Supplemental Table 1 Plasma concentration of TCA-precipitable [^{125}I]A$\beta_{1\text{-}40}$ after intravenous administration from the jugular vein in 2-month-old wild-type and 25-month-old wild-type and *Ttpa*$^{-/-}$ mice.

	Plasma concentration (fmol/mL)		
Time (min)	2-month-old wild-type	25-month-old wild-type	25-month-old *Ttpa*$^{-/-}$
1	1160 ± 56	420 ± 49**	870 ± 170$^{\#}$
3	501 ± 17	265 ± 29**	523 ± 67$^{\#\#}$
5	316 ± 18	238 ± 51	401 ± 64
10	181 ± 8	161 ± 30	301 ± 97
15	131 ± 9	84.9 ± 12.4*	204 ± 80
30	56.1 ± 5.4	54.8 ± 5.6	71.2 ± 13.5
60	30.6 ± 0.6	32.2 ± 1.4	58.1 ± 12.0$^{\#}$
120	15.0 ± 0.7	19.9 ± 3.3	25.5 ± 4.4
360	11.3 ± 0.6	10.2 ± 0.9	29.3 ± 8.0$^{\#}$

Each value represents the average ± SEM (n = 4 - 5).

*$p < 0.05$, **$p < 0.01$, significantly different between 2- and 25-month-old wild-type mice

$^{\#}p < 0.05$, $^{\#\#}p < 0.01$, significantly different between 25-month-old wild-type and *Ttpa*$^{-/-}$ mice.

Supplemental Table 2 Pharmacokinetic parameters of TCA-precipitable [^{125}I]Aβ_{1-40} in 2-month-old wild-type and 25-month-old wild-type and *Ttpa*$^{-/-}$ mice after intravenous administration.

	2-month-old wild-type	25-month-old wild-type	25-month-old *Ttpa*$^{-/-}$
A. Model-independent moment analysis			
AUC (pmol min/mL)	16.1 ± 1.0	13.1 ± 1.5	36.2 ± 17$^{*,\#}$
CLtot (mL/min/kg)	5.05 ± 0.15	4.34 ± 0.32*	2.55 ± 0.50$^{\#\#}$
MRT (min)	184 ± 27	184 ± 43	537 ± 395
Vdss (L/kg)	0.931 ± 0.135	0.802 ± 0.211	1.27 ± 0.86
k_e (min^{-1})	0.00334 ± 0.00049	0.00406 ± 0.00097	0.00196 ± 0.00101$^{\#\#}$
B. Model dependent analysis			
AUC (pmol min/mL)	14.9 ± 0.7	12.5 ± 1.2	33.1 ± 13.7$^{*,\#\#}$
CLtot (mL/min/kg)	5.48 ± 0.38	4.58 ± 0.57	2.71 ± 0.41$^{\#\#}$
A (fmol/mL)	639 ± 48	310 ± 44*	706 ± 210$^{\#\#}$
α (min^{-1})	0.123 ± 0.013	0.126 ± 0.029	0.118 ± 0.027
B (fmol/mL)	26.6 ± 4.0	36.2 ± 13.8	36.7 ± 22.9
β (min^{-1})	0.00276 ± 0.00051	0.00366 ± 0.00154	0.00179 ± 0.00149

The pharmacokinetic parameters of [^{125}I]Aβ_{1-40} plasma concentration profile after intravenous administration were determined by (A) model-independent moment analysis according to Experimental Procedures and (B) model-dependent analysis applying the MULTI program (1) to the bi-exponential equation:

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t}$$

where C(t) = TCA precipitable [^{125}I]Aβ_{1-40} fmol per milliliter of plasma, A and B are the intercepts, and α and β are the slopes of the biexponential curve. The AUC and the total body clearance were calculated by following equation:

$$AUC = A/\alpha + B/\beta$$

$$CLtot = Dose/AUC$$

Each value represents the average ± SD (n = 4 - 5).

*p < 0.05, **p < 0.01, significantly different from 2-month-old wild-type mice.

$^{\#}$p < 0.05, $^{\#\#}$p < 0.01, significantly different from 25-month-old wild-type mice.

