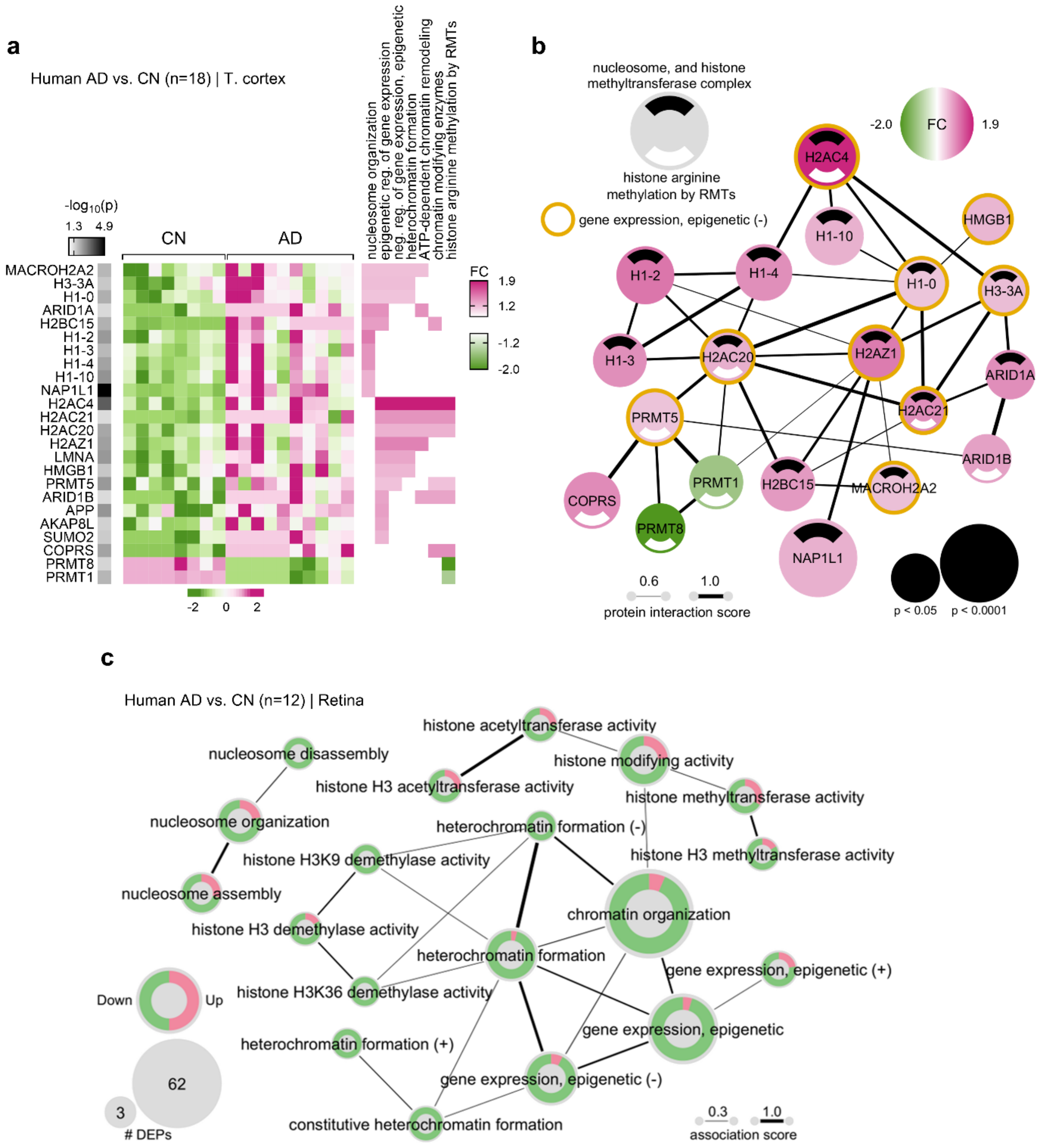
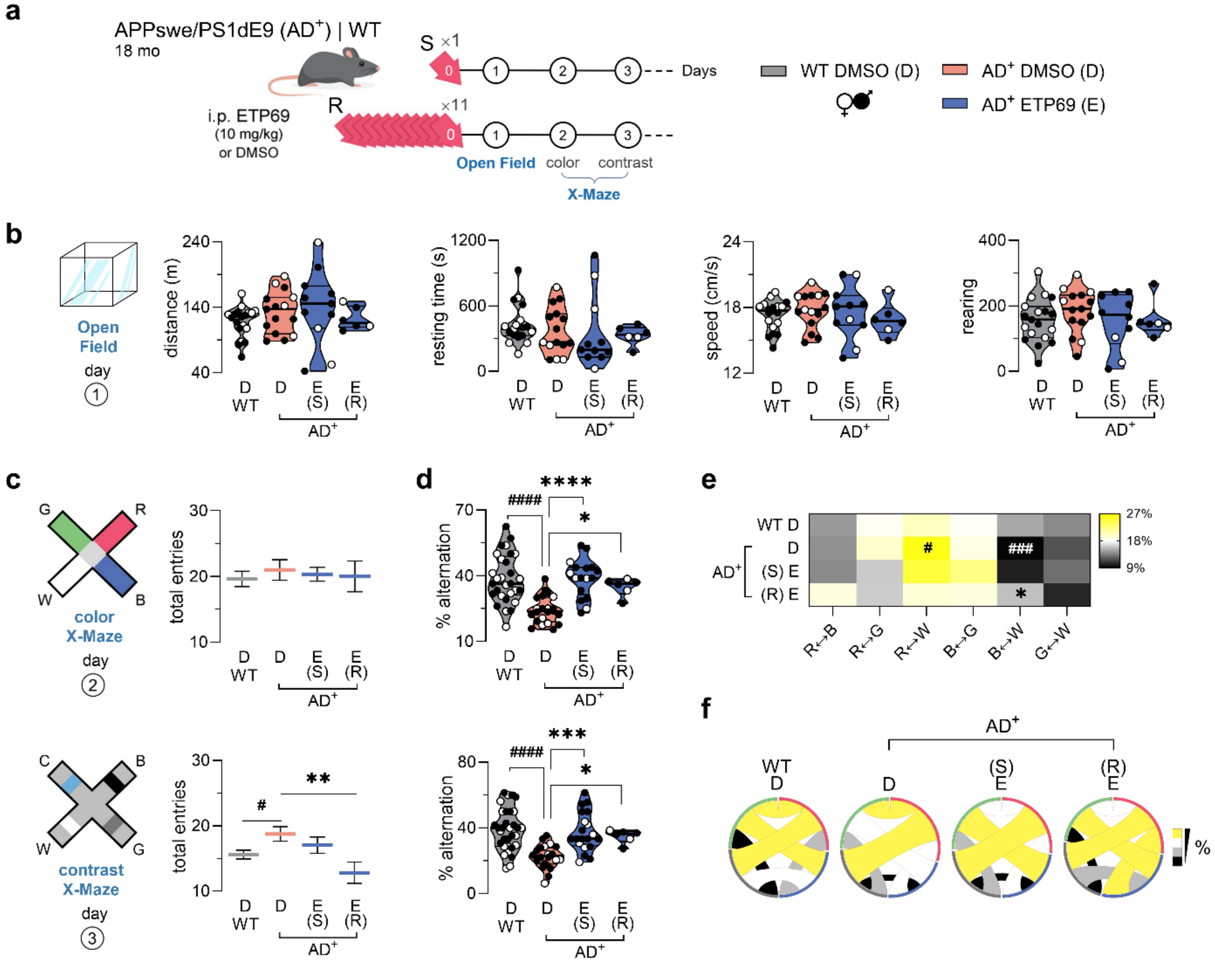


Extended Data Fig. 1. Increased cerebral and retinal H3K9me3 in MCI and AD patients coincides with cognitive decline and neuropathology.

(**a**) Quantification of cortical (Brodmann area 9; A9) H3K9me3 immunoreactivity (IR area, $\mu m^2\times10^3$) in 16 MCI (due to AD) and AD dementia patients (MCI+AD) and 6 CN subjects. (**b**) Comparison of A9 H3K9me3 (IR area, $\mu m^2\times10^2$ per DAPI nuclei count) in male ($n = 7$) versus female ($n = 9$) MCI+AD patients. (**c**) Summary heatmap of Pearson's correlations of A9 H3K9me3 (IR area per nuclei) with MMSE, CDR, ABC scores, A9 Aβ scores, Braak stages, A9 NFT scores, and A9 atrophy scores, for the entire cohort of subjects, or limited to CN+MCI or MCI+AD donors. ★ $p < 0.05$, ★★ $p < 0.01$, ★★★ $p < 0.001$, and ★★★★ $p < 0.0001$. (**d**) Quantification of retinal H3K9me3 (IR area, $\mu m^2\times10^3$) in 18 MCI+AD patients and 6 CN subjects. (**e**) Comparison of retinal H3K9me3 (IR area per nuclei) in male ($n = 8$) versus female ($n = 10$) MCI+AD patients. (**f**) Pearson's correlations of retinal H3K9me3 (IR area per nuclei) against retinal IBA1 IR (% area, microgliosis, $n = 18$) or GFAP IR (% area, astrogliosis, $n = 16$). # $p < 0.05$, and ## $p < 0.01$ by two-tailed unpaired Student's t-test between MCI+AD patients and CN subjects.

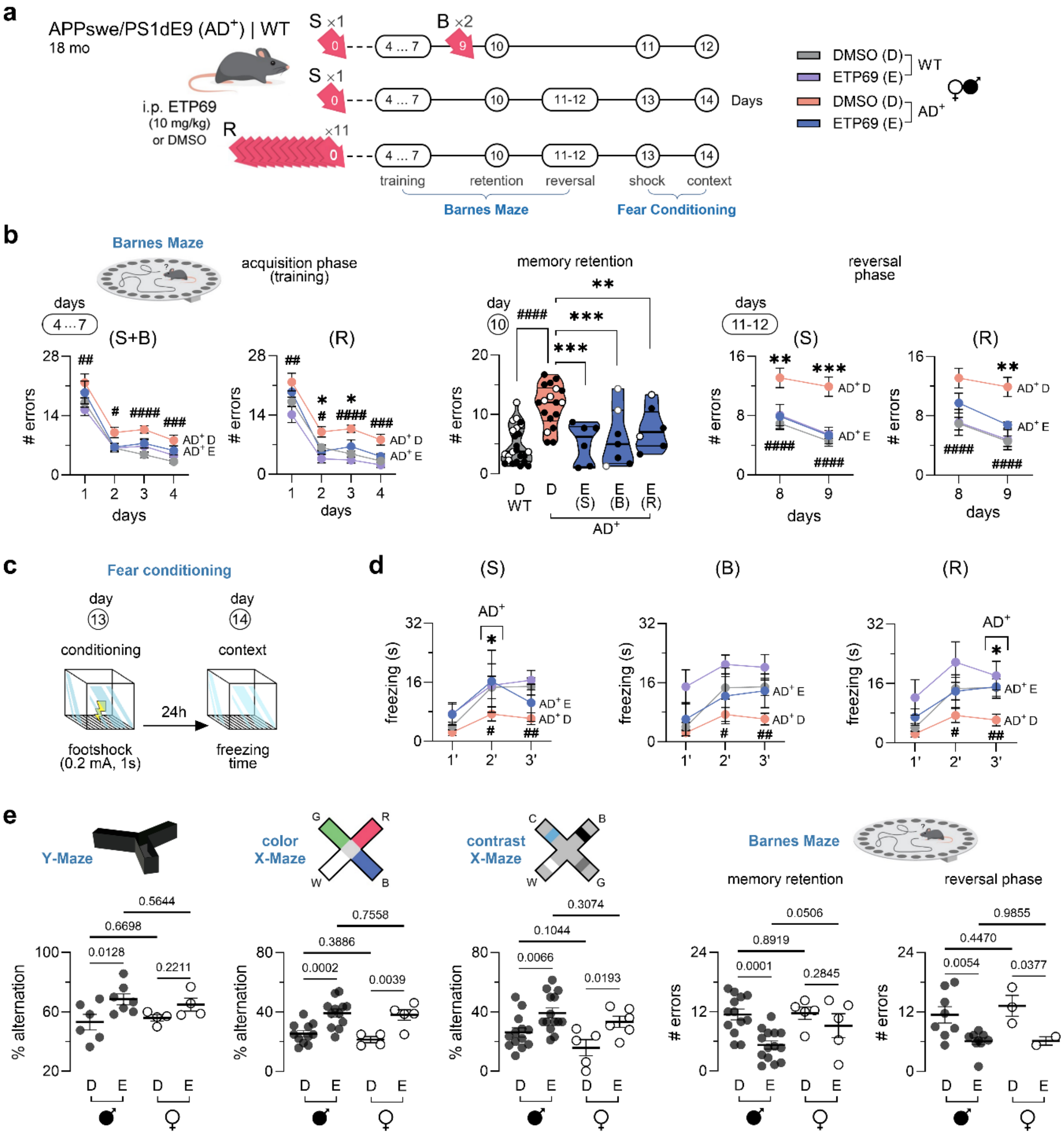

a
Human AD vs. CN (n=18) | T. cortex
-log$_{10}$(p)
1.3 4.9
CN
AD
nucleosome organization
epigenetic reg. of gene expression
neg. reg. of gene expression, epigenetic
heterochromatin formation
ATP-dependent chromatin remodeling
chromatin modifying enzymes
histone arginine methylation by RMTs
FC
1.9
1.2
-1.2
-2.0
MACROH2A2
H3-3A
H1-0
ARID1A
H2BC15
H1-2
H1-3
H1-4
H1-10
NAP1L1
H2AC4
H2AC21
H2AC20
H2AZ1
LMNA
HMGB1
PRMT5
ARID1B
APP
AKAP8L
SUMO2
COPRS
PRMT8
PRMT1
-2 0 2
b
nucleosome, and histone methyltransferase complex
histone arginine methylation by RMTs
gene expression, epigenetic (-)
-2.0 FC 1.9
H2AC4
H1-10
HMGB1
H1-2
H1-4
H1-0
H3-3A
H1-3
H2AC20
H2AZ1
ARID1A
H2AC21
PRMT5
ARID1B
PRMT1
H2BC15
MACROH2A2
COPRS
PRMT8
NAP1L1
0.6 1.0
protein interaction score
p < 0.05 p < 0.0001
c
Human AD vs. CN (n=12) | Retina
histone acetyltransferase activity
nucleosome disassembly
histone modifying activity
histone H3 acetyltransferase activity
histone methyltransferase activity
nucleosome organization
heterochromatin formation (-)
histone H3K9 demethylase activity
histone H3 methyltransferase activity
nucleosome assembly
chromatin organization
histone H3 demethylase activity
heterochromatin formation
gene expression, epigenetic (+)
Down
Up
histone H3K36 demethylase activity
gene expression, epigenetic
heterochromatin formation (+)
62
gene expression, epigenetic (-)
3
DEPs
constitutive heterochromatin formation
0.3 1.0
association score

Extended Data Fig. 2. Dysregulated epigenetic related proteome in AD brain and retina.
(**a**) Normalized expression profiles of DEPs identified by mass spectrometry–based proteomics in the cortex of AD patients versus CN individuals involved in epigenetic regulation of gene expression and heterochromatin formation. (**b**) Protein association network showing select protein roles in epigenetic regulation and histone methylation (indicated by inner ring segments and border of nodes) using the STRING database (v12.0). Nodes are colored according to FC in AD versus CN brains. Node size corresponds to p-values of change in expression. (**c**) Epigenetic related Gene Ontology network of DEPs identified by mass spectrometry–based proteomics displays dysregulated chromatin organization and heterochromatin formation pathways in AD retina. Many proteins with histone modifying activity were altered in the AD retina, including histone H3 methyltransferase, demethylase and acetyltransferase. The size of the node represents the number of DEPs in each pathway. The inner ring indicates the proportion of downregulated and upregulated DEPs.


a
APPswe/PS1dE9 (AD+) | WT
18 mo
i.p. ETP69
(10 mg/kg)
or DMSO
S ×1
R ×11
0
1
2
3
Days
Open Field
color
contrast
X-Maze
WT DMSO (D)
AD+ DMSO (D)
AD+ ETP69 (E)
b
Open Field
day 1
distance (m)
240
140
40
resting time (s)
1200
600
0
speed (cm/s)
24
18
12
rearing
400
200
0
D WT
D
E (S)
E (R)
AD+
c
G
R
W
B
color X-Maze
day 2
total entries
30
20
10
C
B
W
G
contrast X-Maze
day 3
#
**
d
% alternation
70
40
10
####
****
*
80
40
0
####
***
*
e
WT D
D
AD+ (S) E
(R) E
#
###
*
27%
18%
9%
R↔B
R↔G
R↔W
B↔G
B↔W
G↔W
f
AD+
WT D
D
(S) E
(R) E
%

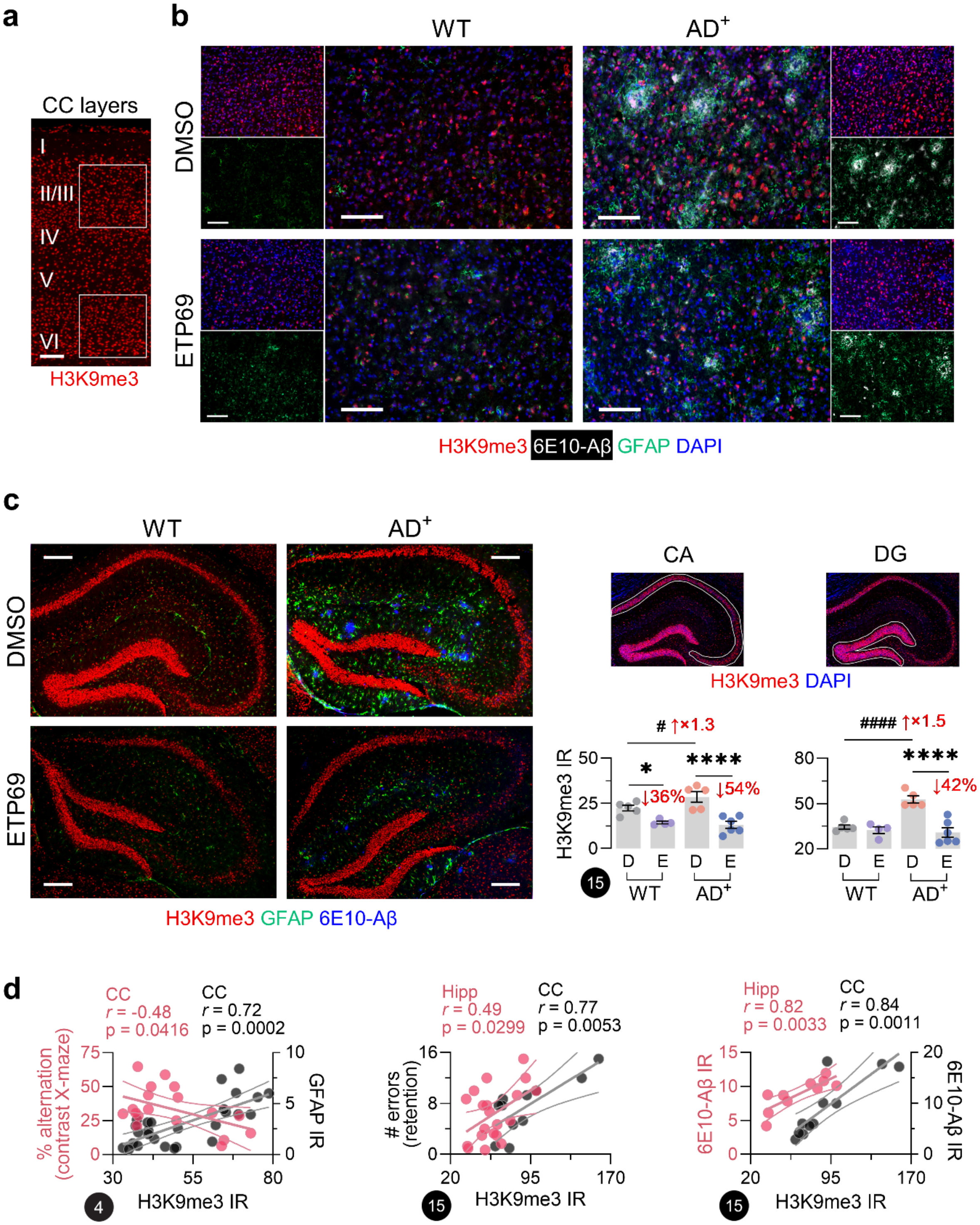
Extended Data Fig. 3. Effects of single or repeated intraperitoneal ETP69 injections on locomotion, cognition, and vision in 18-month-old AD model mice.

