

## Supporting Information

Neuron-specific methylome analysis reveals epigenetic regulation and tau-related dysfunction of BRCA1 in Alzheimer's disease

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## SI Material and Methods

### *Sequential detergent protein extraction*

Sequential detergent protein extraction was performed by modifying previously published methods

(1-6). Inferior temporal gyrus samples were homogenized using a Teflon homogenizer (10-strokes)

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in phosphate buffered saline (PBS), supplemented with protease inhibitor cocktail (Roche), and phosphatase inhibitor cocktail (Roche, Basel, Switzerland). The samples were then centrifuged at 20,000 ×g for 30 min at 4°C, to obtain the PBS-soluble fraction. The pellets were then subjected to sequential fractionation with 1% Triton X-100/PBS, 2% N-lauroylsarcosine (Sarkosyl)/PBS, and 0.1% sodium dodecyl sulfate (SDS)/PBS in a serial manner, each time saving the centrifuged supernatants as the soluble fractions (sup) for each detergent. The SDS insoluble pellet (ppt) was suspended in 70% formic acid (Wako Pure Chemical Industries, Osaka, Japan), and incubated at 50°C for 30 min. After evaporation, samples that had been suspended in formic acid were re-suspended in PBS and subjected to sonication to obtain formic acid-soluble fractions.

*Pyrosequencing*

Bisulfite-conversion of DNA was processed by applying 100 ng of genomic DNA to an EpiTect Bisulfite kit (Qiagen, Hilden, Germany), following the manufacturer's instructions; the final product was eluted with 50 µL buffer. We designed primers for PCR and pyrosequencing using PyroMark Assay Design Software (SI Appendix Table, S4 and S5). Samples were applied to PyroMark Q24 using PyroMark Gold Q24 Reagents (Qiagen), following the amplification of



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bisulfite-converted DNA by PCR using a PyroMark PCR Kit (Qiagen). The results were analyzed using PyroMark Q24 software (Qiagen).

*Cell culture and sample preparation*

The N2a cell line was purchased from ATCC (Manassas, VA, USA). The N2a swe.10 cell line was provided by Sam Sisodia (The University of Chicago). Cells were cultured in 5% CO<sub>2</sub> and 95% air, and incubated at 37°C. The N2a cell line was cultured in high glucose Dulbecco's modified Eagle media (DMEM) (Wako, Japan), supplemented with 10% fetal bovine serum (FBS) (Invitrogen, Carlsbad, CA, USA). The N2a swe.10 cell line was cultured in 50% high glucose DMEM and 50% Opti-MEM (Invitrogen), supplemented with 5% FBS, non-essential amino acids (NEAA), and 200 µg/mL G418 (Roche, Basel, Switzerland). Cells were tested for mycoplasma contamination by visual inspection with 4',6-diamidino-2-phenylindole (DAPI). N2a swe.10 cells were differentiated for 96hours (h) in DMEM supplemented with 1% FBS and 10 µM retinoic acid (Sigma-Aldrich, St. Louis, MO, USA). In co-culture assay, N2a cells were used for recipient cells, and were cultured at the bottom of a dish. while donor cells were cultured in the cell culture inserts. For donor cells, either N2a or N2a swe.10 cells were cultured in the same dish, but within the area of 1 µm-pored

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insert (BD Biosciences, San Jose, CA, USA). For biochemical studies, cells were harvested in PBS with 10 mM ethylenediaminetetraacetic acid (EDTA) at 4°C, and washed twice with pre-chilled PBS. Cells were re-suspended in 50 mM Tris-HCl (pH 8.0), 150 mM sodium chloride, 0.5% (w/v) sodium deoxycholate, 0.1% (w/v) sodium dodecyl sulfate (SDS), 1.0% (w/v) NP-40 substitute (Sigma-Aldrich), protease inhibitor cocktail (Roche), and phosphatase inhibitor cocktail (Roche), and sonicated. The samples were centrifuged at 20,000 ×g for 15 min at 4°C, and the supernatants collected as whole cell lysates. For immunostaining, cells were cultured on φ12 mm coverslips (MATSUNAMI, Tokyo, Japan) and fixed with 4% paraformaldehyde in 0.1 M phosphate-buffer (pH 7.4) for 10 min. For Compound E assay, N2a or N2a swe.10 cells were seeded in 6-well culture dishes at  $1 \times 10^6$ /well. Compound E (Abcam, Cambridge, UK) was added to a final concentration of 25 nM and incubated for 72 h. Cells were harvested for western blot analysis, and conditioned media were subjected to ELISA to determine the concentrations of Aβ<sub>40</sub> and Aβ<sub>42</sub>. Nuclear and cytoplasmic extracts were prepared using an NE-PER Nuclear and Cytoplasmic Extraction Kit (Pierce, Rockford, IL, USA). For recombinant Aβ assay in cultured cells, Aβ peptide (WAKO) was reconstituted in Hexafluoro-2-propanol (HFIP) (Sigma-Aldrich). After evaporation, Aβ peptide was