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Supplemental Table 3A The ratio of mRNA expressions of top 31 genes in the AlzGene profile (http://www.alzgene.org) in brains of 23-month-old *Ttpa*$^{-/-}$ and wild-type mice.

Description	GeneName	Ratio of *Ttpa*$^{-/-}$/WT
Apolipoprotein E (Apoe), mRNA [NM_009696]	Apoe	1.013
Cholinergic receptor, nicotinic, beta polypeptide 2 (neuronal) (Chrnb2), mRNA [NM_009602]	Chrnb2	1.010
Growth factor receptor bound protein 2-associated protein 2 (Gab2), mRNA [NM_010248]	Gab2	no reliable data obtained
Cholesterol 25-hydroxylase (Ch25h), mRNA [NM_009890]	Ch25h	0.556
Hybrid receptor gp250 precursor, mRNA, partial cds. [AF031816]	Sorl1	0.875
Tumor necrosis factor (Tnf), mRNA [NM_013693]	Tnf	no reliable data obtained
Ornithine transcarbamylase (Otc), mRNA [NM_008769]	Otc	no reliable data obtained
Cystatin C (Cst3), mRNA [NM_009976]	Cst3	1.042
Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 (Ace), transcript variant 2, mRNA [NM_009598]	Ace	1.129
Microtubule-associated protein tau (Mapt), transcript variant 1, mRNA [NM_001038609]	Mapt	1.052
Microtubule-associated protein tau (Mapt), transcript variant 2, mRNA [NM_010838]	Mapt	1.016
VPS10 domain receptor protein SORCS 1 (Sorcs1), mRNA [NM_021377]	Sorcs1	1.052
Not defined	hCG2039140	no reliable data obtained
Transcription factor A, mitochondrial (Tfam), mRNA [NM_009360]	Tfam	0.981
RIKEN cDNA 4921509E05 gene, mRNA (cDNA clone IMAGE:6813822), partial cds. [BC059882]	Pgbd1	1.725
Calcium homeostasis modulator 1 (family with sequence similarity 26, member C)	CALHM1	no reliable data obtained
Interleukin 33 (Il33), mRNA [NM_133775]	Il33	0.908
Interleukin 1 beta (Il1b), mRNA [NM_008361]	Il1b	0.642
Transferrin (Trf), mRNA [NM_133977]	Trf	0.934
Tyrosine kinase, non-receptor, 1 (Tnk1), mRNA [NM_031880]	Tnk1	no reliable data obtained
Ribosomal protein S3a (Rps3a), mRNA [NM_016959]	Rps3a	1.011
Glyceraldehyde-3-phosphate dehydrogenase, spermatogenic (Gapdhs), mRNA [NM_008085]	Gapdhs	no reliable data obtained
Death associated protein kinase 1 (Dapk1), transcript variant 1, mRNA [NM_029653]	Dapk1	1.105
Not defined	GWA_14q31.2	no reliable data obtained
Prion protein (Prnp), mRNA [NM_011170]	Prnp	1.074
Galanin-like peptide precursor (Galp), mRNA [NM_178028]	Galp	no reliable data obtained
5,10-methylenetetrahydrofolate reductase (Mthfr), mRNA [NM_010840]	Mthfr	0.972

LOC651924 similar to Ubiquitin-like 1-activating enzyme E1B (SUMO-1-activating enzyme subunit 2) (Anthracycline-associated resistance ARX)	LOC651924	no reliable data obtained
Neural precursor cell expressed, developmentally down-regulated gene 9 (Nedd9), mRNA [NM_017464]	Nedd9	1.042
Ctonucleoside triphosphate diphosphohydrolase 7 (Entpd7), mRNA [NM_053103]	Entpd7	1.098
Brain derived neurotrophic factor (Bdnf), transcript variant 1, mRNA [NM_007540]	Bdnf	1.276
Interleukin 1 alpha (Il1a), mRNA [NM_010554]	Il1a	no reliable data obtained

Supplemental Table 3B The ratio of mRNA expressions of 70 genes which were not in Supplemental Table 3A, but were biologically closely related to Aβ metabolisms in the brain.