(**a**) Experimental timeline of i.p. ETP69 (10 mg/kg) or DMSO injection in 18-month-old AD^+ and age- and sex-matched WT mice under regimen single (S: 21 DMSO-WT, 22 ETP69-WT, 15 DMSO-AD^+, 18 ETP69-AD^+), or repeated (R: 7 DMSO-WT, 6 ETP69-WT, 7 DMSO-AD^+, 6 ETP69-AD^+). (**b**) Distance travelled, resting time, average speed, and rearing number during the 30 min-long open field test. (**c**) Total number of entries (locomotor activity) and (**d**) percentage of alternations (cognition/vision) in the colour- and contrast-mode of the visual-stimuli X-maze. (**e**) Percentage and (**f**) chord diagrams of bidirectional transitions between arms in the colour mode of the X-maze. Individual data points are presented with group means ± SEMs. Violin plots display median and lower and upper quartiles. Filled and empty circles represent male and female mice, respectively. # $p < 0.05$, ### $p < 0.001$, and #### $p < 0.0001$: DMSO-AD^+ versus DMSO-WT mice; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$: ETP69-AD^+ versus DMSO-AD^+ mice; by one-way ANOVA followed by Fisher's least significant difference (LSD) *post hoc* test.


a
APPswe/PS1dE9 (AD+) | WT
18 mo
i.p. ETP69
(10 mg/kg)
or DMSO
S ×1
B ×2
S ×1
R ×11
0
4 … 7
9
10
11
12
11-12
13
14
Days
training
retention
reversal
shock
context
Barnes Maze
Fear Conditioning
DMSO (D)
ETP69 (E)
WT
DMSO (D)
ETP69 (E)
AD+
b
Barnes Maze
acquisition phase (training)
days
4…7
(S+B)
(R)
errors
days
##
#
####
###
AD+ D
AD+ E
*
memory retention
day
10
####
***
***
**
D
WT
E
(S)
(B)
(R)
AD+
reversal phase
days
11-12
(S)
(R)
**
***
####
c
Fear conditioning
day
13
14
conditioning
context
24h
footshock
(0.2 mA, 1s)
freezing time
d
(S)
(B)
(R)
AD+
freezing (s)
1'
2'
3'
AD+ E
AD+ D
e
Y-Maze
color X-Maze
contrast X-Maze
Barnes Maze
memory retention
reversal phase
G
R
W
B
C
% alternation
# errors
0.5644
0.6698
0.0128
0.2211
0.7558
0.3886
0.0002
0.0039
0.3074
0.1044
0.0066
0.0193
0.0506
0.8919
0.0001
0.2845
0.9855
0.4470
0.0054
0.0377
D
E
♂
♀

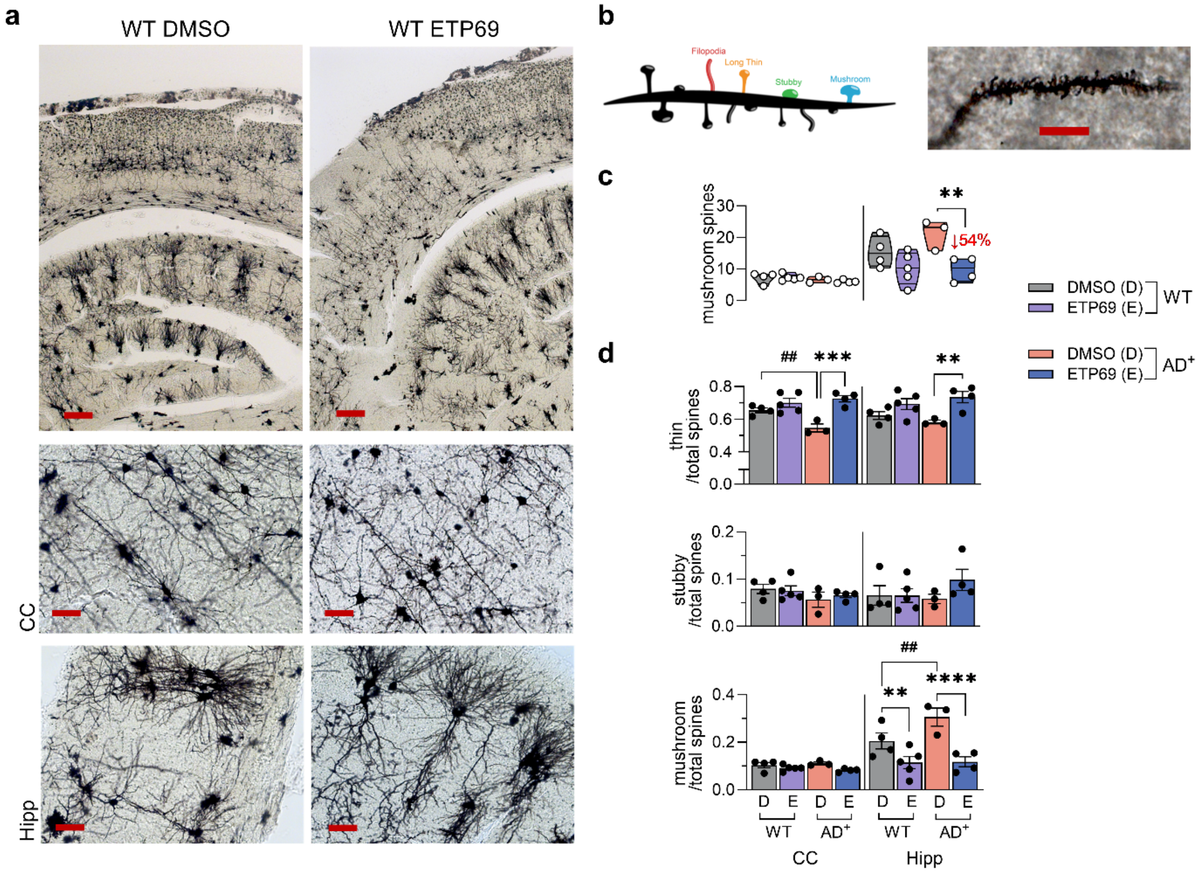
Extended Data Fig. 4. Cognitive effects of different intraperitoneal ETP69 dosing regimens in 18-month-old AD model mice.

(**a**) Experimental timeline of i.p. ETP69 (10 mg/kg) or DMSO injection in 18-month-old AD^+ and age- and sex-matched WT mice under regimen single (S: 21 DMSO-WT, 22 ETP69-WT, 15 DMSO-AD^+, 18 ETP69-AD^+), repeated (R: 7 DMSO-WT, 6 ETP69-WT, 7 DMSO-AD^+, 6 ETP69-AD^+) or boost (B: 9 DMSO-WT, 10 ETP69-WT, 7 DMSO-AD^+, 8 ETP69-AD^+). (**b**) Number of errors before finding the escape box during the acquisition phase (days 1-4), on memory retention day (day 7), and during the reversal phase (days 8-9) of the Barnes maze. (**c**) Conditions of the contextual fear conditioning test. (**d**) Freezing time over a 3-min period in the context-specific fear conditioning test. (**e**) Comparison of performances between aged male (M) and female (F) AD^+ mice following ETP69 or DMSO administration in the Y-maze (6 DMSO-M, 4 DMSO-F, 7 ETP69-M, 4 ETP69-F), the colour-mode (11 DMSO-M, 4 DMSO-F, 12 ETP69-M, 5 ETP69-F) and contrast-mode (13 DMSO-M, 5 DMSO-F, 14 ETP69-M, 6 ETP69-F) X-maze, and in the memory retention (13 DMSO-M, 5 DMSO-F, 14 ETP69-M, 5 ETP69-F) and reversal phase (8 DMSO-M, 3 DMSO-F, 9 ETP69-M, 2 ETP69-F) of the Barnes maze. Individual data points are presented with group means ± SEMs. Violin plots display median and lower and upper quartiles. Filled and empty circles represent male and female mice, respectively. # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$, and #### $p < 0.0001$: DMSO-AD^+ versus DMSO-WT mice; * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$: ETP69 versus DMSO mice; by one- or two-way ANOVA followed by Fisher's LSD *post hoc* test.


a
CC layers
I
II/III
IV
V
VI
H3K9me3
b
WT
AD+
DMSO
ETP69
H3K9me3 6E10-Aβ GFAP DAPI
c
WT
AD+
DMSO
ETP69
H3K9me3 GFAP 6E10-Aβ
CA
DG
H3K9me3 DAPI
↑×1.3
*
****
↓36%
↓54%
H3K9me3 IR
50
25
0
D E D E
WT AD+
15
↑×1.5
****
↓42%
80
50
20
D E D E
WT AD+
d
CC
r = -0.48
p = 0.0416
CC
r = 0.72
p = 0.0002
% alternation (contrast X-maze)
75
50
25
0
10
5
0
GFAP IR
30 55 80
4
H3K9me3 IR
Hipp
r = 0.49
p = 0.0299
CC
r = 0.77
p = 0.0053
# errors (retention)
16
8
0
20 95 170
15
H3K9me3 IR
Hipp
r = 0.82
p = 0.0033
CC
r = 0.84
p = 0.0011
6E10-Aβ IR
15
10
5
0
20
10
0
6E10-Aβ IR
20 95 170
15
H3K9me3 IR

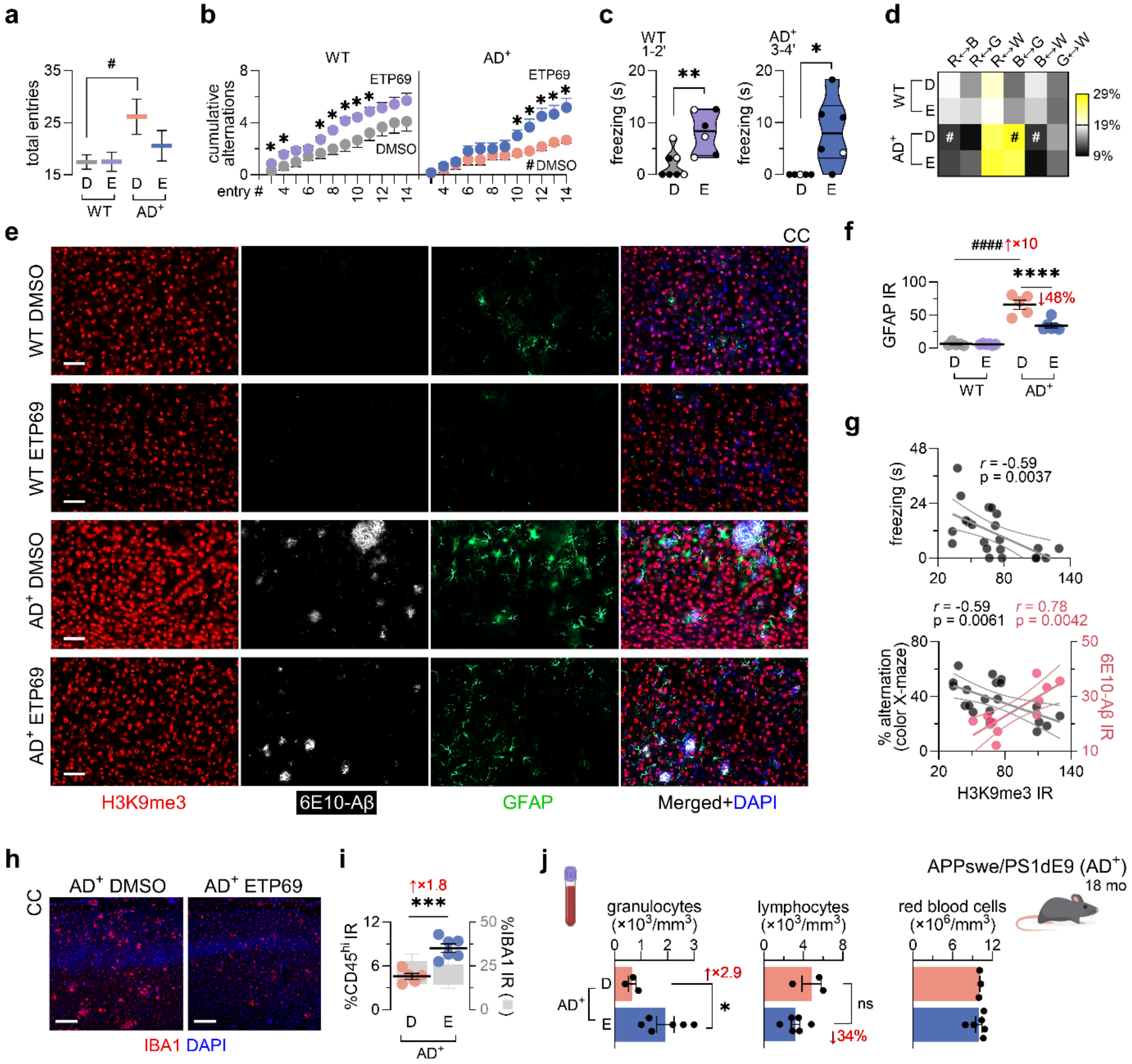
Extended Data Fig. 5. Effects of a single intraperitoneal ETP69 injection on H3K9me3 and AD pathological markers in 18-month-old WT and AD model mice.

(**a**) Immunofluorescence image of H3K9me3 IR in the cerebral cortex showing the region of interest (ROI) for measurements (layers II/III and VI). (**b**) Immunofluorescence images of H3K9me3 (red), 6E10-Aβ plaques (white), GFAP reactive astrocytes (green), and DAPI nuclei (blue) in the cerebral cortex of 18-month-old WT and AD^+ mice after ETP69 or DMSO injection. Scale bar: 100 μm. (**c**) Immunofluorescence images of H3K9me3 (red), 6E10-Aβ (blue) and GFAP (green) in the hippocampus, and quantifications of H3K9me3 IR (% area) in the cornu ammonis (CA) and dentate gyrus (DG) areas 15 days post-ETP69 administration. Scale bars: 200 μm. (**d**) Pearson's correlations of cortical and hippocampal H3K9me3 IR with performance in the contrast-mode X-maze and the Barnes maze, with GFAP IR, and with 6E10-Aβ plaque IR. Black circled numbers represent the end-point day according to the experimental timeline. Individual data points are presented with group means ± SEMs. # $p < 0.05$ and #### $p < 0.0001$: DMSO-AD^+ mice versus DMSO-WT mice; * $p < 0.05$ and **** $p < 0.0001$: ETP69 versus DMSO mice; by one-way ANOVA followed by Fisher's LSD *post hoc* test or two-tailed unpaired Student's t-test.



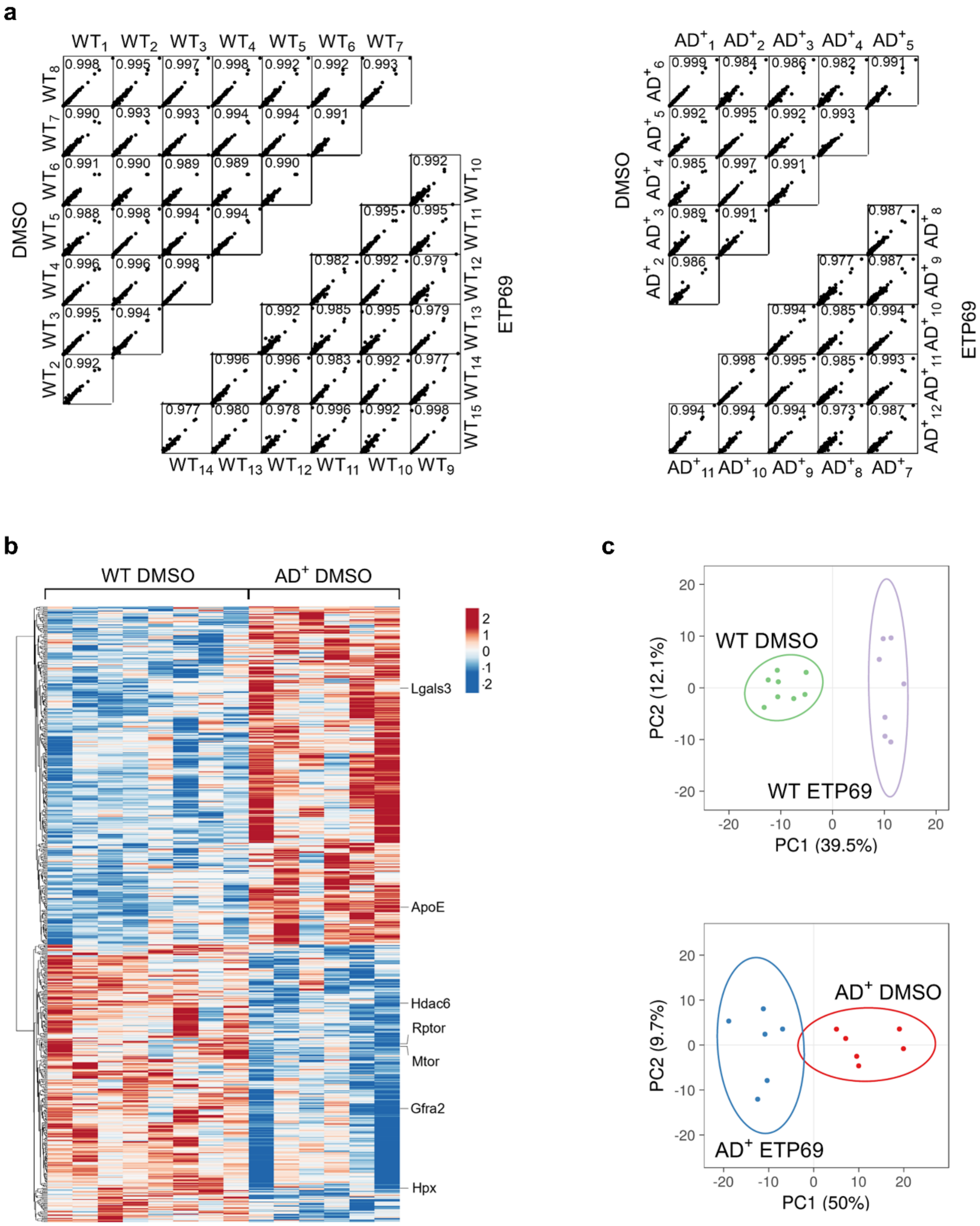
Extended Data Fig. 6. Effects of ETP69 administration on dendritic spine subtypes in 18-month-old AD-model mice.