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reconstituted in DMSO again, and adjusted to 1mM. A $\beta$ <sub>1-40</sub> or A $\beta$ <sub>1-42</sub> was added to the medium and incubated for 36 h. Cells were harvested for western blot analysis.

*Mice brain tissues*

All animal procedures were approved by the Animal Care and Use Committee of the University of Tokyo. 3×Tg-AD mice, harboring mutant amyloid precursor protein (APP KM670/671NL) and mutant tau (MAPT P301L) transgenes, along with knocked-in human mutant Presenilin 1 (PSEN1 M146V), (7), and APP/PS1 mice expressing APP KM670/671NL and PSEN1dE9 (8) were purchased from the Mutant Mouse Regional Resource Center (MMRRC; Davis, CA, USA).

C57BL6/J mice were obtained from CLEA JAPAN, Inc. (Tokyo, Japan). All mice were bred in a pathogen-free environment, housed at no more than four animals per cage in a 12 h-light/dark-cycle, and had access to food and water *ad libitum*. Mice of either sex were subjected to the experiments. Mouse brains were carefully removed after deeply anesthetizing mice using isoflurane (Abbvie, Inc., North Chicago, IL, USA), and were separated into two hemispheres by mid-sagittal dissection. One-half was immediately stored at -80°C for other biochemical procedures (e.g., comet assay), while the other half was placed in 4% paraformaldehyde, 0.1 M phosphate-buffer (pH 7.4)

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for 48 h at 4°C, and embedded in paraffin according to standard procedures. Paraffin-embedded samples were sectioned at a thickness of 6 µm.

*Stereotactic injections*

At the age of 3 months, APP/PS1 mice were anesthetized with isoflurane and placed in a stereotactic frame SR-5M, SM-15M (Narishige, Tokyo, Japan) implemented with microinjector IMS-10 (Narishige). Lentiviral vector preparation in 1 µl volume was injected into the dentate gyrus and hippocampus bilaterally using the following coordinates: ±2.5 mm medial/lateral, -2.9 mm anterior/posterior, 2.7 mm dorsal/ventral from the bregma. The viral preparation was injected with a speed of 1 µl/min using a Hamilton syringe (75RN Neuros Syringe pst-3) (Hamilton company, Reno, NV, USA).

*Total RNA extraction and RT-qPCR analysis*

Total RNA was extracted from the inferior temporal gyrus using an RNeasy mini kit (Qiagen). To determine the RNA integrity number (RIN), we used an RNA 6000 nano assay kit (Agilent Technologies, Santa Clara, CA, USA); samples that achieved RIN > 7 were used for subsequent analysis. Total RNA concentration was measured using a Qubit RNA BR assay kit (Invitrogen).

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Total RNA (1 µg) was reverse-transcribed using ReverTra Ace (TOYOBO, Osaka, Japan) and random primers, and analyzed by TaqMan assay using hs00173233\_m1 (*BRCA1*), hs00152930\_m1 (*AURKC*), hs02743732\_s1 (*ZNF714*), and 4310884e (*GAPDH*) assays on a 7900HT Fast Real-time PCR system (Applied Biosystems, Waltham, MA, USA). Each experiment was performed in quadruplicate and average values were used for further statistical analysis. The expression of each gene was quantified relative to that of *GAPDH*.

*Western blot analysis*

Samples were incubated at 60°C with 4 × lithium dodecyl sulfate (LDS) buffer (Invitrogen) and 1% 2-mercaptoethanol for 15 min, and loaded on 4-15% Mini-PROTEAN TGX gels (Bio-Rad, Hercules, CA, USA), separated by SDS-PAGE, and transferred to polyvinylidene difluoride (PVDF) membrane by Trans-Blot Turbo Blotting System and Trans-Blot Turbo Transfer Pack (Bio-Rad, Hercules, CA, USA). Non-specific binding was blocked with EzBlock CAS (ATTO Corporation, Tokyo, Japan) for 30 min at room temperature. Membranes were then incubated with primary antibodies in Tris-buffered saline / 0.1% Tween (TBST) for 2 h at room temperature, or overnight at 4°C. Anti-BRCA1 (MS110, Abcam Cat# ab16780 Lot# RRID:AB\_2259338, 1:1000),