Description	GeneName	Ratio of *Ttpa*$^{-/-}$/WT
Insulin degrading enzyme (Ide), mRNA [NM_031156]	Ide	0.720
Epidermal growth factor (Egf), mRNA [NM_010113]	Egf	0.787
Matrix metallopeptidase 2 (Mmp2), mRNA [NM_008610]	Mmp2	0.803
ATP-binding cassette, sub-family B (MDR/TAP), member 1A (Abcb1a), mRNA [NM_011076]	Abcb1a	0.804
Low density lipoprotein receptor-related protein 2 (Lrp2), mRNA [NM_001081088]	Lrp2	0.813
Anterior pharynx defective 1c homolog (C. elegans) (Aph1c), mRNA [NM_026674]	Aph1c	0.826
Phospholipase C-alpha (PLC-alpha) mRNA, complete cds. [M73329]	Pdia3	0.853
A disintegrin and metallopeptidase domain 10 (Adam10), mRNA [NM_007399]	Adam10	0.865
Matrix metallopeptidase 9 (Mmp9), mRNA [NM_013599]	Mmp9	0.875
Transthyretin (Ttr), mRNA [NM_013697]	Ttr	0.875
Platelet-derived growth factor, D polypeptide (Pdgfd), mRNA [NM_027924]	Pdgfd	0.893
Gelsolin (Gsn), mRNA [NM_146120]	Gsn	0.902
Nerve growth factor, beta (Ngfb), mRNA [NM_013609]	Ngfb	0.910
Alpha-2-macroglobulin (A2m), mRNA [NM_175628]	A2m	0.917
Endothelin converting enzyme 2 (Ece2), mRNA [NM_139293]	Ece2	0.922
Low density lipoprotein receptor (Ldlr), mRNA [NM_010700]	Ldlr	0.926
Angiotensin I converting enzyme (peptidyl-dipeptidase A) 2 (Ace2), mRNA [NM_027286]	Ace2	0.929
Beta-site APP-cleaving enzyme 2 (Bace2), mRNA [NM_019517]	Bace2	0.934
RAS-related protein-1a (Rap1a), mRNA [NM_145541]	Rap1a	0.935
Ubiquilin 2 (Ubqln2), mRNA [NM_018798]	Ubqln2	0.937
Protein kinase C, theta (Prkcq), mRNA [NM_008859]	Prkcq	0.938
Anterior pharynx defective 1b homolog (C. elegans) (Aph1b), mRNA [NM_177583]	Aph1b	0.938
Membrane metallo endopeptidase (Mme), mRNA [NM_008604]	Mme	0.946
A disintegrin and metallopeptidase domain 17 (Adam17), mRNA [NM_009615]	Adam17	0.950
Presenilin 2 (Psen2), mRNA [NM_011183]	Psen2	0.958
Thymoma viral proto-oncogene 2 (Akt2), mRNA [NM_007434]	Akt2	0.959
Protein kinase C, mu (Prkcm), mRNA [NM_008858]	Prkcm	0.965