(**a**) Low- (scale bars: 200 μm) and high-magnification (scale bars: 50 μm) images of Golgi-Cox staining of neurons in the cerebral cortex (CC) and hippocampus (Hipp) of 18-month-old WT mice following i.p. ETP69 (10 mg/kg) or DMSO injection (4 DMSO-WT, 5 ETP69-WT, 3 DMSO-AD^+, 4 ETP69-AD^+). (**b**) Illustration and high-magnification photograph of dendritic spines classified as filopodia-like, long-thin, stubby, or mushroom spines according to size and shape. Scale bar: 10 μm. (**c**) Density of mushroom spines as counts per 100 μm of dendrite in the cerebral cortex (CC) and hippocampus (Hipp). (**d**) Ratios of thin, mushroom, and stubby spines relative to total dendritic spines. Individual data points are presented with group means ± SEMs. Median and lower and upper quartiles are indicated on each violin plot. ## $p < 0.01$: DMSO-AD^+ mice versus DMSO-WT mice; ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$: ETP69 versus DMSO mice; by one-way ANOVA followed by Fisher's LSD *post hoc* test.


a
total entries
35
25
15
#
D
E
D
E
WT
AD+
b
WT
AD+
cumulative alternations
8
4
0
ETP69
DMSO
#DMSO
entry #
4
6
8
10
12
14
c
WT 1-2'
AD+ 3-4'
freezing (s)
20
10
0
**
*
D
E
d
R↔B
R↔G
R↔W
B↔G
B↔W
G↔W
WT
AD+
D
E
#
29%
19%
9%
e
CC
WT DMSO
WT ETP69
AD+ DMSO
AD+ ETP69
H3K9me3
6E10-Aβ
GFAP
Merged+DAPI
f
####↑×10
****
↓48%
GFAP IR
100
50
0
D
E
WT
AD+
g
freezing (s)
48
24
0
r = -0.59
p = 0.0037
20
80
140
r = -0.59
p = 0.0061
r = 0.78
p = 0.0042
% alternation (color X-maze)
80
40
0
6E10-Aβ IR
50
30
10
H3K9me3 IR
h
CC
AD+ DMSO
AD+ ETP69
IBA1 DAPI
i
↑×1.8
***
%CD45hi IR
12
6
0
%IBA1 IR
50
25
0
D
E
AD+
j
APPswe/PS1dE9 (AD+)
18 mo
granulocytes (×10³/mm³)
0
1
2
3
↑×2.9
*
lymphocytes (×10³/mm³)
0
4
8
ns
↓34%
red blood cells (×10⁶/mm³)
0
6
12
AD+
D
E

Extended Data Fig. 7. Therapeutic effects of a single injection of ETP69 in 14-month-old WT and AD model mice.

(**a–d**) Behavioral testing of 14-month-old AD$^+$ mice and age- and sex-matched WT littermates following a single i.p. ETP69 (10 mg/kg) or DMSO injection (10 DMSO-WT, 10 ETP69-WT, 7 DMSO-AD$^+$, 8 ETP69-AD$^+$). (a) Total number of entries (locomotor activity) in the colour-mode X-maze. (b) Cumulative alternations in the X-maze until the mouse reached 14 entries. (c) Freezing times of WT (first 2 minutes) and AD$^+$ (last 2minutes) mice in the contextual fear conditioning test. (d) Percentage of bidirectional transitions between arms in the colour-mode X-maze. (**e**) Immunofluorescence images of H3K9me3 (red), 6E10-Aβ plaques (white), and GFAP reactive astrocytes (green) in the cerebral cortex of 14-month-old WT and AD$^+$ mice, 4 days after a single i.p. ETP69 or DMSO injection. Scale bars: 50 µm. (**f**) Quantitative analysis of GFAP IR ($\mu m^2 \times 10^3$) in the cerebral cortex. (**g**) Pearson's correlations of cortical H3K9me3 levels with performance in the context-specific fear conditioning and the colour-mode X-maze, and with 6E10-Aβ IR. (**h**) Immunofluorescence images of activated microglia (IBA1, red) and DAPI nuclei (blue). Scale bar: 200 µm. (**i**) Quantitative analysis of IBA1 (white, % area) and CD45 (green, % area) near amyloid plaques in the cerebral cortex. Scale bars: 10 µm. 6E10-Aβ plaques (purple). (**j**) Counts of granulocytes, lymphocytes and red blood cells in the blood of 18-month-old AD$^+$ mice administered ETP69 or DMSO. Individual data points are presented with group means ± SEMs. Median and lower and upper quartiles are indicated on each violin plot. # $p < 0.05$ and #### $p < 0.0001$: DMSO-AD$^+$ versus DMSO-WT mice; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$: ETP69 versus DMSO mice; by one- or two-way ANOVA followed by Fisher's LSD *post hoc* test or two-tailed unpaired Student's t-test.


a
WT_1 WT_2 WT_3 WT_4 WT_5 WT_6 WT_7
WT_8 0.998 0.995 0.997 0.998 0.992 0.992 0.993
WT_7 0.990 0.993 0.993 0.994 0.994 0.991
WT_6 0.991 0.990 0.989 0.989 0.990
WT_5 0.988 0.998 0.994 0.994
WT_4 0.996 0.996 0.998
WT_3 0.995 0.994
WT_2 0.992
DMSO
WT_{10} 0.992
WT_{11} 0.995 0.995
WT_{12} 0.982 0.992 0.979
WT_{13} 0.992 0.985 0.995 0.979
WT_{14} 0.996 0.996 0.983 0.992 0.977
WT_{15} 0.977 0.980 0.978 0.996 0.992 0.998
WT_{14} WT_{13} WT_{12} WT_{11} WT_{10} WT_9
ETP69
AD^+_1 AD^+_2 AD^+_3 AD^+_4 AD^+_5
AD^+_6 0.999 0.984 0.986 0.982 0.991
AD^+_5 0.992 0.995 0.992 0.993
AD^+_4 0.985 0.997 0.991
AD^+_3 0.989 0.991
AD^+_2 0.986
DMSO
AD^+_8 0.987
AD^+_9 0.977 0.987
AD^+_{10} 0.994 0.985 0.994
AD^+_{11} 0.998 0.995 0.985 0.993
AD^+_{12} 0.994 0.994 0.994 0.973 0.987
AD^+_{11} AD^+_{10} AD^+_9 AD^+_8 AD^+_7
ETP69
b
WT DMSO
AD^+ DMSO
2
1
0
-1
-2
Lgals3
ApoE
Hdac6
Rptor
Mtor
Gfra2
Hpx
c
WT DMSO
WT ETP69
PC1 (39.5%)
PC2 (12.1%)
-20 -10 0 10 20
20 10 0 -10 -20
AD^+ DMSO
AD^+ ETP69
PC1 (50%)
PC2 (9.7%)
-20 -10 0 10 20
20 10 0 -10 -20

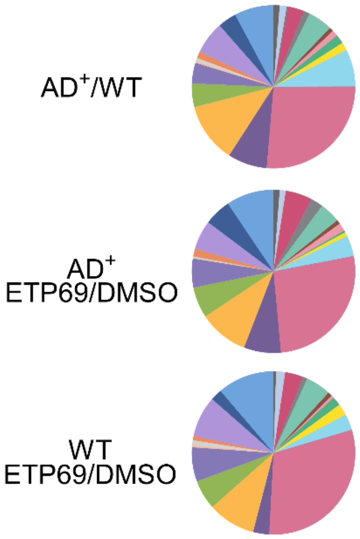
Extended Data Fig. 8. Reproducibility and clustering of mass spectrometry-based proteomics data from 14-month-old WT and AD model mice.

(**a**) Pearson's correlations for all the quantified proteins between animals within each group for WT groups and AD^+ groups. Pearson's coefficients greater than 0.973 between animals from the same group indicate high reproducibility of the MS data. (**b**) Heatmap displaying the hierarchical clustering of all significant DEPs between ETP69-WT and DMSO-WT mice. Blue: downregulated proteins. Red: upregulated proteins. (**c**) Principal component analysis of protein expression profiles in WT mice and AD^+ mice after ETP69 or DMSO treatment. All significant DEPs were included in the analysis (WT mice: 318 proteins, AD^+ mice: 371 proteins).

Extended Data Fig. 9. Select GO terms.

Select GO terms (combination of biological process, cellular compartment, and molecular function terms) displayed as a sunburst chart. GO enrichment analysis of proteins that showed reversal of expression in AD^+ mice after treatment with ETP69. All proteins with a |FC| > 1.04 were included in this analysis. Cell sizes are relative to the total number of proteins for each GO term.

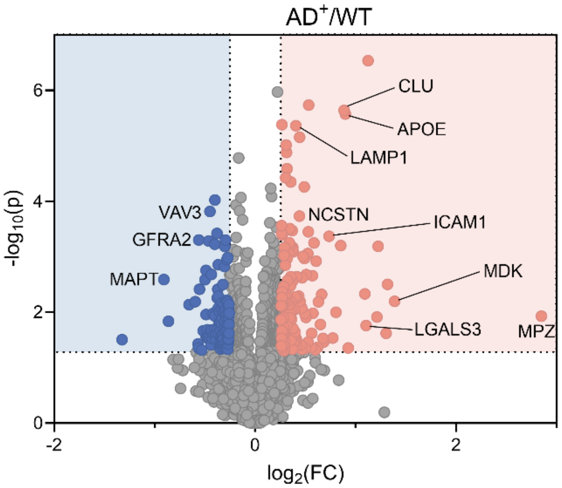
a



		AD$^+$/WT	AD$^+$ ETP69/DMSO	WT ETP69/DMSO
●	metabolite interconversion enzyme	26.5%	26.5%	30.6%
●	protein modifying enzyme	11.9%	9.8%	9.5%
●	nucleic acid metabolism protein	7.8%	7.3%	3.2%
●	transporter	7.8%	9.4%	11.3%
●	membrane traffic protein	7.4%	4.1%	3.2%
●	translational protein	6.4%	5.7%	8.1%
●	cytoskeletal protein	4.9%	4.1%	5.0%
●	protein-binding activity modulator	4.7%	6.1%	5.9%
●	scaffold/adaptor protein	4.1%	5.7%	6.8%
●	transmembrane signal receptor	3.7%	5.3%	2.3%
●	chaperone	3.3%	5.3%	3.6%
●	gene-specific transcriptional regulator	1.8%	0.4%	1.8%
●	intercellular signal molecule	1.6%	0.8%	2.3%
●	cell adhesion molecule	1.4%	1.2%	1.8%
●	transfer/carrier protein	1.4%	1.6%	0.9%
●	calcium-binding protein	1.2%	1.2%	0.5%
●	chromatin/chromatin-binding	1.2%	2.4%	0.9%
●	extracellular matrix protein	1.2%	1.6%	0.5%
●	defense/immunity protein	0.8%	0.8%	0.9%
●	structural protein	0.6%	0.4%	0.9%
●	storage protein	0.4%	-	0.5%
●	cell junction protein	0.2%	-	-

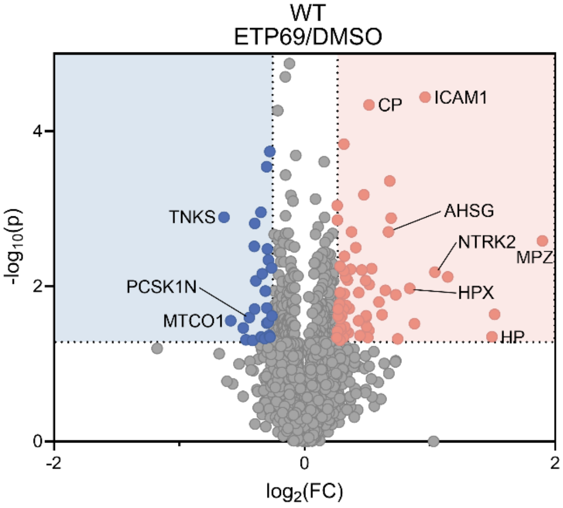
b

Symbol	FC
SLC4A1	-2.50
MAPT	-1.88
MEA1	-1.82
SLC39A7	-1.58
PRPF40A	-1.51
NOP2	-1.48
MTCO1	-1.48
GFRA2	**-1.47**
BCAS2	-1.47
PRKCQ	-1.45
PWWP3A	-1.43
PLCB4	-1.41
ZMAT4	-1.40
CIT	**-1.40**
PDE4A	-1.40
PIK3R3	-1.39
DNM3	-1.39
BCAS1	-1.39
PPP1R9A	-1.38
EFR3A	**-1.38**



Symbol	FC
MPZ	7.20
MDK	2.62
CLSTN3	2.49
GH1	2.47
PDE10A	2.34
CCDC126	2.32
VTN	**2.18**
LGALS3	2.15
AHNAK2	2.13
OLFR703	1.90
APOE	**1.86**
CLU	**1.85**
IFI204	1.80
BORCS5	1.75
VMN2R3	1.71
ICAM1	1.67
RPL14	1.60
SLC6A5	1.60
CRYM	1.58
CNN1	1.57

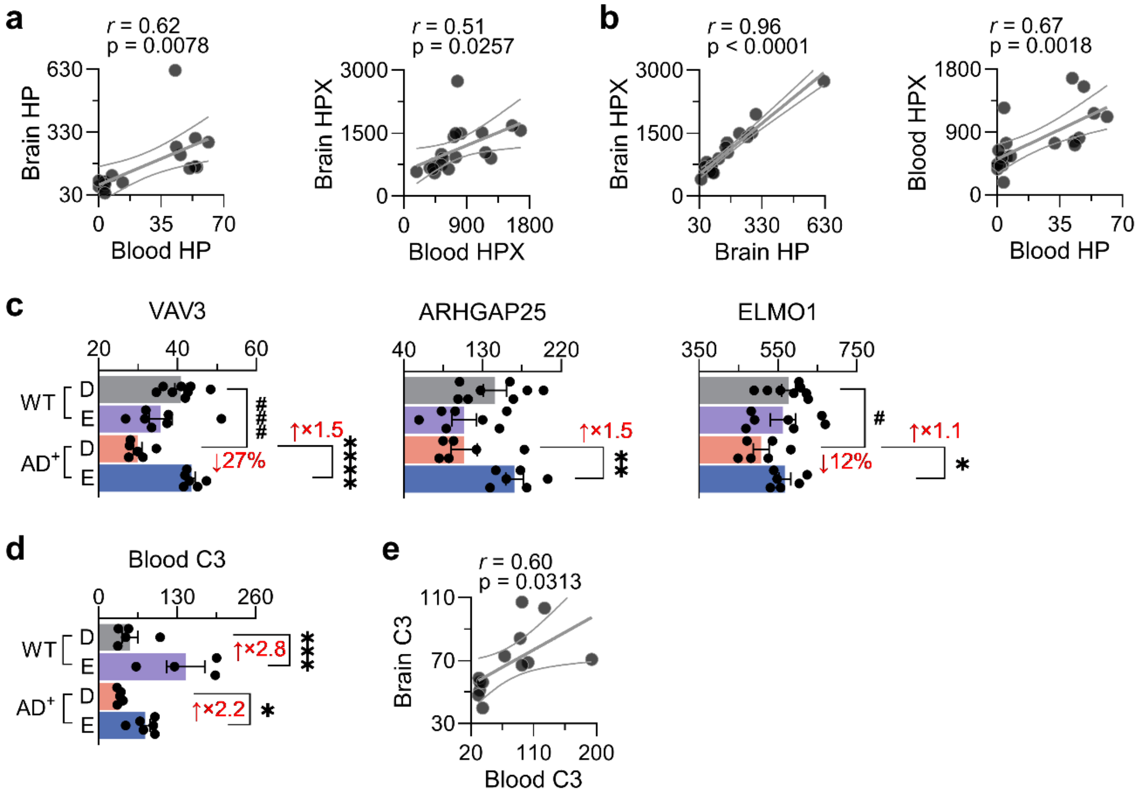
Symbol	FC
TNKS	**-1.56**
MTCO1	-1.50
PRKCQ	-1.40
PAPSS2	-1.38
PCSK1N	-1.36
NLGN4L	-1.33
ZMAT4	-1.32
KCNT1	-1.32
GUF1	-1.32
SLC17A6	-1.31
KCNAB3	**-1.27**
RBM8A	-1.27
PPP1R3G	-1.27
CTBS	-1.26
NUP214	-1.25
PLEKHA1	-1.24
CASK	**-1.23**
BOD1	-1.23
CCDC136	-1.23
SLC38A3	-1.23



Symbol	FC
MPZ	3.73
INTS3	2.86
HP	2.82
AHNAK2	2.21
NTRK2	2.05
ICAM1	**1.95**
FCGR2	1.84
HPX	1.79
MBP	1.67
PDE10a	1.66
PPP1R1B	1.61
H4C1	**1.60**
AHSG	1.59
BORCS5	1.56
CHD7	1.54
CNN1	1.51
BAZ1B	1.45
TLCD3B	1.43
CP	**1.43**
SMC5	1.43

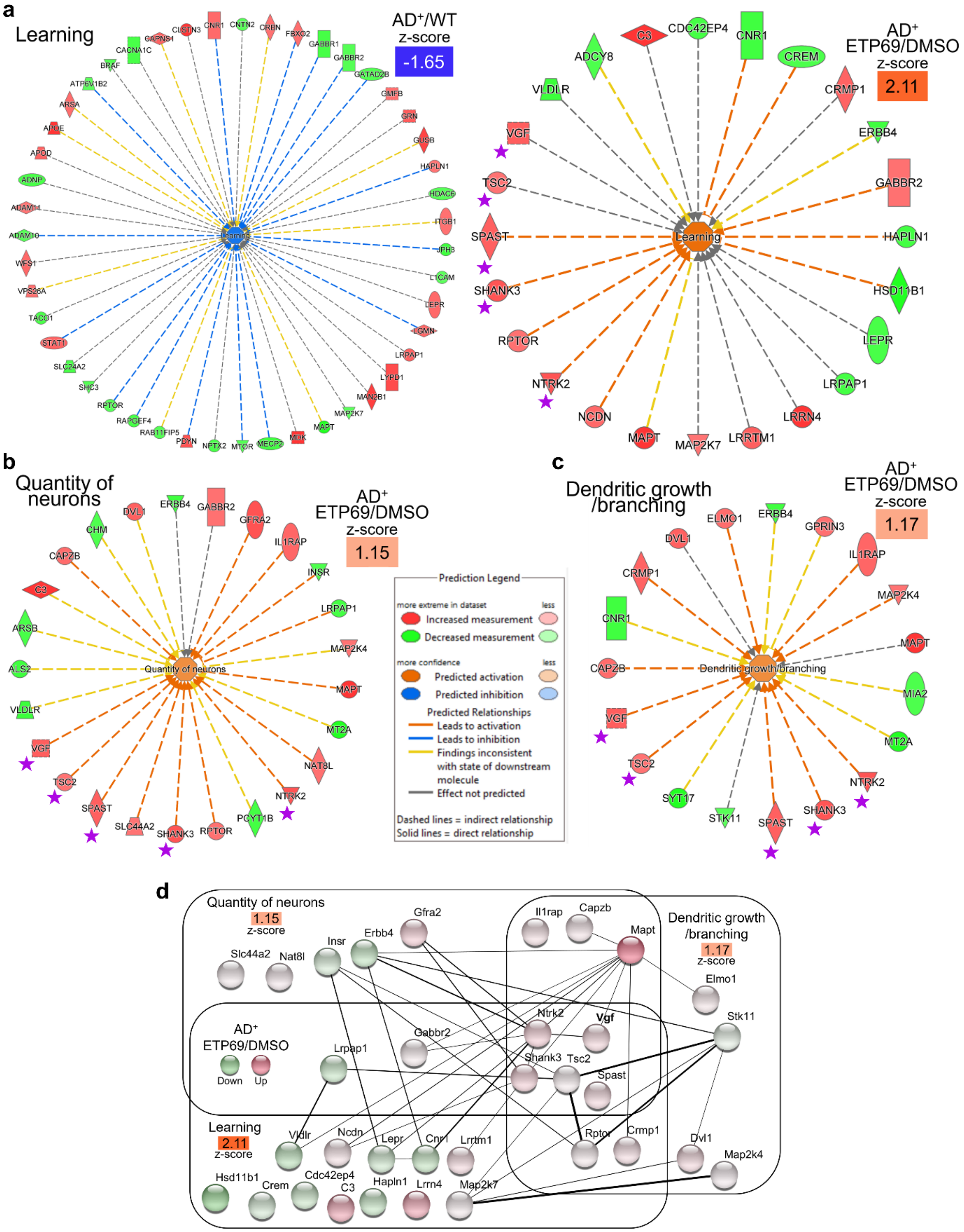
Extended Data Fig. 10. Mass spectrometry-based proteomics analysis of 14-month-old WT and AD-model mice.