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anti-human/mouse BRCA1 C-terminus (440621, R and D Systems Cat# MAB22101 Lot#

RRID:AB\_1964507, Minneapolis, US; 1:500), anti-BRCA1 (Abcam Cat# ab47573 Lot#

RRID:AB\_868473; 1:1000), anti-actin (C4, Millipore Cat# MAB1501 Lot# RRID:AB\_2223041,

Billerica, MA, USA, 1:3000), anti-human Tau (HT7, Thermo Fisher Scientific Cat# MN1000 Lot#

RRID:AB\_223454; 1:1000), anti-pTau (AT8, Thermo Fisher Scientific Cat# MN1020 Lot#

RRID:AB\_223647; 1:1000), anti-pTau (AT180, Thermo Fisher Scientific Cat# MN1040 Lot#

RRID:AB\_223649; 1:1000), and anti-amyloid precursor protein (APP)(Y188, Abcam Cat# ab32136

Lot# RRID:AB\_2289606; 1:5000) were used as primary antibodies. Membranes were washed with

TBST for 10 min three times, and then incubated with secondary horseradish peroxidase-conjugated

antibodies (GE Healthcare, Little Chalfont, UK), diluted by 1:2000 in TBST for 1 h at room

temperature. After membranes were washed with TBST for 10 min three times, they were

visualized by EzWestLumi Plus (ATTO). Images were captured by LuminoGraph I (ATTO), and

were quantified by Image J software (<http://imagej.nih.gov/ij/>). The reactivity of anti-BRCA1

antibodies to murine BRCA1 was validated by transient expression of V5-tagged murine BRCA1

and knock-down with lentiviral shRNA (SI-Fig. S6A-D). Antigen pre-absorption assay with GST-

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tagged N-terminal segment of BRCA1 (residues 1-304) (GST-BR304) was conducted to validate the specificity of anti-BRCA1 antibodies used for immunostaining experiments (SI-Fig. S6E).

*Immunohistochemistry*

Human and mouse paraffin sections were de-paraffinized, rehydrated, and subjected to antigen retrieval procedure in sodium citrate buffer containing 10 mM sodium citrate pH 6.0 and 0.05% Tween 20 for 20 min at 110°C. Immunostaining procedure was performed with VECTASTAIN Elite ABC Kit (Vector Laboratories, Burlingame, CA, USA). Samples were incubated with 10% normal goat serum (NGS)/PBS for 30 min at room temperature to block non-specific binding. Sections were then incubated with primary antibodies diluted by TBST for 2 h at room temperature, or overnight at 4°C. Anti-BRCA1 (MS110, Abcam Cat# ab16780 Lot# RRID:AB\_2259338; 1:1000), anti-BRCA1 (Sigma-Aldrich Cat# HPA034966 Lot# RRID:AB\_10795287, 1:1000), anti-AURKC (Sigma-Aldrich Cat# HPA034859 Lot# RRID:AB\_10670298; 1:1000), anti-  $\gamma$ -H2ax(Ser139) (JBW301, Millipore Cat# 05-636 Lot# RRID:AB\_309864; 1:1000), anti-  $\gamma$ -H2ax(Ser139) (EP854(2)Y, Abcam Cat# 2212-1 Lot# RRID:AB\_1267194; 1:1000), anti-pTau (AT180, Thermo Fisher Scientific Cat# MN1040 Lot# RRID:AB\_223649; 1:1000), anti-pTau (AT8, Thermo Fisher