Platelet-derived growth factor, C polypeptide (Pdgfc), mRNA [NM_019971]	Pdgfc	0.965
Protein kinase C, eta (Prkch), mRNA [NM_008856]	Prkch	0.967
Ubiquilin 1 (Ubqln1), transcript variant 1, mRNA [NM_026842]	Ubqln1	0.970
Protein kinase C, zeta (Prkcz), transcript variant 1, mRNA [NM_008860]	Prkcz	0.973
Presenilin 1 (Psen1), mRNA [NM_008943]	Psen1	0.982
Glycogen synthase kinase 3 beta (Gsk3b), mRNA [NM_019827]	Gsk3b	0.985
Protein kinase C, alpha (Prkca), mRNA [NM_011101]	Prkca	0.991
Thymoma viral proto-oncogene 3 (Akt3), mRNA [NM_011785]	Akt3	0.993
Amyloid beta (A4) precursor protein (App), mRNA [NM_007471]	App	0.993
ATP-binding cassette, sub-family B (MDR/TAP), member 1B (Abcb1b), mRNA [NM_011075]	Abcb1b	1.003
Very low density lipoprotein receptor (Vldlr), mRNA [NM_013703]	Vldlr	1.006
Thymoma viral proto-oncogene 1 (Akt1), mRNA [NM_009652]	Akt1	1.007
Protein kinase C, epsilon (Prkce), mRNA [NM_011104]	Prkce	1.009
Tyrosine kinase 2 (Tyk2), mRNA [NM_018793]	Tyk2	1.011
Nicastrin (Ncstn), mRNA [NM_021607]	Ncstn	1.024
Phospholipase D1 (Pld1), mRNA [NM_008875]	Pld1	1.025
RAS related protein 1b (Rap1b), mRNA [NM_024457]	Rap1b	1.027
Protein kinase C, nu (Prkcn), mRNA [NM_029239]	Prkcn	1.029
Ubiquilin 1 (Ubqln1), transcript variant 2, mRNA [NM_152234]	Ubqln1	1.036
Presenilin enhancer 2 homolog (C. elegans) (Psenen), mRNA [NM_025498]	Psenen	1.040
Beta-site APP cleaving enzyme 1 (Bace1), mRNA [NM_011792]	Bace1	1.050
Low density lipoprotein receptor-related protein 1 (Lrp1), mRNA [NM_008512]	Lrp1	1.053
A disintegrin and metallopeptidase domain 9 (meltrin gamma) (Adam9), mRNA [NM_007404]	Adam9	1.059
RAS-related C3 botulinum substrate 1 (Rac1), mRNA [NM_009007]	Rac1	1.059
Platelet derived growth factor, alpha (Pdgfa), mRNA [NM_008808]	Pdgfa	1.062
Protein kinase C, beta 1 (Prkcb1), mRNA [NM_008855]	Prkcb1	1.071
Somatostatin (Sst), mRNA [NM_009215]	Sst	1.074
Protein kinase C, delta (Prkcd), mRNA [NM_011103]	Prkcd	1.083
Serum response factor (Srf), mRNA [NM_020493]	Srf	1.111
Endothelin converting enzyme 1 (Ece1), mRNA [NM_199307]	Ece1	1.131
Glycogen synthase kinase 3 alpha (Gsk3a), mRNA [NM_001031667]	Gsk3a	1.134
Anterior pharynx defective 1a homolog (C. elegans) (Aph1a), mRNA [NM_146104]	Aph1a	1.139

Tyrosine kinase (arg) mRNA, partial cds. [U40827]	Abl2	1.140
Platelet derived growth factor, B polypeptide (Pdgfb), mRNA [NM_011057]	Pdgfb	1.144
Protein kinase C, iota (Prkci), mRNA [NM_008857]	Prkci	1.167
Plasminogen activator, tissue (Plat), mRNA [NM_008872]	Plat	1.177
Protein kinase C, gamma (Prkcc), mRNA [NM_011102]	Prkcc	1.218
Advanced glycosylation end product-specific receptor (Ager), mRNA [NM_007425]	Ager	no reliable data obtained
G-protein coupled receptor 3 (Gpr3), mRNA [NM_008154]	Gpr3	no reliable data obtained
Interferon gamma (Ifng), mRNA [NM_008337]	Ifng	no reliable data obtained
Matrix metallopeptidase 3 (Mmp3), mRNA [NM_010809]	Mmp3	no reliable data obtained
Plasminogen activator, urokinase (Plau), mRNA [NM_008873]	Plau	no reliable data obtained
Rhodopsin (Rho), mRNA [NM_145383]	Rho	no reliable data obtained

Supplemental Methods for Supplemental Table 3

Gene chip analysis

Three 23-month-old *Ttpa*$^{-/-}$ and three wild-type littermate mice were examined. Total RNA was extracted from the brains using MirVana kit (Ambion, Austin, TX). An aliquot (0.5 μg) of RNA solution was used for preparation of cyanine3-labeled cRNA for hybridization to high-density oligonucleotide arrays. Cyanine3-labeled RNA samples were hybridized to a gene chips (Whole Mouse Genome Oligo Microarray; Agilent Technologies, Santa Clara CA). The images of hybridization signals were scanned with the Agilent Technologies Microarray Scanner. We analyzed 41,252 genes by GeneSpring (Agilent Technologies).