(**a**) PANTHER categories for all significant DEPs in AD^+ mice (versus WT mice), and in ETP69 (versus DMSO) AD^+ and WT mice. (**b**) Volcano plots of all DEPs in AD^+ (versus WT) mice and in ETP69 (versus DMSO) WT mice. Red: upregulated proteins ($FC > 1.2$, $p < 0.05$). Blue: downregulated proteins ($FC < -1.2$, $p < 0.05$). The top 20 downregulated and upregulated proteins are listed.



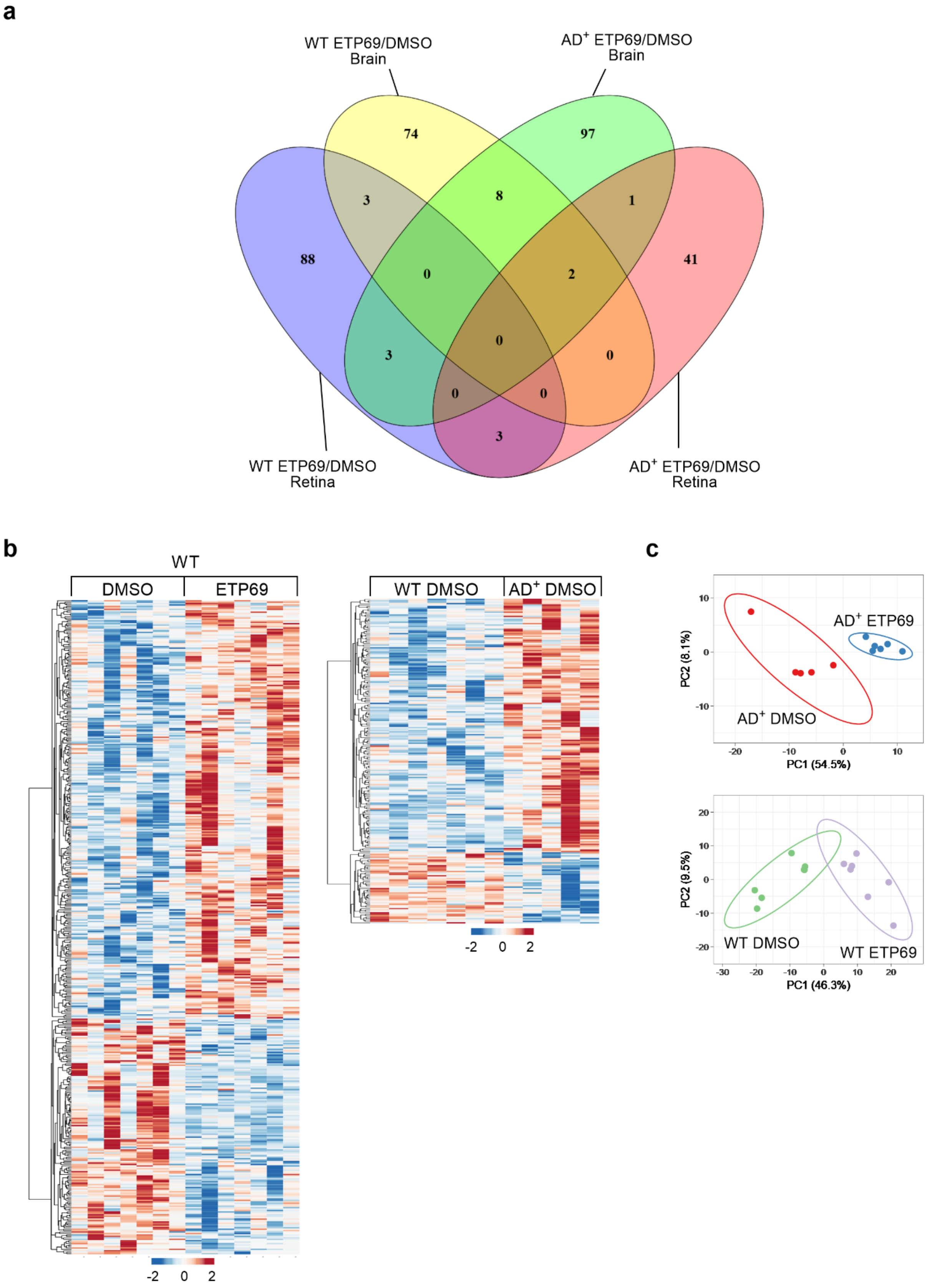
Extended Data Fig. 11. Innate immune response associated with Aβ clearance, microglial phagocytosis, and leukocyte recruitment in WT and AD-model mice.

(**a**–**b**) Pearson's correlations (a) between brain and blood HP and HPX levels, and (b) between HPX and HP levels in the brain and blood. (**c**) Quantifications of VAV3, ARHGAP25 and ELMO1 protein expression by MS in 14-month-old WT and AD$^+$ mice after ETP69 or DMSO administration. (**d**) Quantification of blood C3 levels. (**e**) Pearson's correlation between brain and blood C3 levels. Individual data points are presented with group means ± SEMs. # $p < 0.05$, and ### $p < 0.001$: DMSO-AD$^+$ versus DMSO-WT mice; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$: ETP69 versus DMSO mice; by one-way ANOVA followed by Fisher's LSD *post hoc* test.


a
Learning
AD+/WT
z-score
-1.65
CLSTN3
CNR1
CNTN2
CRBN
CAPNS1
FBXO2
CACNA1C
GABBR1
GABBR2
BRAF
GATAD2B
ATP6V1B2
GMFB
ARSA
GRN
APOE
GUSB
APOD
HAPLN1
ADNP
HDAC6
ADAM11
ITGB1
ADAM10
Learning
JPH3
WFS1
L1CAM
VPS26A
LEPR
TACO1
LGMN
STAT1
LRPAP1
SLC24A2
LYPD1
SHC3
MAN2B1
RPTOR
MAP2K7
RAPGEF4
MAPT
RAB11FIP5
PDYN
NPTX2
MTOR
MECP2
MDK
C3
CDC42EP4
CNR1
AD+
ETP69/DMSO
z-score
2.11
ADCY8
CREM
VLDLR
CRMP1
VGF
ERBB4
TSC2
GABBR2
SPAST
Learning
HAPLN1
SHANK3
HSD11B1
RPTOR
LEPR
NTRK2
LRPAP1
NCDN
LRRN4
MAPT
MAP2K7
LRRTM1
b
Quantity of neurons
AD+
ETP69/DMSO
z-score
1.15
DVL1
ERBB4
GABBR2
GFRA2
CHM
IL1RAP
CAPZB
INSR
C3
LRPAP1
ARSB
MAP2K4
ALS2
Quantity of neurons
MAPT
VLDLR
MT2A
VGF
NAT8L
TSC2
NTRK2
SPAST
PCYT1B
SLC44A2
SHANK3
RPTOR
Prediction Legend
more extreme in dataset
less
Increased measurement
Decreased measurement
more confidence
less
Predicted activation
Predicted inhibition
Predicted Relationships
Leads to activation
Leads to inhibition
Findings inconsistent with state of downstream molecule
Effect not predicted
Dashed lines = indirect relationship
Solid lines = direct relationship
c
Dendritic growth /branching
AD+
ETP69/DMSO
z-score
1.17
ELMO1
ERBB4
DVL1
GPRIN3
IL1RAP
CRMP1
MAP2K4
CNR1
MAPT
CAPZB
Dendritic growth/branching
MIA2
VGF
MT2A
TSC2
NTRK2
SYT17
STK11
SHANK3
SPAST
d
Quantity of neurons
1.15
z-score
Gfra2
Il1rap
Capzb
Dendritic growth /branching
Insr
Erbb4
Mapt
1.17
z-score
Slc44a2
Nat8l
Elmo1
Ntrk2
Vgf
Stk11
AD+
ETP69/DMSO
Gabbr2
Lrpap1
Shank3
Tsc2
Down
Up
Spast
Learning
2.11
z-score
Vldlr
Ncdn
Lepr
Cnr1
Lrrtm1
Rptor
Crmp1
Dvl1
Map2k4
Hsd11b1
Crem
Cdc42ep4
C3
Hapln1
Lrrn4
Map2k7

Extended Data Fig. 12. Mass spectrometry-based proteomics analysis of 14-month-old WT and AD model mice.

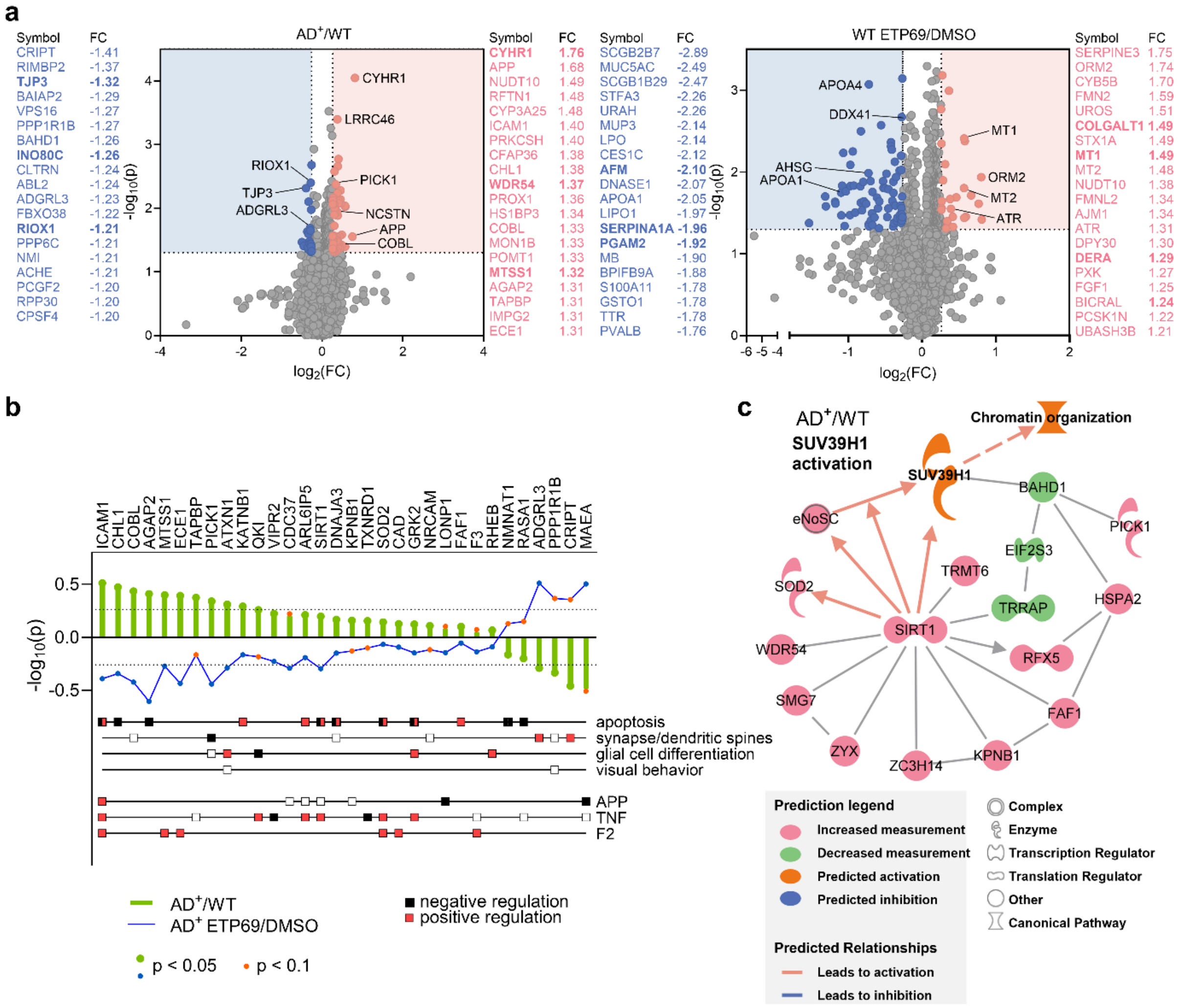
(**a**) Ingenuity Pathway Analysis (IPA) diagrams of DEPs associated with learning in AD^+ mice (versus WT) and in ETP69-AD^+ mice (versus DMSO-AD^+). (**b–c**) IPA diagrams of DEPs in ETP69-AD^+ mice (versus DMSO-AD^+) associated with (b) quantity of neurons and (c) dendritic growth/branching. Purple stars indicate the five overlapping proteins in the three pathways: NTRK2, SHANK3, SPAST, TSC2, and VGF. (**d**) STRING v11.5 protein association network showing overlapping proteins involved in learning, quantity of neurons, and dendritic growth/branching pathways according to IPA. Red nodes: upregulated proteins; green nodes: downregulated proteins. Edge thickness ranges from a medium (0.4) to high-confidence (0.9) protein association.



a
WT ETP69/DMSO Brain
AD$^+$ ETP69/DMSO Brain
WT ETP69/DMSO Retina
AD$^+$ ETP69/DMSO Retina
74
97
3
8
1
88
0
2
41
0
3
0
0
0
3
b
WT
DMSO
ETP69
-2
0
2
WT DMSO
AD$^+$ DMSO
-2
0
2
c
AD$^+$ ETP69
AD$^+$ DMSO
PC2 (8.1%)
PC1 (54.5%)
10
0
-10
-20
-10
0
10
WT DMSO
WT ETP69
PC2 (9.5%)
PC1 (46.3%)
20
10
0
-10
-20
-30
-20
-10
0
10
20

Extended Data Fig. 13. Clustering of mass spectrometry-based proteomics data from retina of 14-month-old WT and AD model mice.

(**a**) Venn diagram showing the minimal overlap of DEPs ($|FC| > 1.2$, $p < 0.05$) between genotypes and between tissues. (**b**) Heatmaps displaying the hierarchical clustering of all significant DEPs between ETP69-WT mice and DMSO-WT mice and between control AD^+ and WT mice. Blue: downregulated proteins. Red: upregulated proteins. (**c**) Principal component analysis of protein expression profiles in AD^+ mice and WT mice after ETP69 or DMSO treatment. All significant DEPs were included in the analysis (WT mice: 452 proteins, AD^+ mice: 152 proteins).



Symbol	FC
CRIPT	-1.41
RIMBP2	-1.37
TJP3	**-1.32**
BAIAP2	-1.29
VPS16	-1.27
PPP1R1B	-1.27
BAHD1	-1.26
INO80C	**-1.26**
CLTRN	-1.24
ABL2	-1.24
ADGRL3	-1.23
FBXO38	-1.22
RIOX1	**-1.21**
PPP6C	-1.21
NMI	-1.21
ACHE	-1.21
PCGF2	-1.20
RPP30	-1.20
CPSF4	-1.20

Symbol	FC
CYHR1	**1.76**
APP	1.68
NUDT10	1.49
RFTN1	1.48
CYP3A25	1.48
ICAM1	1.40
PRKCSH	1.40
CFAP36	1.38
CHL1	1.38
WDR54	**1.37**
PROX1	1.36
HS1BP3	1.34
COBL	1.33
MON1B	1.33
POMT1	1.33
MTSS1	**1.32**
AGAP2	1.31
TAPBP	1.31
IMPG2	1.31
ECE1	1.31

Symbol	FC
SCGB2B7	-2.89
MUC5AC	-2.49
SCGB1B29	-2.47
STFA3	-2.26
URAH	-2.26
MUP3	-2.14
LPO	-2.14
CES1C	-2.12
AFM	**-2.10**
DNASE1	-2.07
APOA1	-2.05
LIPO1	-1.97
SERPINA1A	**-1.96**
PGAM2	**-1.92**
MB	-1.90
BPIFB9A	-1.88
S100A11	-1.78
GSTO1	-1.78
TTR	-1.78
PVALB	-1.76

Symbol	FC
SERPINE3	1.75
ORM2	1.74
CYB5B	1.70
FMN2	1.59
UROS	1.51
COLGALT1	**1.49**
STX1A	1.49
MT1	**1.49**
MT2	1.48
NUDT10	1.38
FMNL2	1.34
AJM1	1.34
ATR	1.31
DPY30	1.30
DERA	**1.29**
PXK	1.27
FGF1	1.25
BICRAL	**1.24**
PCSK1N	1.22
UBASH3B	1.21

Extended Data Fig. 14. Mass spectrometry-based proteomics analysis of retina from 14-month-old WT and AD-model mice.

(**a**) Volcano plots of all DEPs in AD$^+$ mice (versus WT) mice and in ETP69-WT mice (versus DMSO-WT). Red: upregulated proteins (FC > 1.2, $p < 0.05$). Blue: downregulated proteins (FC < -1.2, $p < 0.05$). The top 20 downregulated and upregulated proteins are listed. (**b**) Expression profiles of proteins associated with apoptosis, glial cell differentiation, synapse organization and visual behaviour (upper panel), and with the upstream regulators, APP, TNF and F2 (lower panel), in the retina of AD$^+$ mice (versus WT, green bars) and reversed in ETP69-AD$^+$ mice (versus control AD$^+$, blue line). Dots indicate levels of significance. (**c**) Expression profiles of select first and second neighbours upstream and downstream of SUV39H1 predicting its activation in the retina of 14-month-old AD-model mice, according to IPA.

Extended Data Table 1. Human donor information.

Donor	Diagnosis	Age	Sex	MMSE	CDR	Braak stage	ABC score	Aβ score (A9)	NFT score (A9)	Atrophy score (A9)
#1	CN	81	M	23	0	1.5	2.3	3	0	1
#2	CN	95	F	30	0	5.5	2.7	2.3	0	1
#3	CN	93	F	27	1	3.5	2.7	2.7	0	3
#4	CN	85	F	30	0	1.5	1.7	2.3	0.5	0
#5	CN	99	F	29	0	3	1.3	0.7	0	1
#6	CN	95	M	30	0	1	1	0.7	0	3
#7	MCI	94	F	29	0.5	1.5	1.7	2.3	0	3
#8	MCI	87	F	13	3	5.5	3	3.7	3	3
#9	MCI	88	M	28	3	3	1.7	1	1	1
#10	MCI	85	M	N/A	0.5	1.5	1.3	2	0	0
#11	MCI	89	F	24	0.5	3.5	1.7	0.5	0.5	1
#12	MCI	98	F	15	2	5	2.3	3	3	3
#13	MCI	97	M	28	1	5	2.7	2.3	1	0
#14	AD	88	M	16	1	5.5	3	5	1	1
#15	AD	93	F	20	3	3.5	2.3	1	0	3
#16	AD	86	F	18	3	5.5	2.7	5	1	5
#17	AD	93	F	17	3	3.5	2	3	0	1
#18	AD	90	F	N/A	3	5.5	3	4.3	1	3
#19	AD	81	M	12	3	5	3	5	5	5
#20	AD	90	M	N/A	3	6	3	5	3	1
#21	AD	77	M	18	2	6	3	5	3	1
#22	AD	66	F	2	3	6	3	5	5	5
#23	AD	88	M	18	1	5.5	2.3	N/A	N/A	1
#24	AD	100	F	16	2	5.5	2.7	1.7	1	3
#25	AD	70	F	24	0.5	5	3	N/A	N/A	N/A
#26	AD	90	M	18	2	5	2.7	2	0	1

CN—cognitively normal, MCI—mild cognitive impairment, AD—Alzheimer's disease. Age at death in years. M—male, F—female. MMSE—mini mental state examination. CDR—clinical dementia rating: 0—normal cognition, 1—mild dementia, 2—moderate dementia, 3—severe dementia. ABC score: A—Aβ plaque score modified from Thal, B—NFT stage modified from Braak, C—Neuritic plaque score modified from CERAD. Aβ, NFT and atrophy severity scores: 0—none, 1—sparse, 3—moderate, 5—frequent. A9—Brodmann area A9, dorsolateral prefrontal cortex. N/A—not available.