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Scientific Cat# MN1020 Lot# RRID:AB\_223647; 1:1000), anti-human total tau (HT7, Thermo  
Fisher Scientific Cat# MN1000 Lot# RRID:AB\_223454; 1:1000), anti-amyloid  $\beta$ (1-16) (6E10,  
BioLegend; 1:1000), anti-phospho-ATR (Ser428) (Cell Signaling Technology Cat# 2853S Lot#  
RRID:AB\_2290281, MA, USA; 1:500), anti-phospho-ATM (Ser1981) (D6H9, Cell Signaling  
Technology Cat# 5883 Lot# RRID:AB\_10013749; 1:500), anti-phospho-Chk1 (Ser345) (133D3,  
Cell Signaling Technology Cat# 2348S Lot# RRID:AB\_331212; 1:500), anti-phospho-Chk2  
(Thr68) (C13C1, Cell Signaling Technology Cat# 2197S Lot# RRID:AB\_2080501; 1:500), anti-  
phospho-p53 (Ser15) (16G8, Cell Signaling Technology Cat# 9286L Lot# RRID:AB\_331742;  
1:500), anti-RAD51 (Santa Cruz Biotechnology Cat# sc-8349 Lot# RRID:AB\_2253533, CA, USA;  
1:100), anti-BRCA2 (Abcam Cat# ab123491 Lot# RRID:AB\_10972163; 1:1000), anti-Mre11  
(Abcam Cat# ab214 Lot# RRID:AB\_302859; 1:1000), anti-ATR (Abcam Cat# ab2905 Lot#  
RRID:AB\_303400; 1:1000), and anti-p95 NBS1 (Abcam Cat# ab32074 Lot# RRID:AB\_777007;  
1:1000) were used as primary antibodies. Sections were washed with TBST for 10 min three times  
and incubated with biotinylated secondary antibody (Vector Laboratories). Sections were repeatedly  
washed with TBST for 10 min three times, and specific antibody binding was visualized with



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avidin-biotin enzyme complex (Vector Laboratories) and 3,3'-Diaminobenzidine (Sigma-Aldrich).

For immunofluorescence study, sections were de-paraffinized, rehydrated, and were subjected to antigen retrieval in sodium citrate buffer containing 10 mM sodium citrate pH 6.0 and 0.05% Tween 20 for 20 min at 110°C. Sections were then incubated with Sudan black solution (0.1% Sudan Black B in 70% ethanol) to reduce auto-fluorescence and nonspecific antibody binding, followed by blocking with 10% NGS / PBS for 30 min at room temperature. After sections were incubated with primary antibodies for anti-NeuN (A60, Millipore Cat# MAB377 Lot# RRID: AB\_10048713; 1:1000) or anti- $\gamma$ -H2ax (Ser139) (JBW301, Millipore Cat# 05-636 Lot# RRID: AB\_309864; 1:1000), anti-BRCA1 (D54A8, Cell Signaling Technology Cat# 9025S Lot# RRID:AB\_11217634; 1:1000), anti-53BP1 (Novus Cat# NB100-904 Lot# RRID:AB\_10002714; 1:1000) and anti-tubulin  $\beta$ -3 (Abcam Cat# ab18207 Lot# RRID:AB\_444319) diluted by TBST for 2 h at room temperature, they were washed with TBST and the immunoreactivity was visualized with Alexa 594-conjugated secondary antibody (Life Technologies, Carlsbad, CA, USA). As for co-immunostaining of BRCA1 (MS110) and pTau (AT8), primary antibodies were labeled with Alexa 488 or Alexa 594 using Zenon labeling kit (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's

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instructions. Nucleus was visualized by DAPI. Images were captured by Axioplan 2 fluorescent microscope (Carl Zeiss, Oberkochen, Germany) with Axiocam HRc Charge-Coupled Device (CCD) camera system (Carl Zeiss) or BZ-X700 (Keyence, Tokyo, Japan) or confocal microscope LSM510 (Carl Zeiss).

*Complimentary DNAs and expression constructs*

Complimentary DNA of murine *Brca1* mRNA was obtained from pCMV-SPORT6-mBrca1 (clone ID 30431022), purchased from DNAFORM (Yokohama, Japan) and used to generate entry clone vectors by BP recombination with pDONR221, after addition of attB1 and attB2 sequences. For internal ribosomal entry site (IRES) constructs, AcGFP1 cDNA of pIRES2-AcGFP1 (Clontech, Mountain View, CA, USA) was replaced with mCherry to generate pIRES2-mCherry.

Complimentary DNA of APP mutant (KM670/671NL) was sub-cloned into the multiple cloning sites of pIRES2-mCherry to generate entry clone vectors. Two murine BRCA1 shRNA target sequences, 5'-AGCGGGCGACCATGAAGTATA-3', 5'-AATTCAGAGCCAGATTATGTA-3', and three human BRCA1 shRNA target sequence, 5'-CAGCAGTTTATTACTCACTAA-3', 5'-CAGGAAATGGCTGAACTAGAA-3', and 5'-CCCACCTAATTGTACTGAATT-3' were sub-cloned

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into pcDNA6.2-GW/EmGFP-miR (Life Technologies). pcDNA6.2-GW/EmGFP-miR-nega control (Life Technologies) was used as negative control shRNA construct. These plasmids were subjected to BP recombination with pDONR221 to generate entry clone vectors. The resulting plasmids were subjected to LR recombination with pLenti6.4/R4R2/V5-DEST MultiSite and pENTR-5feCMVp to generate recombinant lentivirus vectors.