Quantitative reverse transcription polymerase chain reaction (qRT-PCR)

The extracted RNAs were also reverse-transcribed with Superscript III and random hexamers (Invitrogen, Carlsbad, CA). The qRT-PCR was performed using the LightCycler 480 Probes Master (Roche Diagnostics, Rotkreuz, Switzerland), in accordance with the manufacturer's instructions. The amplification conditions were 45 cycles of denaturation at 95 °C for 10 seconds and annealing at 60 °C for 30 seconds and 72 °C for 1 second with Light Cycler 480 II (Roche Diagnostics). Primers for mouse *Ide* and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) mRNAs were designed by Applied Biosystems (Foster City, CA) and *Gapdh* was used to normalize the qRT-PCR values.

Supplemental Results for Supplemental Table 3

mRNA level of IDE was most influenced in Ttpa$^{-/-}$ *mouse brains concerning of AD related genes.*

By the gene chip analysis, we evaluated important genes associated with AD pathology, which are listed in an online database of AlzGene (http://www.alzgene.org) (1). We showed the results of top 31 gene expressions in the AlzGene profile (Supplemental Table 3A). Out of 31 genes, 2 genes, *Ch25h* and *Il1b,* were reduced by more than 20%, and 2 genes, *Bdnf* and *Pgbd1,* were increased by more than 20% in *Ttpa*$^{-/-}$ mice. Moreover, we also listed the results of the genes which were biologically closely related to Aβ metabolism in the brain (2-6) (Supplemental Table 3B). Two genes, *Ide* and *Egf,* were decreased and only *Prkcc* was increased by more than 20% in *Ttpa*$^{-/-}$ mice. The followings are explanations of potential biological roles/influences of each 7 gene on Aβ metabolism.

Altered-regulated genes in AlzGene profiling list

1) Cholesterol 25-hydroxylase (*Ch25h)* polymorphisms are possibly associated with different rates of brain Aβ deposition (7). However the relationship between the expression level of *Ch25h* and Aβ metabolism is unknown.
2) RIKEN cDNA 4921509E05 gene (*Pgbd1*) polymorphisms are possibly associated with AD. However, its function is unknown.
3) Interleukin 1 beta (*Il1b*) is an inflammatory cytokine that could stimulate γ-secretase activity and increases the production of Aβ (8).
4) Brain derived neurotrophic factor (*Bdnf*) exerts substantial protective effects on crucial neuronal circuitry involved in AD, acting through amyloid-independent mechanisms (9). However, it has been also reported that the interruption of BDNF signaling in hippocampal neurons rapidly activates the amyloidogenic pathway and causes neuronal apoptotic death (10).

Down regulated genes in Aβ metabolism-related genes
1) Insulin degrading enzyme (*Ide*) is one of Aβ degradation enzymes.
2) Stimulation of receptor tyrosine kinases, such as the receptors for epidermal growth factor (EGF), make BACE activity and subsequent Aβ production enhanced in cultured cells as well as in mouse hippocampus (11).

Up regulated genes in Aβ metabolism-related genes
1) Concerning of protein kinase C, gamma (*Prkcc*), the inhibition or impairment of PKC activity leads to compromised learning and memory, whereas an appropriate activation of PKC isozymes has been found to enhance learning and memory and/or to produce antidementic effects (12).

The decreased expression of *Ide* is the only biologically reasonable change which can be responsible for the enhanced accumulation of Aβ in the brain, and in contrast, expression change of other six genes were predicted to reduce Aβ accumulation except for those of *Ch25h* and *Pgbd1* of unknown function.
Therefore, we furthermore confirmed the expression change of *Ide* in *Ttpa*$^{-/-}$ mice brains by qRT-PCR, which is almost same result; reduction of the mRNA levels of IDE was 36.4% by qRT-PCR (38.0% by gene chip analysis) .

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