Extended Data Table 2. Significant brain DEPs upregulated in ETP69-AD$^+$ versus DMSO-AD$^+$ mice.

Accession	Symbol	Description	ETP69-AD$^+$ (Mean)	DMSO-AD$^+$ (Mean)	FC	p-value
Q61646	HP	Haptoglobin	208.9	68.3	3.06	0.0170
P10637-3	MAPT	Isoform Tau-B of Microtubule-associated protein tau	54.3	22.9	2.37	0.0188
Q91X72	HPX	Hemopexin	1366.3	589.2	2.32	0.00003
Q9JJV4	CACNG4	Voltage-dependent calcium channel gamma-4 subunit	18.1	9.5	1.91	0.0097
P59383	LRRN4	Leucine-rich repeat neuronal protein 4	237.0	136.7	1.73	0.0149
P01027	C3	Complement C3	81.6	47.7	1.71	0.0265
Q80TT2	BAIAP3	BAI1-associated protein 3	308.9	184.3	1.68	0.0243
O88492	PLIN4	Perilipin-4	600.8	368.1	1.63	0.0047
Q8BYW1	ARHGAP25	Rho GTPase-activating protein 25	165.1	104.7	1.58	0.0098
Q9DBD0	ICA	Inhibitor of carbonic anhydrase	235.4	149.4	1.58	0.0279
Q61838	PZP	Pregnancy zone protein	203.3	130.0	1.56	0.0240
A2ALK8	PTPN3	Tyrosine-protein phosphatase non-receptor type 3	68.2	43.7	1.56	0.0007
A0A1Y7VNZ6	MARK3	Non-specific serine/threonine protein kinase	101.9	65.5	1.56	0.0252
Q9JLR1	SEC61A2	Protein transport protein Sec61 subunit alpha isoform 2	30.2	19.6	1.54	0.0018
Q8C0P5	CORO2A	Coronin-2A	786.1	511.3	1.54	0.00003
Q64327	MEA1	Male-enhanced antigen 1	61.3	40.2	1.52	0.0474
Q9R0C8	VAV3	Guanine nucleotide exchange factor VAV3	43.5	29.8	1.46	0.000002
E9PV24	FGA	Fibrinogen alpha chain	78.6	54.5	1.44	0.0172
Q9Z321	TOP3B	DNA topoisomerase 3-beta-1	33.3	23.6	1.41	0.0057
P49025	CIT	Citron Rho-interacting kinase	2563.9	1817.5	1.41	0.0023
Q9R1C7	PRPF40A	Pre-mRNA-processing factor 40 homolog A	119.9	85.4	1.40	0.0338
Q9D2G5	SYNJ2	Synaptojanin-2	267.4	192.1	1.39	0.0260
Q8CEI3	CCDC28A	Coiled-coil domain-containing 28A	32.4	23.3	1.39	0.0159

P19258	MPV17	Protein Mpv17	25.1	18.3	1.37	0.0173
Q3TVA9	CCDC136	Coiled-coil domain-containing protein 136	365.2	271.8	1.34	0.0021
O70496	CLCN7	H(+)/Cl(-) exchange transporter 7	30.8	23.1	1.33	0.0100
Q8BZR9	NCBP3	Nuclear cap-binding protein subunit 3	21.3	16.0	1.33	0.0006
Q9R0N8	SYT6	Synaptotagmin-6	36.4	27.5	1.33	0.0070
O08842	GFRA2	GDNF family receptor alpha-2	350.3	264.3	1.33	0.0056
P15209	NTRK2	BDNF/NT-3 growth factors receptor	96.5	73.4	1.32	0.0287
P70170-2	ABCC9	Isoform SUR2B of ATP-binding cassette sub-family C member 9	112.0	85.4	1.31	0.0174
P08101	FCGR2	Low affinity immunoglobulin gamma Fc region receptor II	18.6	14.3	1.31	0.0216
Q4ACU6	SHANK3	SH3 and multiple ankyrin repeat domains protein 3	1954.7	1497.0	1.31	0.0459
Q9DB72	BTBD17	BTB/POZ domain-containing protein 17	667.2	511.8	1.30	0.0014
P58058	NADK	NAD kinase	32.5	25.0	1.30	0.0204
Q64343	ABCG1	ATP-binding cassette sub-family G member 1	31.7	24.4	1.30	0.0052
Q6PEE2	CTIF	Isoform 2 of CBP80/20-dependent translation initiation factor	65.6	50.8	1.29	0.0494
O08677	KNG1	Kininogen-1	55.0	42.5	1.29	0.0476
Q8BIE6-2	FRMD4A	Isoform 2 of FERM domain-containing protein 4A	64.3	49.8	1.29	0.0426
P62311	LSM3	U6 snRNA-associated Sm-like protein LSm3	69.1	53.8	1.29	0.0202
Q9JLQ0	CD2AP	CD2-associated protein	87.2	67.9	1.28	0.0476
P13597	ICAM1	Intercellular adhesion molecule 1	19.9	15.5	1.28	0.0269
P47743	GRM8	Metabotropic glutamate receptor 8	46.6	36.6	1.28	0.0116
P06909	CFH	Complement factor H	145.1	113.7	1.28	0.0002
F7AA26	PAKAP	Paralemmin A kinase anchor protein (Fragment)	695.3	548.4	1.27	0.0277
O89084	PDE4A	cAMP-specific 3',5'-cyclic phosphodiesterase 4A	137.5	109.0	1.26	0.0437
A2AAE1-2	BLTP1	Isoform 2 of Transmembrane protein KIAA1109	141.1	112.0	1.26	0.0150
Q8BWP8	B4GAT1	Beta-1,4-glucuronyltransferase 1	44.8	35.7	1.26	0.0205

O88196	TTC3	E3 ubiquitin-protein ligase TTC3	22.4	17.8	1.25	0.0103
Q9JIK5	DDX21	Nucleolar RNA helicase 2	47.9	38.4	1.25	0.0204
P39098	MAN1A2	Mannosyl-oligosaccharide 1,2-alpha-mannosidase IB	111.8	90.1	1.24	0.0073
Q0VGU4	VGF	Neurosecretory protein VGF	759.1	613.5	1.24	0.0417
Q91X58	ZFAND2B	AN1-type zinc finger protein 2B	56.6	45.9	1.23	0.0220
Q8K377	LRRTM1	Leucine-rich repeat transmembrane neuronal protein 1	176.2	143.3	1.23	0.0074
P51141	DVL1	Segment polarity protein dishevelled homolog DVL-1	33.7	27.5	1.23	0.0364
Q922J6	TSPAN2	Tetraspanin-2	525.5	429.1	1.22	0.0077
Q9ER47	KCNH7	Potassium voltage-gated channel subfamily H member 7	59.4	48.5	1.22	0.0236
Q6P5D3	DHX57	Putative ATP-dependent RNA helicase DHX57	75.6	61.9	1.22	0.0251
Q9QYY8	SPAST	Spastin	137.5	112.6	1.22	0.0298
Q91UZ1	PLCB4	1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase	909.2	745.0	1.22	0.0345
Q9JI39	ABCB10	ATP-binding cassette sub-family B member 10, mitochondrial	216.2	177.2	1.22	0.0309
Q8BHL3	TBC1D10B	TBC1 domain family member 10B	656.6	540.0	1.22	0.0305
Q8VHE0	SEC63	Translocation protein SEC63 homolog	112.8	92.9	1.22	0.0105
Q7TPV4	MYBBP1A	Myb-binding protein 1A	39.2	32.3	1.21	0.0363
Q9Z2C5	MTM1	Myotubularin	37.9	31.2	1.21	0.0073
Q8VBY2	CAMKK1	Calcium/calmodulin-dependent protein kinase kinase 1	1245.2	1026.4	1.21	0.0064
P63056	OLFM3	Noelin-3	158.4	130.7	1.21	0.0206
Q6P542	ABCF1	ATP-binding cassette sub-family F member 1	765.0	632.1	1.21	0.0051
Q70IV5	SYNM	Synemin	230.8	190.9	1.21	0.0229
Q9R049-2	AMFR	Isoform 2 of E3 ubiquitin-protein ligase AMFR	38.9	32.2	1.21	0.0320
Q9Z2B2	SLC25A14	Brain mitochondrial carrier protein 1	121.6	100.6	1.21	0.0196
Q921T2	TOR1AIP1	Torsin-1A-interacting protein 1	51.1	42.4	1.21	0.0305
Q922P8	TMEM132A	Transmembrane protein 132A	31.6	26.3	1.20	0.0393

Q8BJL0	SMARCAL1	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1	60.2	50.2	1.20	0.0191
Q6P1J1	CRMP1	Crmp1 protein	536.7	448.4	1.20	0.0440

FC, fold change. DEPs are defined as |FC| > 1.20 and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 3. Significant brain DEPs downregulated in ETP69-AD$^+$ versus DMSO-AD$^+$ mice.

Accession	Symbol	Description	ETP69-AD$^+$ (Mean)	DMSO-AD$^+$ (Mean)	FC	p-value
Q64518	ATP2A3	Sarcoplasmic/endoplasmic reticulum calcium ATPase 3	122.0	222.1	-1.82	0.0308
P02802	MT1	Metallothionein-1	903.6	1424.7	-1.58	0.0123
P02798	MT2	Metallothionein-2	246.2	364.1	-1.48	0.0189
Q920M7	SYT17	Synaptotagmin-17	56.6	81.4	-1.44	0.0212
A2AQ89	SHF	SH2 domain-containing adapter protein F (Fragment)	48.6	69.3	-1.43	0.0003
Q7TMW6-2	CIAO3	Isoform 2 of Cytosolic iron-sulfur assembly component 3	15.9	22.5	-1.42	0.0130
P50172	HSD11B1	Corticosteroid 11-beta-dehydrogenase isozyme 1	108.8	153.8	-1.41	0.0136
Q61001	LAMA5	Laminin subunit alpha-5	37.8	53.0	-1.40	0.0370
A0A5F8MPE1	EPB41L3	Band 4.1-like protein 3	343.6	481.5	-1.40	0.0449
P55065	PLTP	Phospholipid transfer protein	30.6	42.5	-1.39	0.0242
O55186	CD59A	CD59A glycoprotein	19.2	26.1	-1.36	0.0454
D3YZS5	TARBP2	RISC-loading complex subunit TARBP2 (Fragment)	102.6	138.9	-1.35	0.0281
Q8VHG2	AMOT	Angiomotin	40.2	54.1	-1.35	0.0304
P28667	MARCKSL1	MARCKS-related protein	1612.9	2169.0	-1.34	0.0381
Q8K1S4	UNC5A	Netrin receptor UNC5A	106.8	141.9	-1.33	0.0093
Q8CA72	GAN	Gigaxonin	15.8	20.8	-1.32	0.0403
P11930	NUDT19	Nucleoside diphosphate-linked moiety X motif 19	15.7	20.2	-1.29	0.0160
Q61599	ARHGDIB	Rho GDP-dissociation inhibitor 2	173.6	223.2	-1.29	0.0042
Q6PCN7	HLTF	Helicase-like transcription factor	117.8	149.3	-1.27	0.0183
Q3UNH4	GPRIN1	G protein-regulated inducer of neurite outgrowth 1	11457.6	14474.5	-1.26	0.0136
Q9CYI0	NJMU-R1	Protein Njmu-R1	27.0	33.8	-1.25	0.0278
Q64522	H2AC21	Histone H2A type 2-B	91.6	114.4	-1.25	0.0195

P07356	ANXA2	Annexin A2	2041.7	2546.9	-1.25	0.0276
P62911	RPL32	60S ribosomal protein L32	900.4	1111.8	-1.23	0.0040
P30681	HMGB2	High mobility group protein B2	135.8	167.6	-1.23	0.0140
P98156	VLDLR	Very low-density lipoprotein receptor	56.4	69.1	-1.23	0.0006
Q8BH27	MEGF9	Multiple epidermal growth factor-like domains protein 9	138.2	169.3	-1.22	0.0335
Q9Z2X1	HNRNPF	Heterogeneous nuclear ribonucleoprotein F	156.5	190.6	-1.22	0.0348
P16045	LGALS1	Galectin-1	757.4	922.5	-1.22	0.0474
Q920R0	ALS2	Alsin	503.2	609.9	-1.21	0.0016
Q5SQF8	SAP30L	Histone deacetylase complex subunit SAP30L	41.5	50.1	-1.21	0.0142
Q9D7V9	NAAA	N-acylethanolamine-hydrolyzing acid amidase	128.0	154.3	-1.21	0.0246
Q9D0J8	PTMS	Parathymosin	884.2	1065.4	-1.20	0.0051
P56383	ATP5MC2	ATP synthase F(0) complex subunit C2, mitochondrial	4264.7	5129.8	-1.20	0.0191
Q61527	ERBB4	Receptor tyrosine-protein kinase erbB-4	92.4	110.6	-1.20	0.0147
P47746	CNR1	Cannabinoid receptor 1	1056.8	1264.2	-1.20	0.0123

FC, fold change. DEPs are defined as $|FC| > 1.20$ and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 4. Significant brain DEPs upregulated in DMSO-AD$^+$ versus DMSO-WT mice.

Accession	**Symbol**	**Description**	**DMSO-AD$^+$ (Mean)**	**DMSO-WT (Mean)**	**FC**	**p-value**
A0A5F8MPM4	MPZ	Myelin protein P0	88.3	12.3	7.20	0.0118
P12025	MDK	Midkine	57.3	21.9	2.62	0.0064
Q99JH7	CLSTN3	Calsyntenin-3	179.7	72.1	2.49	0.0031
P06880	GH1	Somatotropin	1043.9	423.0	2.47	0.0239
Q8CA95	PDE10A	Isoform 3 of cAMP and cAMP-inhibited cGMP 3',5'-cyclic phosphodiesterase 10A	637.9	273.0	2.34	0.0006
Q8BIS8	CCDC126	Coiled-coil domain-containing protein 126	617.9	266.8	2.32	0.0122
P29788	VTN	Vitronectin	317.1	145.5	2.18	0.0000003
P16110	LGALS3	Galectin-3	67.0	31.1	2.15	0.0173
F7DBB3	AHNAK2	AHNAK nucleoprotein 2	1566.9	734.9	2.13	0.0047
Q9EPF5	OLFR703	Olfactory receptor 703	1105.1	581.7	1.90	0.0441
P08226	APOE	Apolipoprotein E	8567.1	4595.1	1.86	0.000003
Q06890	CLU	Clusterin	2718.7	1471.3	1.85	0.000002
P0DOV2	IFI204	Interferon-activable protein 204	36.3	20.1	1.80	0.0006
Q9D920	BORCS5	BLOC-1-related complex subunit 5	16.7	9.6	1.75	0.0100
H3BJ88	VMN2R3	Vomeronasal 2, receptor 3	134.9	79.0	1.71	0.0292
P13597	ICAM1	Intercellular adhesion molecule 1	15.5	9.3	1.67	0.0004
Q9CR57	RPL14	60S ribosomal protein L14	1008.2	628.2	1.60	0.0342
Q761V0	SLC6A5	Sodium- and chloride-dependent glycine transporter 2	595.9	373.1	1.60	0.0295
O54983	CRYM	Ketimine reductase mu-crystallin	5718.3	3616.2	1.58	0.0048
Q08091	CNN1	Calponin-1	59.3	37.8	1.57	0.0166
P01029	C4B	Complement C4-B	85.8	55.5	1.55	0.0065

Q61001	LAMA5	Laminin subunit alpha-5	53.0	34.5	1.54	0.0430
Q99LB4	CAPG	Capping protein (Actin filament), gelsolin-like	192.0	126.0	1.52	0.0012
P08101	FCGR2	Low affinity immunoglobulin gamma Fc region receptor II	14.3	9.4	1.51	0.0473
Q9D3X9	MFAP3L	Microfibrillar-associated protein 3-like	47.8	31.9	1.50	0.0006
P26883	FKBP1A	Peptidyl-prolyl cis-trans isomerase FKBP1A	1308.5	878.5	1.49	0.0105
O09159	MAN2B1	Lysosomal alpha-mannosidase	137.0	92.2	1.48	0.0022
Q62422	OSTF1	Osteoclast-stimulating factor 1	92.0	62.3	1.48	0.0240
Q8K1X1	WDR11	WD repeat-containing protein 11	130.5	88.5	1.47	0.0430
P17897	LYZ1	Lysozyme C-1	128.4	88.8	1.45	0.000002
P12265	GUSB	Beta-glucuronidase	53.6	37.1	1.44	0.0004
P62878	RBX1	E3 ubiquitin-protein ligase RBX1	371.4	258.2	1.44	0.0346
Q9CYI0	NJMU-R1	Protein Njmu-R1	33.8	23.5	1.44	0.0009
Q6AXF6	SIDT1	SID1 transmembrane family member 1	95.2	66.9	1.42	0.0021
Q9D1J1	NECAP2	Adaptin ear-binding coat-associated protein 2	46.6	32.8	1.42	0.0124
Q9JI11	STK4	Serine/threonine-protein kinase 4	220.4	155.7	1.42	0.0450
P02802	MT1	Metallothionein-1	1424.7	1012.0	1.41	0.0105
P35969	FLT1	Vascular endothelial growth factor receptor 1	987.7	703.4	1.40	0.0011
Q8BH64	EHD2	EH domain-containing protein 2	145.1	103.4	1.40	0.0001
Q922S4	PDE2A	cGMP-dependent 3',5'-cyclic phosphodiesterase	6259.1	4500.7	1.39	0.0010
P07356	ANXA2	Annexin A2	2546.9	1842.1	1.38	0.0024
Q8BLC3	LYPD1	Ly6/PLAUR domain-containing protein 1	32.2	23.3	1.38	0.0468
P28063	PSMB8	Proteasome subunit beta type-8	52.1	37.8	1.38	0.0084
Q8BGZ1	HPCAL4	Hippocalcin-like protein 4	1572.7	1147.4	1.37	0.0391
P49710	HCLS1	Hematopoietic lineage cell-specific protein	147.2	108.1	1.36	0.0063
Q9WUU7	CTSZ	Cathepsin Z	1123.4	826.9	1.36	0.00001
P57716	NCSTN	Nicastrin	77.7	57.2	1.36	0.0002