*Lentivirus production and concentration*

293FT cells were transfected with the recombinant lentivirus vector and packaging plasmids mix (Life Technologies) using polyethylenimine (PEI) (Polysciences, Warrington, PA, USA) following a previously published protocol (9). Produced lentivirus was harvested 72 h post-transfection, centrifuged to eliminate cell debris, and filtered through a 0.22  $\mu$ m PVDF filter (Millipore).

Lentivirus was centrifuged at 20,000  $\times g$  for 24 h and re-suspended with Hank's Balanced Salt Solution (HBSS) for purification and concentration. Infectious titers were determined by Lenti-X qRT-PCR Titration Kit (Clontech), according to the manufacturer's instructions, to obtain  $1 \times 10^{8-9}$  IFU/mL.

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*Primary neuronal culture*

Mouse primary neuronal culture was prepared as previously described with some modifications

(10). Briefly, cortex from P0 mouse brains were dissociated using Nerve-Cell Culture System

(SUMITOMO, Tokyo, Japan) and seeded at  $1 \times 10^4$ /mL on poly-D-lysine pre-coated coverslips

(Neuvitro, Vancouver, WA, USA) in Neurobasal medium (Invitrogen) containing 2% B27

supplement (Invitrogen). Cells were transduced with lentivirus at day *in vitro* (DIV) 1, fixed with

4% PFA at DIV 5, and subjected to immunofluorescence staining. Half of the media was replaced

with fresh media every 2 days. Cytarabine (5  $\mu$ M) was added at DIV 1 to inhibit glial proliferation.

The length of neurites was measured using ImageJ software ([www.rsweb.nih.gov/ij/](http://www.rsweb.nih.gov/ij/)).

*Enzyme-Linked Immuno-Sorbent Assay (ELISA)*

The concentration of A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> in culture medium was measured using a Human/Rat amyloid-

$\beta$  ELISA Kit (Wako) following the manufacturer's instructions. The conditioned media from N2a

or N2a swe.10 cells was collected and subjected to ELISA.

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*Seed-dependent aggregation of tau in cultured cells*

Tau 4R1N wild-type or P301L mutant was transiently overexpressed in SH-SY5Y cells by transfection of 1 µg wild-type human tau 4R1N or mutant P301L cDNA in pSG5 (pSG5-tau 4R1N or pSG5-P301L) with 3 µl of X-treameGENE 9 (Sigma-Aldrich) in 100 µL of Opti-MEM. After overnight incubation, 4 µg of recombinant tau 4R1N (full-length: FL) or C-terminal fragment (residues 251-441) fibrils (11) was introduced with MultiFectam (Promega, Fitchburg, WI, USA) as described (12). After incubation for 5 h, the medium was replaced with fresh DMEM/F12 and culture was continued for 2 days. The cells were prepared for immunofluorescence and/or immunoblotting analyses as described below.

*Fractionation of cellular proteins and immunoblotting*

SH-SY5Y cells grown in a six-well plate were transfected with several expression vectors and introduced with tau fibrils as described above. After incubation for 2 days, cells were prepared for immunoblotting as described (13). Cells were lysed in 300 µL of homogenization buffer (HB buffer: 10 mM Tris-HCl, pH 7.5 containing 0.8 M NaCl, 1 mM ethyleneglycol bis (2-aminoethyl ether)-*N,N,N,N*-tetraacetic acid (EGTA), 1 mM dithiothreitol (DTT) and 1% N-lauroylsarcosine

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sodium salt (Sarkosyl)) by brief sonication. The lysates were centrifuged at 100,000 ×g for 20 min at room temperature. The supernatant was recovered as Sarkosyl (Sar)-soluble fraction (sup). The pellet was suspended in 100 μL SDS-sample buffer and sonicated. The resulting samples were used as the Sar-insoluble fraction (ppt). Each sample was separated by SDS-PAGE and immunoblotted with the indicated antibodies.

*Immunoelectron microscopy*

Sarkosyl-insoluble fractions were prepared from AD patients' brains as described (14). The samples were dropped onto carbon-coated nickel grids (Nissin EM, Tokyo, Japan). The grids were immunostained with primary antibodies (anti-BRCA1 antibody, MS110, 1:100) and secondary antibody conjugated to 10 nm gold particles (BBI Solutions, Cardiff, UK, 1:50) as described (15). Electron micrograph images were recorded with a JEOL JEM-1400 electron microscope (JEOL, Tokyo, Japan).