O08992	SDCBP	Syntenin-1	643.2	475.9	1.35	0.0051
Q8CA71	SHISA4	Protein shisa-4	87.2	65.4	1.33	0.0390
A2TJV2	PALM3	Paralemmin-3	75.3	56.5	1.33	0.0023
Q3TBL6	TNFAIP8L3	Tumor necrosis factor alpha-induced protein 8-like protein 3	149.3	112.1	1.33	0.0055
O35417	PDYN	Proenkephalin-B	115.5	87.0	1.33	0.0302
Q8R143	PTTG1IP	Pituitary tumor-transforming gene 1 protein-interacting protein	44.7	33.7	1.32	0.0329
P11438	LAMP1	Lysosome-associated membrane glycoprotein 1	454.9	343.5	1.32	0.000004
Q920M7	SYT17	Synaptotagmin-17	81.4	61.8	1.32	0.0347
Q61599	ARHGDIB	Rho GDP-dissociation inhibitor 2	223.2	169.4	1.32	0.0052
Q9R1J0	NSDHL	Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating	55.4	42.1	1.32	0.0227
P50285	FMO1	Dimethylaniline monooxygenase [N-oxide-forming] 1	32.2	24.6	1.31	0.0091
Q64669	NQO1	NAD(P)H dehydrogenase [quinone] 1	477.7	366.2	1.30	0.0362
Q5U5V2	HYKK	Hydroxylysine kinase	83.5	64.2	1.30	0.0008
P59108	CPNE2	Copine-2	94.9	73.1	1.30	0.0194
E9Q236	ABCC4	ATP-binding cassette, sub-family C (CFTR/MRP), member 4	47.5	36.7	1.30	0.0007
P11835	ITGB2	Integrin beta-2	320.1	247.3	1.29	0.0007
Q920R0	ALS2	Alsin	609.9	471.3	1.29	0.0028
F7BX42	NPTXR	Neuronal pentraxin receptor	977.5	756.5	1.29	0.0465
Q9CQE1	NIPSNAP3B	Protein NipSnap homolog 3B	917.7	710.9	1.29	0.0003
P61514	RPL37A	60S ribosomal protein L37a	1581.0	1231.1	1.28	0.0095
P14069	S100A6	Protein S100-A6	236.5	184.2	1.28	0.0134
Q8VHC3	SELENOM	Selenoprotein M	113.8	88.9	1.28	0.0320
Q8K215	LYRM4	LYR motif-containing protein 4	118.9	92.9	1.28	0.0064
Q9DCJ9	NPL	N-acetylneuraminate lyase	417.0	326.1	1.28	0.0023
Q9D379	EPHX1	Epoxide hydrolase 1	1050.9	821.7	1.28	0.00004
P20060	HEXB	Beta-hexosaminidase subunit beta	2214.4	1735.4	1.28	0.0033

Q9WV32	ARPC1B	Actin-related protein 2/3 complex subunit 1B	197.7	155.5	1.27	0.0003
Q8R4V2	DUSP15	Dual specificity protein phosphatase 15	235.8	185.7	1.27	0.0106
Q91WG7	DGKG	Diacylglycerol kinase gamma	913.2	719.4	1.27	0.0126
P97372	PSME2	Proteasome activator complex subunit 2	392.5	309.5	1.27	0.0006
P29416	HEXA	Beta-hexosaminidase subunit alpha	296.8	234.4	1.27	0.0006
P28798	GRN	Progranulin	432.6	342.8	1.26	0.0072
P05555	ITGAM	Integrin alpha-M	112.6	89.2	1.26	0.0009
E9PWM3	ARMCX4	Armadillo repeat-containing, X-linked 4	37.8	30.0	1.26	0.0073
O09114	PTGDS	Prostaglandin-H2 D-isomerase	3129.0	2502.0	1.25	0.0027
P70202	LXN	Latexin	1467.7	1175.4	1.25	0.0063
P01887	B2M	Beta-2-microglobulin	78.8	63.2	1.25	0.0011
P34914	EPHX2	Bifunctional epoxide hydrolase 2	929.5	745.9	1.25	0.00003
Q61809	LRRN1	Leucine-rich repeat neuronal protein 1	40.7	32.7	1.24	0.0176
Q8VHL0	SLC14A1	Isoform 2 of Urea transporter 1	186.9	150.5	1.24	0.0049
Q920E5	FDPS	Farnesyl pyrophosphate synthase	1421.0	1144.0	1.24	0.00001
O70456	SFN	14-3-3 protein sigma	5979.5	4826.4	1.24	0.00001
P18242	CTSD	Cathepsin D	2309.0	1870.9	1.23	0.00004
Q9ERE7	MESD	LRP chaperone MESD	777.7	631.6	1.23	0.0014
A3KFX0	NT5C1A	Cytosolic 5'-nucleotidase 1A	141.6	115.3	1.23	0.0061
P51880	FABP7	Fatty acid-binding protein, brain	687.0	560.8	1.23	0.0398
P55302	LRPAP1	Alpha-2-macroglobulin receptor-associated protein	1658.8	1354.8	1.22	0.0051
Q8C7K6	PCYOX1L	Prenylcysteine oxidase-like	445.2	363.6	1.22	0.0007
Q3SXD3	HDDC2	5'-deoxynucleotidase HDDC2	37.9	31.0	1.22	0.0338
Q920P5	AK5	Adenylate kinase isoenzyme 5	1694.7	1386.6	1.22	0.0492
Q9QZ08	NAGK	N-acetyl-D-glucosamine kinase	188.6	154.5	1.22	0.0009

Q91XE4	ACY3	N-acyl-aromatic-L-amino acid amidohydrolase (carboxylate-forming)	101.1	82.8	1.22	0.0218
Q76LS9	MINDY1	Ubiquitin carboxyl-terminal hydrolase MINDY-1	563.1	461.5	1.22	0.0260
Q3UNZ8	CRYZL2	Quinone oxidoreductase-like protein 2	632.9	519.3	1.22	0.0383
O70370	CTSS	Cathepsin S	33.5	27.5	1.22	0.0035
Q9DBG5	PLIN3	Perilipin-3	753.3	618.9	1.22	0.0401
Q9WTR5	CDH13	Cadherin-13	1817.9	1495.2	1.22	0.0488
P59672	ANKS1A	Isoform 2 of Ankyrin repeat and SAM domain-containing protein 1A	44.8	36.9	1.22	0.0184
Q9DBL2	GDAP2	Isoform 2 of Ganglioside-induced differentiation-associated protein 2	84.2	69.4	1.21	0.0125
Q6NS52	DGKB	Diacylglycerol kinase beta	1989.4	1643.7	1.21	0.0074
Q8R1B5	CPLX3	Complexin-3	382.4	316.0	1.21	0.0079
Q61112	SDF4	45 kDa calcium-binding protein	193.5	160.1	1.21	0.0057
Q8R1I1	UQCR10	Cytochrome b-c1 complex subunit 9	317.0	262.4	1.21	0.0266
E9QA16	CALD1	Caldesmon 1	126.3	104.7	1.21	0.0438
Q60854	SERPINB6	Serpin B6	3524.7	2922.2	1.21	0.0043
Q00915	RBP1	Retinol-binding protein 1	944.5	783.3	1.21	0.0004
Q91W43	GLDC	Glycine dehydrogenase (decarboxylating), mitochondrial	297.3	246.8	1.20	0.0258
O88456	CAPNS1	Calpain small subunit 1	723.1	600.9	1.20	0.0054
P51910	APOD	Apolipoprotein D	824.1	685.1	1.20	0.000004
P97352	S100A13	Protein S100-A13	1349.9	1122.5	1.20	0.0217
Q9D328	TMEM35A	Transmembrane protein 35A	412.7	343.4	1.20	0.0078
Q8BR86	KIRREL3	Kin of IRRE-like protein 3	76.9	64.1	1.20	0.0296
Q920A5	SCPEP1	Retinoid-inducible serine carboxypeptidase	226.5	188.8	1.20	0.0004
Q08274	DMWD	Dystrophia myotonica WD repeat-containing protein	152.4	127.0	1.20	0.0003

P10639	TXN	Thioredoxin	3364.4	2808.7	1.20	0.0403
P42225	STAT1	Signal transducer and activator of transcription 1	189.4	158.2	1.20	0.0076
Q8VEE1	LMCD1	LIM and cysteine-rich domains protein 1	106.9	89.5	1.20	0.0136

FC, fold change. DEPs are defined as $|FC| > 1.20$ and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 5. Significant brain DEPs downregulated in DMSO-AD$^+$ versus DMSO-WT mice.

Accession	Symbol	Description	DMSO-AD$^+$ (Mean)	DMSO-WT (Mean)	FC	p-value
P04919	SLC4A1	Band 3 anion transport protein	16.8	42.0	-2.50	0.0311
P10637-3	MAPT	Isoform Tau-B of Microtubule-associated protein tau	22.9	42.9	-1.88	0.0026
Q64327	MEA1	Male-enhanced antigen 1	40.2	73.1	-1.82	0.0145
Q31125	SLC39A7	Zinc transporter SLC39A7	138.8	219.0	-1.58	0.0073
Q9R1C7	PRPF40A	Pre-mRNA-processing factor 40 homolog A	85.4	129.2	-1.51	0.0064
Q922K7	NOP2	Probable 28S rRNA (cytosine-C(5))-methyltransferase	27.8	41.2	-1.48	0.0372
P00397	MTCO1	Cytochrome c oxidase subunit 1	166.2	245.9	-1.48	0.0441
O08842	GFRA2	GDNF family receptor alpha-2	264.3	389.8	-1.47	0.0005
Q9D287	BCAS2	Pre-mRNA-splicing factor SPF27	37.6	55.2	-1.47	0.0038
Q02111	PRKCQ	Protein kinase C theta type	69.5	100.5	-1.45	0.0482
Q6DID5	PWWP3A	PWWP domain-containing DNA repair factor 3A	22.7	32.5	-1.43	0.0216
Q91UZ1	PLCB4	1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase	745.0	1053.6	-1.41	0.0026
Q8BZ94	ZMAT4	Zinc finger matrin-type protein 4	106.7	149.6	-1.40	0.0110
P49025	CIT	Citron Rho-interacting kinase	1817.5	2549.2	-1.40	0.0018
O89084	PDE4A	cAMP-specific 3',5'-cyclic phosphodiesterase 4A	109.0	152.8	-1.40	0.0275
Q64143	PIK3R3	Phosphatidylinositol 3-kinase regulatory subunit gamma	198.3	276.1	-1.39	0.0206
E0CXZ8	DNM3	Dynamin-3	121.2	168.6	-1.39	0.0292
F7BNZ5	BCAS1	Breast carcinoma-amplified sequence 1 homolog (Fragment)	893.7	1242.5	-1.39	0.0281
H3BJD6	PPP1R9A	Protein phosphatase 1, regulatory subunit 9A	912.1	1257.5	-1.38	0.0284
Q8BG67-2	EFR3A	Isoform 2 of Protein EFR3 homolog A	81.5	112.3	-1.38	0.0005
Q7TSJ2	MAP6	Microtubule-associated protein 6	11485.6	15735.2	-1.37	0.0255
Q9R0C8	VAV3	Guanine nucleotide exchange factor VAV3	29.8	40.7	-1.37	0.0002

Q8BYW9	EOGT	EGF domain-specific O-linked N-acetylglucosamine transferase	14.4	19.6	-1.36	0.0220
E9Q8T1	TACC2	Transforming acidic coiled-coil-containing protein 2	113.6	154.1	-1.36	0.0385
Q3TVA9	CCDC136	Coiled-coil domain-containing protein 136	271.8	368.0	-1.35	0.0021
Q99KX1	MLF2	Myeloid leukemia factor 2	646.1	874.2	-1.35	0.0209
Q9CWZ3	RBM8A	RNA-binding protein 8A	88.5	118.9	-1.34	0.0297
Q99LT0	DPY30	Protein dpy-30 homolog	27.0	36.1	-1.34	0.0105
Q61464	ZNF638	Zinc finger protein 638	287.5	382.9	-1.33	0.0251
Q91X72	HPX	Hemopexin	589.2	781.2	-1.33	0.0203
Q9CW07	PPP1R3G	Protein phosphatase 1 regulatory subunit 3G	35.4	46.8	-1.32	0.0116
Q60803	TRAF3	TNF receptor-associated factor 3	1146.0	1513.8	-1.32	0.0006
Q9DB72	BTBD17	BTB/POZ domain-containing protein 17	511.8	675.3	-1.32	0.0001
Q5BLK4	TUT7	Terminal uridylyltransferase 7	35.0	46.0	-1.32	0.0252
Q8BJH1	ZC2HC1A	Zinc finger C2HC domain-containing protein 1A	1369.7	1797.9	-1.31	0.0308
B2M1R6	HNRNPK	Heterogeneous nuclear ribonucleoprotein K	4815.4	6307.6	-1.31	0.0230
Q7TPV4	MYBBP1A	Myb-binding protein 1A	32.3	42.0	-1.30	0.0004
Q8C1M2	ZNF428	Zinc finger protein 428	25.9	33.7	-1.30	0.0055
E9Q5K9	YTHDC1	YTH domain-containing protein 1	140.7	182.7	-1.30	0.0199
Q99MR1	GIGYF1	GRB10-interacting GYF protein 1	30.8	39.9	-1.29	0.0039
Q923D5	WBP11	WW domain-binding protein 11	203.4	262.8	-1.29	0.0085
Q8C0P5	CORO2A	Coronin-2A	511.3	659.9	-1.29	0.0051
O70496	CLCN7	H(+)/Cl(-) exchange transporter 7	23.1	29.8	-1.29	0.0014
Q8VHM5	HNRNPR	Heterogeneous nuclear ribonucleoprotein R	1661.2	2137.0	-1.29	0.0232
P09405	NCL	Nucleolin	12798.6	16400.7	-1.28	0.0153
Q8K2F8	LSM14A	Protein LSM14 homolog A	198.6	254.3	-1.28	0.0097
Q8R4U7	LUZP1	Leucine zipper protein 1	624.0	798.3	-1.28	0.0433
P98191	CDS1	Phosphatidate cytidylyltransferase 1	105.1	134.3	-1.28	0.0412

Q8VDM6	HNRNPUL1	Heterogeneous nuclear ribonucleoprotein U-like protein 1	412.2	526.4	-1.28	0.0345
O88532	ZFR	Zinc finger RNA-binding protein	298.5	380.3	-1.27	0.0156
Q9QXL2-4	KIF21A	Isoform 4 of Kinesin-like protein KIF21A	29.3	37.2	-1.27	0.0218
O09044	SNAP23	Synaptosomal-associated protein 23	487.8	618.6	-1.27	0.0462
Q91VR8	BRK1	Protein BRICK1	81.3	103.0	-1.27	0.0385
Q14B02	RNF133	E3 ubiquitin-protein ligase RNF133	99.7	125.8	-1.26	0.0157
Q810U5	CCDC50	Coiled-coil domain-containing protein 50	76.9	97.0	-1.26	0.0256
Q9QX47	SON	Protein SON	272.3	343.5	-1.26	0.0089
Q9JJP2	TP73	Tumor protein p73	60.6	76.4	-1.26	0.0396
Q8VD73	KCNAB3	Potassium voltage-gated channel, shaker-related subfamily, beta member 3	370.8	466.5	-1.26	0.0068
Q8BG81	POLDIP3	Polymerase delta-interacting protein 3	538.2	677.1	-1.26	0.0329
Q9ET77	JPH3	Junctophilin-3	243.5	306.3	-1.26	0.0128
Q9D824	FIP1L1	Pre-mRNA 3'-end-processing factor FIP1	128.9	161.8	-1.25	0.0359
P13864	DNMT1	DNA (cytosine-5)-methyltransferase 1	146.5	183.1	-1.25	0.0259
B2KF50	UHRF1BP1	UHRF1 (ICBP90)-binding protein 1	99.0	123.7	-1.25	0.0032
A2AJI0	MAP7D1	MAP7 domain-containing protein 1	1540.1	1923.1	-1.25	0.0437
Q62376	SNRNP70	U1 small nuclear ribonucleoprotein 70 kDa	795.7	991.2	-1.25	0.0363
Q8K327	CHAMP1	Chromosome alignment-maintaining phosphoprotein 1	112.6	140.1	-1.24	0.0101
Q8BI72	CDKN2AIP	CDKN2A-interacting protein	20.0	24.9	-1.24	0.0301
Q69Z26	CNTN4	Contactin-4	160.6	199.3	-1.24	0.0072
Q9DBS9	OSBPL3	Oxysterol-binding protein-related protein 3	41.4	51.2	-1.24	0.0015
Q9Z2D6-2	MECP2	Isoform B of Methyl-CpG-binding protein 2	1926.2	2381.7	-1.24	0.0417
Q80TY0	FNBP1	Formin-binding protein 1	972.4	1201.6	-1.24	0.0153
E9Q7G0	NUMA1	Nuclear mitotic apparatus protein 1	474.8	586.1	-1.23	0.0148
Q9D2U5	NAA38	N-alpha-acetyltransferase 38, NatC auxiliary subunit	54.3	67.0	-1.23	0.0203

Q64343	ABCG1	ATP-binding cassette subfamily G member 1	24.4	30.1	-1.23	0.0007
Q5DTX6	JCAD	Junctional protein associated with coronary artery disease	166.3	204.8	-1.23	0.0376
Q62172	RALBP1	RalA-binding protein 1	67.5	83.0	-1.23	0.0108
Q6NV83	U2SURP	U2 snRNP-associated SURP motif-containing protein	294.3	361.7	-1.23	0.0185
Q61730	IL1RAP	Interleukin-1 receptor accessory protein	259.1	318.0	-1.23	0.0005
O55003	BNIP3	BCL2/adenovirus E1B 19 kDa protein-interacting protein 3	36.4	44.7	-1.23	0.0354
A2AAE1-2	BLTP1	Isoform 2 of Transmembrane protein KIAA1109	112.0	137.3	-1.23	0.0092
F8VQ70	SCAPER	S phase cyclin A-associated protein in the ER	141.0	172.9	-1.23	0.0215
Q9JJF3	RIOX1	Ribosomal oxygenase 1	39.7	48.5	-1.22	0.0116
Q9ESK9	RB1CC1	RB1-inducible coiled-coil protein 1	201.7	246.0	-1.22	0.0061
Q80YR5	SAFB2	Scaffold attachment factor B2	112.6	137.3	-1.22	0.0429
Q9CY66	GAR1	H/ACA ribonucleoprotein complex subunit 1	168.8	205.5	-1.22	0.0011
Q0P678	ZC3H18	Zinc finger CCCH domain-containing protein 18	118.0	143.4	-1.22	0.0429
P62311	LSM3	U6 snRNA-associated Sm-like protein LSm3	53.8	65.4	-1.22	0.0061
Q922J6	TSPAN2	Tetraspanin-2	429.1	521.4	-1.22	0.0131
P26339	CHGA	Chromogranin-A	236.9	287.5	-1.21	0.0257
Q8BHL3	TBC1D10B	TBC1 domain family member 10B	540.0	655.3	-1.21	0.0167
Q5XG69	FAM169A	Soluble lamin-associated protein of 75 kDa	410.8	497.4	-1.21	0.0207
O88196	TTC3	E3 ubiquitin-protein ligase TTC3	17.8	21.6	-1.21	0.0065
Q99LE6	ABCF2	ATP-binding cassette sub-family F member 2	395.6	478.1	-1.21	0.0010
Q8K296	MTMR3	Myotubularin-related protein 3	30.3	36.6	-1.21	0.0468
P30999	CTNND1	Catenin delta-1	865.6	1043.7	-1.21	0.0270
G5E924	HNRNPL	Heterogeneous nuclear ribonucleoprotein L	4866.2	5864.2	-1.21	0.0342
Q9EQZ6	RAPGEF4	Rap guanine nucleotide exchange factor 4	1064.9	1283.2	-1.20	0.0473
Q56A08	GPKOW	G-patch domain and KOW motifs-containing protein	49.6	59.7	-1.20	0.0369
P62317	SNRPD2	Small nuclear ribonucleoprotein Sm D2	759.2	914.2	-1.20	0.0313

Q67BT3	SLC13A5	Solute carrier family 13 member 5	171.2	206.0	-1.20	0.0306
Q9WV18	GABBR1	Gamma-aminobutyric acid type B receptor subunit 1	1505.2	1810.9	-1.20	0.0306
P70170	ABCC9	Isoform SUR2B of ATP-binding cassette sub-family C member 9	85.4	102.7	-1.20	0.0088
Q8CJF7	AHCTF1	Protein ELYS	440.4	529.5	-1.20	0.0345
Q8CCP0	NEMF	Nuclear export mediator factor Nemf	281.9	338.8	-1.20	0.0117
Q8K4R4	PITPNC1	Cytoplasmic phosphatidylinositol transfer protein 1	1452.2	1745.3	-1.20	0.0137
P63056	OLFM3	Noelin-3	130.7	157.1	-1.20	0.0080
Q8CCJ4	AMER2	APC membrane recruitment protein 2	580.7	697.4	-1.20	0.0314
Q8BTV2	CPSF7	Cleavage and polyadenylation specificity factor subunit 7	273.9	328.7	-1.20	0.0095
Q66L44	CBARP	Voltage-dependent calcium channel beta subunit-associated regulatory protein	546.4	655.2	-1.20	0.0073
Q3TKT4	SMARCA4	Isoform 2 of Transcription activator BRG1	169.8	203.5	-1.20	0.0164
Q8VD37	SGIP1	SH3-containing GRB2-like protein 3-interacting protein 1	2582.2	3093.3	-1.20	0.0239
Q8BJL0	SMARCAL1	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1	50.2	60.0	-1.20	0.0104

FC, fold change. DEPs are defined as $|FC| > 1.20$ and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 6. Significant brain DEPs upregulated in ETP69-WT versus DMSO-WT mice.