*Immunoprecipitation*

Anti-tau antibody (HT7, 1:100) was covalently conjugated with protein G magnetic beads (MBL, Nagoya, Japan) using dimethylpiperimidate (DMP). Brain tissue was homogenized in

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immunoprecipitation (IP) buffer (50 mM Tris-HCl pH 7.5, 150 mM NaCl, 1% NP-40, 0.5% sodium deoxycholate, 1 mM EDTA, protease inhibitor cocktail (Roche), and phosphatase inhibitor cocktail (Roche)) and centrifuged at 20,000 ×g for 15 min at 4°C. The supernatant was mixed with antibody-coupled magnetic beads at 4°C for 1 h, and washed with IP buffer three times. The samples were eluted with 0.1 M Glycine-HCl pH 2.5 and 2M Urea, and subjected to western blot analysis.

*Genetic study*

*TREM2* gene was amplified using primers shown in SI Appendix Table S1. Direct sequence analysis was performed by using the ABI 3700 instrument (Applied Biosystems, Carlsbad, CA, USA) with sequencing primers.

*Statistical analyses*

We used GraphPad Prism 6 software (GraphPad, San Diego, CA, USA) for statistical analyses.

Unless otherwise noted, the significance of differences between groups were determined using *t*-tests. P-values are shown as \*\*\*\*\* P < 0.00001, \*\*\*\* P < 0.0001, \*\*\* P < 0.001, \*\* P < 0.01, \* P < 0.05 respectively unless otherwise noted.

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**Table S1**

Analysis of *TREM2* gene in NC and AD samples.

Single variant analysis		Position	Allele		NC (frequency)			AD (frequency)		
Variant	dbSNP		M	m	MM	Mm	mm	MM	Mm	mm
L211P	rs2234256	41126655	A	g	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
H157Y	rs2234255	41127543	G	a	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
R136Q	rs149622783	41127605	C	t	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
R98W	rs147564421	41129100	G	a	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
T96K	rs2234253	41129105	G	t	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
D87N	rs142232675	41129133	C	t	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
N68K	NA	41129188	G	c	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
T66M	rs201258663	41129195	G	a	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
R62H	rs143332484	41129207	C	t	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
R47H	rs75932628	41129252	C	t	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
Y38C	NA	41129279	A	g	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)
Q33X	rs104894002	41129295	G	a	30 (1.0)	0 (0.0)	0 (0.0)	30 (1.0)	0 (0.0)	0 (0.0)

M, major allele; m, minor allele; MM, major genotype; Mm, heterozygous genotype; mm, minor

genotype. Position refers to the location of the variant in base pairs in chromosome 6 (hg19).

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**Table S2**

Clinical demographics of postmortem DLB brains used in methylation analysis. P values are

calculated by *t*-test or chi-square test.

	NC	DLB	statistics
# of samples	30	21	
male ratio (%)	50	61.9	P = 0.558
age at death	76.7 ± 7.4	81.2 ± 8.5	P = 0.0504
<i>APOE</i> ε4 ratio	26.7	28.6	P = 1.00

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**Table S3**

Clinical demographics of postmortem NC and AD brains used in expression analysis. P values are

calculated by *t*-test or chi-square test.

	NC	AD	statistics
# of samples	9	9	
male ratio (%)	67	33	P = 0.35
age at death	75.8 ± 3.9	79.8 ± 6.8	P = 0.14

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**Table S4**

Pyrosequencing primers used for validation experiment. Forward and Reverse are initial PCR

primers and Sequence corresponds to sequencing primers. [Biotin] corresponds to biotinylated

primer.