Accession	Symbol	Description	ETP69-WT (Mean)	DMSO-WT (Mean)	FC	p-value
A0A5F8MPM4	MPZ	Myelin protein P0	45.7	12.3	3.73	0.0026
Q7TPD0	INTS3	Integrator complex subunit 3	77.1	26.9	2.86	0.0230
Q61646	HP	Haptoglobin	227.7	80.8	2.82	0.0448
F7DBB3	AHNAK2	AHNAK nucleoprotein 2 (Fragment)	1622.3	734.9	2.21	0.0076
P15209-2	NTRK2	Isoform GP95-TRKB of BDNF/NT-3 growth factors receptor	144.1	70.1	2.05	0.0066
P13597	ICAM1	Intercellular adhesion molecule 1	18.2	9.3	1.95	0.00004
P08101	FCGR2	Low affinity immunoglobulin gamma Fc region receptor II	17.3	9.4	1.84	0.0304
Q91X72	HPX	Hemopexin	1397.5	781.2	1.79	0.0107
P04370	MBP	Isoform 9 of Myelin basic protein	625.5	373.8	1.67	0.0477
Q8CA95	PDE10A	Isoform 3 of cAMP and cAMP-inhibited cGMP 3’,5’-cyclic phosphodiesterase 10A	452.3	273.0	1.66	0.0129
Q60829	PPP1R1B	Protein phosphatase 1 regulatory subunit 1B	468.7	290.5	1.61	0.0013
P62806	H4C1	Histone H4	13777.0	8602.4	1.60	0.0004
P29699	AHSG	Alpha-2-HS-glycoprotein	156.5	98.4	1.59	0.0020
Q9D920	BORCS5	BLOC-1-related complex subunit 5	14.9	9.6	1.56	0.0113
A2AJK6	CHD7	Chromodomain-helicase-DNA-binding protein 7	35.6	23.2	1.54	0.0233
Q08091	CNN1	Calponin-1	57.0	37.8	1.51	0.0159
Q9Z277	BAZ1B	Tyrosine-protein kinase BAZ1B	1742.8	1202.8	1.45	0.0059
Q7TNV1	TLCD3B	Ceramide synthase	25.6	17.9	1.43	0.0095
Q61147	CP	Ceruloplasmin	262.7	183.9	1.43	0.00005
Q8CG46	SMC5	Structural maintenance of chromosomes protein 5	77.5	54.3	1.43	0.0371
Q91VJ2	CAVIN3	Caveolae-associated protein 3	58.0	40.9	1.42	0.0458
Q62422	OSTF1	Osteoclast-stimulating factor 1	87.9	62.3	1.41	0.0333
Q9CXJ4	ABCB8	Mitochondrial potassium channel ATP-binding subunit	1987.1	1413.9	1.41	0.0250

Q9JKY7	CYP2D22	Cytochrome P450 CYP2D22	46.7	33.3	1.40	0.0240
Q60709	APLP2	Amyloid-like protein 2	21.8	15.5	1.40	0.0084
P17897	LYZ1	Lysozyme C-1	123.4	88.8	1.39	0.0007
P84244	H3-3A	Histone H3.3	1100.1	801.8	1.37	0.0062
P0DOV2	IFI204	Interferon-activable protein 204	27.3	20.1	1.36	0.0431
Q640M6	GDPD5	Glycerophosphodiester phosphodiesterase domain-containing protein 5	26.3	19.5	1.35	0.0121
O54983	CRYM	Ketimine reductase mu-crystallin	4874.2	3616.2	1.35	0.0278
Q8BJ05	ZC3H14	Zinc finger CCCH domain-containing protein 14	118.3	89.2	1.33	0.0032
P07356	ANXA2	Annexin A2	2388.9	1842.1	1.30	0.0020
Q91WG7	DGKG	Diacylglycerol kinase gamma	928.2	719.4	1.29	0.0061
Q8BJ05	DGKB	Diacylglycerol kinase beta	2104.9	1643.7	1.28	0.0194
Q9Z321	TOP3B	DNA topoisomerase 3-beta-1	29.8	23.4	1.27	0.0396
O70250	PGAM2	Phosphoglycerate mutase 2	119.1	93.9	1.27	0.0083
Q00519	XDH	Xanthine dehydrogenase/oxidase	93.1	73.9	1.26	0.0177
P98086	C1QA	Complement C1q subcomponent subunit A	230.4	183.3	1.26	0.0379
Q80W37	SNUPN	Snurportin-1	45.3	36.1	1.26	0.0076
Q61285	ABCD2	ATP-binding cassette, sub-family D, member 2	43.9	35.2	1.25	0.0334
E9Q236	ABCC4	ATP-binding cassette, sub-family C (CFTR/MRP), member 4	45.7	36.7	1.25	0.0041
Q91XE4	ACY3	N-acyl-aromatic-L-amino acid amidohydrolase (carboxylate-forming)	103.2	82.8	1.25	0.0125
P35969	FLT1	Vascular endothelial growth factor receptor 1	874.8	703.4	1.24	0.0001
Q8C788	SNX18	Sorting nexin-18	102.5	82.5	1.24	0.0063
Q8BYJ6	TBC1D4	TBC1 domain family member 4	24.4	19.7	1.24	0.0456
Q9DCB4	ARPP21	Isoform 3 of cAMP-regulated phosphoprotein 21	112.9	91.0	1.24	0.0198
Q922S4	PDE2A	cGMP-dependent 3’,5’-cyclic phosphodiesterase	5534.5	4500.7	1.23	0.0240
Q6P1B3	PIANP	PILR alpha-associated neural protein	70.3	57.4	1.22	0.0364

P28667	MARCKSL1	MARCKS-related protein	2244.4	1840.5	1.22	0.0340
E9QA16	CALD1	Caldesmon 1	127.4	104.7	1.22	0.0262
Q9DCJ9	NPL	N-acetylneuraminate lyase	396.9	326.1	1.22	0.0055
Q9D1Q4	DPM3	Dolichol-phosphate mannosyltransferase subunit 3	56.2	46.2	1.22	0.0121
Q8K215	LYRM4	LYR motif-containing protein 4	113.1	92.9	1.22	0.0497
A2TJV2	PALM3	Paralemmin-3	68.6	56.5	1.21	0.0169
P06909	CFH	Complement factor H	116.6	96.8	1.20	0.0242
P56380	NUDT2	Bis(5'-nucleosyl)-tetraphosphatase [asymmetrical]	52.9	43.9	1.20	0.0197
Q9CY18	SNX7	Sorting nexin-7	88.9	74.1	1.20	0.0380
Q9D379	EPHX1	Epoxide hydrolase 1	985.1	821.7	1.20	0.0014
Q8CHQ9	NAT8F2	N-acetyltransferase family 8 member 2	102.7	85.7	1.20	0.0009
O08992	SDCBP	Syntenin-1	568.9	475.9	1.20	0.0460

FC, fold change. DEPs are defined as $|FC| > 1.20$ and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 7. Significant brain DEPs downregulated in ETP69-WT versus DMSO-WT mice.

Accession	Symbol	Description	ETP69-WT (Mean)	DMSO-WT (Mean)	FC	p-value
Q6PFX9	TNKS	Poly [ADP-ribose] polymerase tankyrase-1	10.7	16.7	-1.56	0.0013
P00397	MTCO1	Cytochrome c oxidase subunit 1	163.4	245.9	-1.50	0.0278
Q02111	PRKCQ	Protein kinase C theta type	71.6	100.5	-1.40	0.0344
O88428	PAPSS2	Bifunctional 3'-phosphoadenosine 5'-phosphosulfate synthase 2	13.1	18.1	-1.38	0.0490
Q9QXV0	PCSK1N	ProSAAS	406.2	551.3	-1.36	0.0253
B0F2B4	NLGN4L	Neuroligin 4-like	66.9	89.2	-1.33	0.0500
Q8BZ94	ZMAT4	Zinc finger matrin-type protein 4	113.2	149.6	-1.32	0.0031
Q6ZPR4	KCNT1	Potassium channel subfamily T member 1	21.8	28.7	-1.32	0.0197
Q8C3X4	GUF1	Translation factor Guf1, mitochondrial	53.0	69.8	-1.32	0.0015
Q8BLE7	SLC17A6	Vesicular glutamate transporter 2	1183.4	1549.0	-1.31	0.0085
Q8VD73	KCNAB3	Potassium voltage-gated channel, shaker-related subfamily, beta member 3	366.4	466.5	-1.27	0.0011
Q9CWZ3	RBM8A	RNA-binding protein 8A	93.4	118.9	-1.27	0.0451
Q9CW07	PPP1R3G	Protein phosphatase 1 regulatory subunit 3G	36.9	46.8	-1.27	0.0451
Q8R242	CTBS	Di-N-acetylchitobiase	21.1	26.7	-1.26	0.0069
Q80U93	NUP214	Nuclear pore complex protein Nup214	31.2	38.8	-1.25	0.0472
Q8BUL6	PLEKHA1	Pleckstrin homology domain-containing family A member 1	29.5	36.7	-1.24	0.0115
B1AUH5	CASK	Peripheral plasma membrane CASK (Fragment)	50.3	62.1	-1.23	0.0003
Q5SQY2	BOD1	Biorientation of chromosomes in cell division protein 1	60.1	74.1	-1.23	0.0299
Q3TVA9	CCDC136	Coiled-coil domain-containing protein 136	298.7	368.0	-1.23	0.0191
Q9DCP2	SLC38A3	Sodium-coupled neutral amino acid transporter 3	63.5	78.0	-1.23	0.0033
Q8K296	MTMR3	Myotubularin-related protein 3	29.9	36.6	-1.22	0.0290
Q5XG69	FAM169A	Soluble lamin-associated protein of 75 kDa	407.4	497.4	-1.22	0.0046
A0A140LIW3	FRMPD3	FERM and PDZ domain-containing 3	64.0	77.8	-1.22	0.0429

P60755	MDGA2	MAM domain-containing glycosylphosphatidylinositol anchor protein 2	148.6	180.1	-1.21	0.0002
Q9D0D3	MTPAP	Poly(A) RNA polymerase, mitochondrial	39.3	47.6	-1.21	0.0453
Q9CQ56	USE1	Vesicle transport protein USE1	71.6	85.8	-1.20	0.0058
Q9JHG2	RCAN2	Calcipressin-2	43.0	51.5	-1.20	0.0241

FC, fold change. DEPs are defined as $|FC| > 1.20$ and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 8. Significant retinal DEPs upregulated in ETP69-AD$^+$ versus DMSO-AD$^+$ mice.

Accession	Symbol	Description	ETP69-AD$^+$ (Mean)	DMSO-AD$^+$ (Mean)	FC	p-value
Q61646	HP	Haptoglobin	4849.2	1478.8	3.28	0.0084
P07361	ORM2	Alpha-1-acid glycoprotein 2	817.2	263.3	3.10	0.0289
P18155	MTHFD2	Bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase, mitochondrial	93.1	54.2	1.72	0.0191
E9Q286	ICE1	Little elongation complex subunit 1	95.3	64.0	1.49	0.0232
Q4VC33	MAEA	E3 ubiquitin-protein transferase MAEA	62.4	43.3	1.44	0.0295
Q80TS3	ADGRL3	Adhesion G protein-coupled receptor L3	335.9	236.1	1.42	0.0052
P52482	UBE2E1	Ubiquitin-conjugating enzyme E2 E1	130.3	92.8	1.40	0.0232
Q9D7M8	POLR2D	DNA-directed RNA polymerase II subunit RPB4	195.4	141.6	1.38	0.0159
O88796	RPP30	Ribonuclease P protein subunit p30	33.5	26.1	1.28	0.0027
Q9JJF3	RIOX1	Ribosomal oxygenase 1	31.1	24.5	1.27	0.0060
Q3U4X8	LIG1	DNA ligase	61.5	49.3	1.25	0.0431
Q9CQR6	PPP6C	Serine/threonine-protein phosphatase 6 catalytic subunit	678.1	548.7	1.24	0.0387
Q3UYK3	TBC1D9	TBC1 domain family member 9	49.4	40.5	1.22	0.0154
G5E8P0	TUBGCP6	Gamma-tubulin complex component 6	33.6	27.7	1.21	0.0083
Q80T69	RSBN1	Lysine-specific demethylase 9	412.9	343.0	1.20	0.0218
Q8R5K4	NOL6	Nucleolar protein 6	36.2	30.2	1.20	0.0210
Q9CSH3	DIS3	Exosome complex exonuclease RRP44	1622.7	1353.0	1.20	0.0466
Q9WTR6	SLC7A11	Cystine/glutamate transporter	67.9	56.7	1.20	0.0127
P26339	CHGA	Chromogranin-A	48.1	40.2	1.20	0.00003
Q9Z1T6	PIKFYVE	1-phosphatidylinositol 3-phosphate 5-kinase	61.7	51.6	1.20	0.0424

FC, fold change. DEPs are defined as $|FC| > 1.20$ and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 9. Significant retinal DEPs downregulated in ETP69-AD$^+$ versus DMSO-AD$^+$ mice.

Accession	Symbol	Description	ETP69-AD$^+$ (Mean)	DMSO-AD$^+$ (Mean)	FC	p-value
Q3UHD9	AGAP2	Arf-GAP with GTPase, ANK repeat and PH domain-containing protein 2	93.3	147.3	-1.58	0.0327
P48437	PROX1	Prospero homeobox protein 1	366.2	550.5	-1.50	0.0375
Q3TJD7	PDLIM7	PDZ and LIM domain protein 7	22.2	33.4	-1.50	0.0218
Q91VN6	DDX41	Probable ATP-dependent RNA helicase DDX41	415.2	605.5	-1.46	0.0466
Q9CXY6	ILF2	Interleukin enhancer-binding factor 2	2379.1	3424.7	-1.44	0.0215
Q0VGU4	VGF	Neurosecretory protein VGF	32.8	46.5	-1.42	0.0245
Q62083	PICK1	PRKCA-binding protein	294.5	401.6	-1.36	0.0189
P28656	NAP1L1	Nucleosome assembly protein 1-like 1	917.0	1239.0	-1.35	0.0384
Q4PZA2	ECE1	Endothelin-converting enzyme 1	76.3	102.7	-1.35	0.0378
Q5NBX1	COBL	Protein cordon-bleu	43.9	58.1	-1.32	0.0203
Q8CHP5	PYM1	Partner of Y14 and mago	40.9	53.3	-1.30	0.0360
P13597	ICAM1	Intercellular adhesion molecule 1	52.1	67.5	-1.30	0.0440
Q8R2R1	POMT1	Protein O-mannosyl-transferase 1	41.0	53.0	-1.29	0.0314
Q69ZJ7	RIC1	Guanine nucleotide exchange factor subunit RIC1	49.1	63.3	-1.29	0.0179
Q6X7S9	EID2	EP300-interacting inhibitor of differentiation 2	40.3	51.8	-1.29	0.0474
Q9DAP0	LRRC46	Leucine-rich repeat-containing protein 46	32.6	41.2	-1.26	0.0002
P70232	CHL1	Neural cell adhesion molecule L1-like protein	231.9	291.8	-1.26	0.0467
P97821	CTSC	Dipeptidyl peptidase 1	60.9	76.1	-1.25	0.0477
Q923E4	SIRT1	NAD-dependent protein deacetylase sirtuin-1	36.7	45.7	-1.25	0.0492
E9Q8M1	ZFP358	Zinc finger protein 358	47.8	59.5	-1.25	0.0176
O08785	CLOCK	Circadian locomoter output cycles protein kaput	48.0	58.9	-1.23	0.0378
Q8BZ36	RINT1	RAD50-interacting protein 1	51.5	62.6	-1.22	0.0371
Q61081	CDC37	Hsp90 co-chaperone Cdc37	2678.3	3254.2	-1.22	0.0495

Q8R1S4	MTSS1	Protein MTSS 1	89.6	108.4	-1.21	0.0063
Q5RJH6	SMG7	Protein SMG7	110.0	132.9	-1.21	0.0072
Q60841	RELN	Reelin	146.7	176.0	-1.20	0.0438
Q91YH5	ATL3	Atlastin-3	35.5	42.6	-1.20	0.0478

FC, fold change. DEPs are defined as $|FC| > 1.20$ and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 10. Significant retinal DEPs upregulated in DMSO-AD$^+$ versus DMSO-WT mice.

Accession	Symbol	Description	DMSO-AD$^+$ (Mean)	DMSO-WT (Mean)	FC	p-value
Q9QXA1-2	CYHR1	Isoform 2 of Cysteine and histidine-rich protein 1	164.5	93.5	1.76	0.0001
P12023	APP	Amyloid-beta A4 protein	1699.7	1010.5	1.68	0.0279
P0C027	NUDT10	Diphosphoinositol polyphosphate phosphohydrolase 3-alpha	25.8	17.3	1.49	0.0095
Q6A0D4	RFTN1	Raftlin	28.1	18.9	1.48	0.0403
D3Z707	CYP3A25	####Cytochrome P450 3A25	33.7	22.7	1.48	0.0092
P13597	ICAM1	Intercellular adhesion molecule 1	67.5	48.1	1.40	0.0261
O08795-2	PRKCSH	Isoform 2 of Glucosidase 2 subunit beta	5105.0	3646.3	1.40	0.0377
Q8C6E0	CFAP36	Cilia- and flagella-associated protein 36	1426.6	1032.1	1.38	0.0084
P70232	CHL1	Neural cell adhesion molecule L1-like protein	291.8	212.1	1.38	0.0073
Q9R0D8	WDR54	WD repeat-containing protein 54	47.5	34.6	1.37	0.0053
P48437	PROX1	Prospero homeobox protein 1	550.5	405.4	1.36	0.0427
Q3TC93	HS1BP3	HCLS1-binding protein 3	160.5	119.5	1.34	0.0277
Q5NBX1	COBL	Protein cordon-bleu	58.1	43.5	1.33	0.0353
Q8BMQ8	MON1B	Vacuolar fusion protein MON1 homolog B	23.5	17.6	1.33	0.0076
Q8R2R1	POMT1	Protein O-mannosyl-transferase 1	53.0	39.9	1.33	0.0084
Q8R1S4	MTSS1	Protein MTSS 1	108.4	81.8	1.32	0.0017
Q3UHD9	AGAP2	Arf-GAP with GTPase, ANK repeat and PH domain-containing protein 2	147.3	112.3	1.31	0.0420
Q9R233	TAPBP	Tapasin	79.0	60.3	1.31	0.0022
Q80XH2	IMPG2	Interphotoreceptor matrix proteoglycan 2	3515.7	2689.8	1.31	0.0339
Q4PZA2	ECE1	Endothelin-converting enzyme 1	102.7	78.6	1.31	0.0130
Q810B7	SLITRK5	SLIT and NTRK-like protein 5	29.7	22.8	1.30	0.0058
P57716	NCSTN	Nicastrin	263.3	202.4	1.30	0.0113

Q9DAP0	LRRC46	Leucine-rich repeat-containing protein 46	41.2	31.7	1.30	0.0004
Q69ZJ7	RIC1	Guanine nucleotide exchange factor subunit RIC1	63.3	49.2	1.29	0.0285
Q6P5D4	CEP135	Centrosomal protein of 135 kDa	88.0	68.3	1.29	0.0471
Q80Z25	OFD1	Oral-facial-digital syndrome 1 protein homolog	54.0	42.0	1.29	0.0314
Q8R1U1	COG4	Conserved oligomeric Golgi complex subunit 4	568.8	443.7	1.28	0.0325
Q62083	PICK1	PRKCA-binding protein	401.6	317.2	1.27	0.0042
Q8BIF9	ZNF787	Zinc finger protein 787	297.7	238.3	1.25	0.0115
F6U3S2	MFSD6	Major facilitator superfamily domain-containing protein 6	32.5	26.2	1.24	0.0486
Q8K2Q9	SHTN1	Shootin-1	108.0	87.1	1.24	0.0100
P54254	ATXN1	Ataxin-1	154.3	124.6	1.24	0.0026
E9PWI3	MCC	Mutated in colorectal cancers	66.4	53.9	1.23	0.0189
Q8BG40	KATNB1	Katanin p80 WD40 repeat-containing subunit B1	170.4	138.6	1.23	0.0127
P42337	PIK3CA	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform	46.4	37.8	1.23	0.0086
P35762	CD81	CD81 antigen	415.4	339.4	1.22	0.0295
Q99KB8	HAGH	Hydroxyacylglutathione hydrolase, mitochondrial	2408.4	1970.5	1.22	0.0329
Q9CY52	THG1L	Probable tRNA(His) guanylyltransferase	40.8	33.6	1.22	0.0339
Q9D164	FXYD6	FXYD domain-containing ion transport regulator 6	97.9	80.6	1.21	0.0269
Q9QZ49	UBXN8	UBX domain-containing protein 8	205.5	169.2	1.21	0.0081
Q6P5H2	NES	Nestin	97.1	80.0	1.21	0.0476
O35226	PSMD4	26S proteasome non-ATPase regulatory subunit 4	43.9	36.2	1.21	0.0360
P17156	HSPA2	Heat shock-related 70 kDa protein 2	2072.9	1715.3	1.21	0.0448
Q91VM3	WDR45	WD repeat domain phosphoinositide-interacting protein 4	77.8	64.4	1.21	0.0069
Q00560	IL6ST	Interleukin-6 receptor subunit beta	70.6	58.8	1.20	0.0075
Q78WZ7	POLR1F	DNA-directed RNA polymerase I subunit RPA43	65.7	54.7	1.20	0.0434
Q70IV5	SYNM	Synemin	1586.5	1323.0	1.20	0.0087

Q9CR59	GADD45GIP	Growth arrest and DNA damage-inducible proteins-interacting protein 1	196.6	164.3	1.20	0.0275

FC, fold change. DEPs are defined as |FC| > 1.20 and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 11. Significant retinal DEPs downregulated in DMSO-AD$^+$ versus DMSO-WT mice.

Accession	Symbol	Description	DMSO-AD$^+$ (Mean)	DMSO-WT (Mean)	FC	p-value
O70333	CRIPT	Cysteine-rich PDZ-binding protein	128.0	180.9	-1.41	0.0341
Q80U40	RIMBP2	RIMS-binding protein 2	50.1	68.6	-1.37	0.0393
Q9QXY1	TJP3	Tight junction protein ZO-3	32.0	42.1	-1.32	0.0049
Q8BKX1	BAIAP2	Brain-specific angiogenesis inhibitor 1-associated protein 2	20.8	26.8	-1.29	0.0234
Q920Q4	VPS16	Vacuolar protein sorting-associated protein 16 homolog	389.9	496.5	-1.27	0.0435
Q60829	PPP1R1B	Protein phosphatase 1 regulatory subunit 1B	81.3	103.4	-1.27	0.0403
Q497V6	BAHD1	Bromo adjacent homology domain-containing 1 protein	38.3	48.3	-1.26	0.0252
Q8BHA0	INO80C	INO80 complex subunit C	15.7	19.8	-1.26	0.0079
Q9ESG4	CLTRN	Collectrin	118.4	147.3	-1.24	0.0330
Q4JIM5	ABL2	Tyrosine-protein kinase ABL2	39.7	49.0	-1.24	0.0361
Q80TS3	ADGRL3	Adhesion G protein-coupled receptor L3	236.1	290.4	-1.23	0.0205
Q8BMI0	FBXO38	F-box only protein 38	77.3	94.4	-1.22	0.0224
Q9JJF3	RIOX1	Ribosomal oxygenase 1	24.5	29.8	-1.21	0.0040
Q9CQR6	PPP6C	Serine/threonine-protein phosphatase 6 catalytic subunit	548.7	665.0	-1.21	0.0485
O35309	NMI	N-myc-interactor	27.2	32.9	-1.21	0.0368
P21836	ACHE	Acetylcholinesterase	116.2	140.2	-1.21	0.0399
P23798	PCGF2	Polycomb group RING finger protein 2	269.5	324.6	-1.20	0.0106
O88796	RPP30	Ribonuclease P protein subunit p30	26.1	31.3	-1.20	0.0021
Q8BQZ5	CPSF4	Cleavage and polyadenylation specificity factor subunit 4	157.0	187.8	-1.20	0.0474

FC, fold change. DEPs are defined as |FC| > 1.20 and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 12. Significant retinal DEPs upregulated in ETP69-WT versus DMSO-WT mice.

Accession	**Symbol**	**Description**	**ETP69-WT (Mean)**	**DMSO-WT (Mean)**	**FC**	**p-value**
E9Q6A2	SERPINE3	Serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 3	36.0	20.5	1.75	0.0381
P07361	ORM2	Alpha-1-acid glycoprotein 2	451.3	258.7	1.74	0.0116
Q9CQX2	CYB5B	Cytochrome b5 type B	270.7	159.0	1.70	0.0245
Q9JL04	FMN2	Formin-2	64.1	40.4	1.59	0.0193
P51163	UROS	Uroporphyrinogen-III synthase	86.3	57.2	1.51	0.0353
Q8K297	COLGALT1	Procollagen galactosyltransferase 1	77.3	51.7	1.49	0.0042
O35526	STX1A	Syntaxin-1A	921.8	619.9	1.49	0.0363
P02802	MT1	Metallothionein-1	907.8	610.8	1.49	0.0039
P02798	MT2	Metallothionein-2	410.3	276.5	1.48	0.0157
P0C027	NUDT10	Diphosphoinositol polyphosphate phosphohydrolase 3-alpha	23.9	17.3	1.38	0.0204
A2APV2	FMNL2	Formin-like protein 2	94.2	70.4	1.34	0.0468
A2AJA9	AJM1	Apical junction component 1 homolog	108.0	80.9	1.34	0.0352
Q9JKK8	ATR	Serine/threonine-protein kinase ATR	137.2	104.5	1.31	0.0282
Q99LT0	DPY30	Protein dpy-30 homolog	134.6	103.5	1.30	0.0214
Q91YP3	DERA	Deoxyribose-phosphate aldolase	141.3	109.7	1.29	0.0010
Q8BX57	PXK	PX domain-containing protein kinase-like protein	62.3	49.2	1.27	0.0400
P61148	FGF1	Fibroblast growth factor 1	320.3	255.7	1.25	0.0489
Q8CHH5	BICRAL	BRD4-interacting chromatin-remodeling complex-associated protein-like	48.7	39.3	1.24	0.0080
Q9QXV0	PCSK1N	ProSAAS	66.2	54.4	1.22	0.0126
Q8BGG7	UBASH3B	Ubiquitin-associated and SH3 domain-containing protein B	91.3	75.4	1.21	0.0007
Q8VDP2	STEEP1	UPF0428 protein CXorf56 homolog	593.3	492.7	1.20	0.0227

A2ANY6	MDN1	Midasin	67.5	56.1	1.20	0.0278
Q3U2V3	NUDT18	8-oxo-dGDP phosphatase NUDT18	25.8	21.5	1.20	0.0289
O88741	GDAP1	Ganglioside-induced differentiation-associated protein 1	752.4	626.7	1.20	0.0045
Q99LB7	SARDH	Sarcosine dehydrogenase, mitochondrial	230.7	192.8	1.20	0.0017

FC, fold change. DEPs are defined as $|FC| > 1.20$ and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 13. Significant retinal DEPs downregulated in ETP69-WT versus DMSO-WT mice.

Accession	Symbol	Description	ETP69-WT (Mean)	DMSO-WT (Mean)	FC	p-value
D3YYY1	SCGB2B7	Secretoglobin, family 2B, member 7	243.1	703.5	-2.89	0.0421
E9QAQ8	MUC5AC	Mucin 5, subtypes A and C, tracheobronchial/gastric	65.0	161.6	-2.49	0.0199
D2XZ31	SCGB1B29	Secretoglobin, family 1B, member 29	348.8	861.8	-2.47	0.0263
P35173	STFA3	Stefin-3	243.3	550.3	-2.26	0.0232
Q9CRB3	URAH	5-hydroxyisourate hydrolase	28.6	64.6	-2.26	0.0244
P04939	MUP3	Major urinary protein 3	158.5	339.4	-2.14	0.0179
Q5SW46	LPO	Lactoperoxidase	110.4	235.8	-2.14	0.0339
P23953	CES1C	Carboxylesterase 1C	1036.2	2195.9	-2.12	0.0146
O89020-3	AFM	Isoform 3 of Afamin	150.3	315.0	-2.10	0.0058
P49183	DNASE1	Deoxyribonuclease-1	558.4	1156.2	-2.07	0.0457
Q00623	APOA1	Apolipoprotein A-I	2833.0	5795.0	-2.05	0.0173
F6WYC8	LIPO1	Lipase	178.3	350.9	-1.97	0.0336
P07758	SERPINA1A	Alpha-1-antitrypsin 1-1	1002.3	1967.1	-1.96	0.0082
O70250	PGAM2	Phosphoglycerate mutase 2	562.3	1077.4	-1.92	0.0056
P04247	MB	Myoglobin	1525.5	2897.8	-1.90	0.0147
Q80XI7	BPIFB9A	Vomeromodulin	175.8	329.7	-1.88	0.0312
P50543	S100A11	Protein S100-A11	631.3	1126.2	-1.78	0.0149
O09131	GSTO1	Glutathione S-transferase omega-1	8263.0	14698.5	-1.78	0.0237
P07309	TTR	Transthyretin	2040.9	3625.1	-1.78	0.0032
P32848	PVALB	Parvalbumin alpha	3581.4	6299.8	-1.76	0.0293
P21614	GC	Vitamin D-binding protein	2305.9	4007.5	-1.74	0.0133
Q08652	RBP2	Retinol-binding protein 2	88.8	153.3	-1.73	0.0227
P10648	GSTA2	Glutathione S-transferase A2	186.7	315.9	-1.69	0.0244

P29699	AHSG	Alpha-2-HS-glycoprotein	2809.5	4650.7	-1.66	0.0103
P70124	SERPINB5	Serpin B5	147.9	244.2	-1.65	0.0434
P06728	APOA4	Apolipoprotein A-IV	827.7	1363.5	-1.65	0.0008
P16015	CA3	Carbonic anhydrase 3	1208.1	1987.9	-1.65	0.0460
P07310	CKM	Creatine kinase M-type	5564.6	9022.1	-1.62	0.0129
Q9JM83	CALM4	Calmodulin-4	138.4	224.0	-1.62	0.0394
Q149L6	DNAJB14	DnaJ homolog subfamily B member 14	530.0	848.1	-1.60	0.0321
A0A3B2WD20	ESP6	Exocrine gland secreted peptide 6	856.8	1366.7	-1.60	0.0445
P00329	ADH1	Alcohol dehydrogenase 1	1815.7	2892.9	-1.59	0.0175
G3X9C2	NCCRP1	F-box only protein 50	188.6	294.7	-1.56	0.0359
B2RWW0	TAGAP	T-cell activation Rho GTPase-activating protein	186.6	285.1	-1.53	0.0205
P51885	LUM	Lumican	883.5	1336.2	-1.51	0.0278
P56394	COX17	Cytochrome c oxidase copper chaperone	529.4	793.5	-1.50	0.0487
Q9R111	GDA	Guanine deaminase	78.9	117.8	-1.49	0.0229
Q61599	ARHGDIB	Rho GDP-dissociation inhibitor 2	187.2	275.0	-1.47	0.0027
P49182	SERPIND1	Heparin cofactor 2	156.6	225.9	-1.44	0.0130
P32261	SERPINC1	Antithrombin-III	1043.6	1500.2	-1.44	0.0157
Q9D154	SERPINB1A	Leukocyte elastase inhibitor A	402.1	568.4	-1.41	0.0158
P19221	F2	Prothrombin	97.7	136.6	-1.40	0.0105
P08071	LTF	Lactotransferrin	214.1	296.8	-1.39	0.0355
Q9WV91	PTGFRN	Prostaglandin F2 receptor negative regulator	20.1	27.6	-1.37	0.0279
Q8K370	ACAD10	Acyl-CoA dehydrogenase family member 10	55.5	76.1	-1.37	0.0162
O70585	DTNB	Dystrobrevin beta	53.9	72.1	-1.34	0.0043
P14602	HSPB1	Heat shock protein beta-1	1313.9	1757.8	-1.34	0.0049
O35309	NMI	N-myc-interactor	24.8	32.9	-1.33	0.0053
Q9DC28	CSNK1D	Casein kinase I isoform delta	237.8	314.2	-1.32	0.0225
Q91WF7	FIG4	Polyphosphoinositide phosphatase	46.5	61.0	-1.31	0.0464

Q99MQ4	ASPN	Asporin	137.8	180.4	-1.31	0.0131
Q920Q4	VPS16	Vacuolar protein sorting-associated protein 16 homolog	379.6	496.5	-1.31	0.0180
Q9DBY5	CBX6	Chromobox protein homolog 6	23.9	31.1	-1.30	0.0419
P20065	TMSB4X	Thymosin beta-4	1247.9	1611.6	-1.29	0.0075
O35316	SLC6A6	Sodium- and chloride-dependent taurine transporter	317.5	407.7	-1.28	0.0258
Q5EBG6	HSPB6	Heat shock protein beta-6	265.3	338.6	-1.28	0.0115
P13020	GSN	Gelsolin	3748.6	4736.8	-1.26	0.0402
Q01339	APOH	Beta-2-glycoprotein 1	173.4	218.9	-1.26	0.0363
P63254	CRIP1	Cysteine-rich protein 1	594.3	733.7	-1.23	0.0096
Q91X51	GORASP1	Golgi reassembly-stacking protein 1	16.5	20.3	-1.23	0.0361
Q9JMD0	ZNF207	BUB3-interacting and GLEBS motif-containing protein	1240.6	1521.6	-1.23	0.0330
Q8CHX7	RFTN2	Raftlin-2	84.3	103.1	-1.22	0.0257
O35972	MRPL23	39S ribosomal protein L23, mitochondrial	27.9	34.0	-1.22	0.0419
Q60854	SERPINB6	Serpin B6	3091.3	3760.4	-1.22	0.0063
Q99KI3	EMC3	ER membrane protein complex subunit 3	88.2	107.2	-1.22	0.0095
P40936	INMT	Indolethylamine N-methyltransferase	388.5	471.2	-1.21	0.0276
Q91VN6	DDX41	Probable ATP-dependent RNA helicase DDX41	382.0	462.3	-1.21	0.0021
Q9WTY4	AQP5	Aquaporin-5	41.6	50.3	-1.21	0.0331
Q149F3	GSPT2	Eukaryotic peptide chain release factor GTP-binding subunit ERF3B	71.9	86.9	-1.21	0.0390
Q3UFF7	LYPLAL1	Lysophospholipase-like protein 1	104.3	125.6	-1.20	0.0200
P21460	CST3	Cystatin-C	519.5	625.3	-1.20	0.0007
Q9CXY6	ILF2	Interleukin enhancer-binding factor 2	2272.9	2730.0	-1.20	0.0356

FC, fold change. DEPs are defined as $|FC| > 1.20$ and unadjusted $p < 0.05$ by two-sided *t*-test.

Extended Data Table 14. List of antibodies.

Primary antibody	Host	IHC dilution	WB dilution	Source	Catalog#
Annexin A2 (ANXA2)	Rat	1:200		Biolegend	671001
β-actin	Mouse		1:1000	Santa Cruz	sc-47778
β-amyloid 1-42 (12F4)	Mouse		1:1000	Biolegend	805501
β-amyloid 1-16 (6E10)	Mouse	1:200-1:500		Biolegend	803001
β-amyloid 17-24 (4G8)	Mouse	1:200		Biolegend	800701
BDNF	Mouse	1:200	1:500	Abcam	ab205067
CD45	Rat	1:25		BD Pharmagen	550539
GFAP	Goat	1:500		Novus	NB100-53809
GFAP	Rat		1:1000	Invitrogen	13-0300
GAPDH (D16H11)	Rabbit		1:1000	Cell signaling	5174
H3	Rabbit		1:1000	Novus	NB100-57135
H3K9me3	Rabbit	1:500	1:1000	Abcam	ab8898
IBA1	Rabbit	1:250		Wako	019-19741
IBA1	Goat	1:250		Novus	NB-100-1028
MT2A	Rabbit	1:100		Invitrogen	PA5-76652
NeuN	Mouse	1:1000		Abcam	ab177487
PLTP	Sheep	1:40		R&D system	AF4918
PSD95	Rabbit	1:600		Abcam	ab76115
Synaptophysin (SYP)	Mouse		1:1000	Biolegend	837101
T22 (Oligo-tau)	Rabbit	1:200		Provided by Dr. Rakez Kayed	
PHF-Tau	Mouse	1:200		Provided by Dr. Peter Davies lab	
VGF	Rabbit	1:200	1:500	Novus	NBP1-76906
Secondary antibody					
Cy2	Goat, Mouse, Rabbit, Rat, Sheep	1:200		Jackson ImmunoResearch Laboratories	
Cy3		1:200			
Cy5		1:200			
Cy7		1:200			
HRP	Mouse		1:10000		
IRDye® 680RD pAb	Rabbit		1:10000	Licorbio	926-68071
IRDye® 800CW pAb	Rabbit		1:10000	Licorbio	926-32211
IRDye® 680RD pAb	Mouse		1:10000	Licorbio	926-68070
IRDye® 800CW pAb	Mouse		1:10000	Licorbio	926-32210

Cyanine dyes – Cy2, Cy3, Cy5, Cy7; IHC, Immunohistochemistry; HRP – Horseradish peroxidase; WB, Western blotting.