Probe ID	Purpose	Sequence		
cg25802888	Forward	5'-	[Biotin]-TTTTGGTTGTGAGTAGGTATAGT	-3'
	Reverse	5'-	AAAACCTCAATCCAAAATTCC	-3'
	Sequence	5'-	AATATACATACCTCAACTAAAAAA	-3'
cg19603903	Forward	5'-	[Biotin]-GGGAATTTTGGATTGAGGTT	-3'
	Reverse	5'-	AAAATACTTCCTAACTA ACTCCTATTA ACT	-3'
	Sequence	5'-	ACTCCTATTA ACTAAAATTCCT	-3'
cg06643849	Forward	5'-	TTAGTTAATAGGAGTTAGTTAGGAAGTAT	-3'
	Reverse	5'-	[Biotin]-CCTACTCCTCCTACAACCTCACTAATATC	-3'
	Sequence	5'-	GTTGGTGTAGGGTATAAAAGA	-3'
cg15128510 cg25432232	Forward	5'-	GTGGGAGGAGAGGGGTAA	-3'
	Reverse	5'-	[Biotin]-CCCAAACCTTACTTCA	-3'
	Sequence	5'-	GGAGAGTGGTTTGAAT	-3'
cg23371413	Forward	5'-	TAGTTAATAGGAGTTAGTTAGGAAGTAT	-3'
	Reverse	5'-	[Biotin]-CCTACTCCTCCTACAACCTCACTAATATC	-3'
	Sequence	5'-	GGAGTTAGTTAGGAAGTATT	-3'
cg22711741	Forward	5'-	AGTTAATAGGAGTTAGTTAGGAAGTAT	-3'
	Reverse	5'-	[Biotin]-TCCTACTCCTCCTACAACCTCACTAATATC	-3'
	Sequence	5'-	GTAGTTAAGGTTGTTT	-3'
cg26730619	Forward	5'-	GAAGGGAAAGAGGTAGAGGAAGGATAT	-3'
	Reverse	5'-	[Biotin]-CTTTCCTTAAACCCAACCAATACACATTC	-3'
	Sequence	5'-	GTTAGGAGGAGTTTATAGT	-3'
cg25067162	Forward	5'-	GAAATTGTAGTTTTATGGAGAGGAATATT	-3'
	Reverse	5'-	[Biotin]-AACATAACTCCAATCCATAACT	-3'
	Sequence	5'-	GGATAGATTGGAGATTTG	-3'
cg02286533	Forward	5'-	TGTTTGGGGTAGGGGAAAT	-3'
	Reverse	5'-	[Biotin]-CCTCAAACCAACCAACCAATTAAC	-3'

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	Sequence	5'-	GGGGTAGGGGAAATG	-3'
cg16006004	Forward	5'-	TTGTTTGGGGTAGGGGAAAT	-3'
	Reverse	5'-	[Biotin]-CCAAAAAATTA ACTCTTACCACTTATCC	-3'
	Sequence	5'-	TTTTAGTTTTAGTGT TTGTTATTTT	-3'
cg26276233	Forward	5'-	TGGGGTAAGTAGTTTTGT AAGG	-3'
	Reverse	5'-	[Biotin]-CATAAACCAAAACCCATTTCCCCTACCC	-3'
	Sequence	5'-	GGTAAGTAGTTTTGT AAGGT	-3'
cg06001716	Forward	5'-	AGTTTGGGGTAAGTAGTTTTGT A	-3'
	Reverse	5'-	[Biotin]-CATAAACCAAAACCCATTTCCCCTACCC	-3'
	Sequence	5'-	GTAAGGTTAGTGGTTTG	-3'
cg18372208	Forward	5'-	[Biotin]-AGGAGTTTGGGGTAAGTAGT	-3'
	Reverse	5'-	TCCCTCAA AACCAACCACCCCATTA	-3'
	Sequence	5'-	TTGTTATTTTTAGGGTTTAGTTTG	-3'
cg14687474	Forward	5'-	[Biotin]-TGTTTGGGGTAGGGGAAATG	-3'
	Reverse	5'-	CCAAAAAATTA ACTCTTACCACTTATCC	-3'
	Sequence	5'-	CCACCCCATTA ACTAAT	-3'
cg01483656	Forward	5'-	GGGAGGAAGTTTTGTTTGAGAA	-3'
	Reverse	5'-	[Biotin]-ATTAAATAACTTTTAAAACCCACCTT	-3'
	Sequence	5'-	GATTATATTTTTGTTATTTAGGGT	-3'
cg15174294	Forward	5'-	GGGAAGGGGAGGGTTGT AAG	-3'
	Reverse	5'-	[Biotin]-CCCTCCAATAATCCCTACACAATC	-3'
	Sequence	5'-	AGGTTTTTTAGTAGTTAATTTTATA	-3'
cg09352518	Forward	5'-	GGGAAGGGGAGGGTTGT AAG	-3'
	Reverse	5'-	[Biotin]-CCCTCCAATAATCCCTACACAATC	-3'
	Sequence	5'-	AGGTTTTTTAGTAGTTAATTTTATA	-3'

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**Table S5**

Pyrosequencing primers used for analysis of murine *Brcal* promoter. Forward and Reverse are initial PCR primers and Sequence corresponds to sequencing primers. [Biotin] corresponds to biotinylated primer.

CpG #	Distance from TSS (bp)	Purpose	Sequence		
#1	15	Forward	5'-	GAGGTGTTGGATTTTTTGGTTGTA	-3'
		Reverse	5'-	[Biotin]-CCCCAACTCCCTCCTCCCTTC	-3'
		Sequence	5'-	AGTTTTTAGGAATATAAGATTTAGA	-3'
#2	503	Forward	5'-	AGTGTAGTTTTAAGGGAAAAGAGTTT	-3'
		Reverse	5'-	[Biotin]-ACCCACAACCTCTTTAATCTA	-3'
		Sequence	5'-	AGGTAAGAGTATTATAGGAATTTAG	-3'
#3	620	Forward	5'-	AGTTGTGGGTTTTAGGAAGATTAT	-3'
		Reverse	5'-	[Biotin]-TTTCCCAAACCCATTAACCACCTCTACTT	-3'
		Sequence	5'-	GGGTTTTAGGAAGATTATAATT	-3'
#4	720	Forward	5'-	TGATTTGGGAAAAGTAGAGGG	-3'
		Reverse	5'-	[Biotin]-TATCTACCCCTCAAATAACCTCTCTAC	-3'
		Sequence	5'-	GGGAAAGGGAAATTTAATTAG	-3'
#5	797	Forward	5'-	ATGTTAGTGATTTGGGAAAAGTAGA	-3'
		Reverse	5'-	[Biotin]-CCACAAAATAATTAACCTCTTCTATCTACC	-3'
		Sequence	5'-	AGAGTTTTTGTTTTTTTTTTTGTAA	-3'
#6, #7	893, 904	Forward	5'-	TGGAAAATTTAGGGAAATATGGGATTAGG	-3'
		Reverse	5'-	[Biotin]-ACCCCTACTTCTAAATAACAATAATAACTT	-3'
		Sequence	5'-	GGAAATATGGGATTAGGT	-3'
#8, #9	938, 949	Forward	5'-	GAGAGGTTATTTTGAGGGGTAGATAGAAAG	-3'
		Reverse	5'-	[Biotin]-CCCTAAACACCAAAAATCACTCCTCTTTAC	-3'
		Sequence	5'-	AGATTTATTTAGTAGGGATAGTAG	-3'

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**Table S6**

Sequencing primers used for analysis of *TREM2* variants. Forward and Reverse are initial PCR

primers and Sequence corresponds to sequencing primers (seq).

Variants	Purpose	Sequence	
L211P	PCR1	5'-	GCCAAGTGGCAAGTATGCAGGC -3'
	PCR2, seq	5'-	GGCTGGTCCCTGGTGGGACTTC -3'
	PCR2, seq	5'-	CCTGAGAGAAGATTCTAATCTGTAGGCC -3'
	PCR1	5'-	GTCCTGGTTTCTCCCCATTCCCTG -3'
H157Y, R136Q	PCR1	5'-	ACTAACTAACATGTAGCAGCTGGTGG -3'
	PCR2, seq	5'-	GGAGGGGTGTTTACATAAGAGATATCCAGGGCCC -3'
	PCR1	5'-	AATGACCTGATCCACATAGGACCAG -3'
	PCR2	5'-	CCCACCCATAAAGGTTCTCCCGCC -3'
R98W, T96K, D87N	PCR2, seq	5'-	TTCCCAGGATCCCTGAGAGCC -3'
	PCR1	5'-	GTAGGGAGATGAGACCATACGATGGGTTTTCCC -3'
	PCR1	5'-	CCAGTCCCTGCAGGTGTCTTG -3'
	PCR2	5'-	AGCCCACAACACCACAGTGTTCCAGGG -3'
N68K, T66M, R62H, R47H, Y38C, Q33X	PCR, seq	5'-	GCATCATGGGGTTGTAGATTCCGC -3'
	PCR	5'-	AAACACATGCTGTGCCATCCGC -3'



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**Table S7**

Result of Infinium methylome analysis of AD related genes.

CHR: chromosome number, MAPINFO: Chromosomal coordinates of the CpG, arm: chromosome

arm, feature and CpG islands are defined by Illumina.  $\beta$ value NC-AD:  $\beta$ value of average AD was

subtracted from average of NC samples. P value was calculated by one-sided *t*-test. TSS:

transcription start site. UTR: untranslated region. IGR: intergenic region.

CpG #	CHR	MAPINFO	arm	gene	feature	CpG islands	$\beta$ value NC-AD	P value (one-sided <i>t</i> -test)
cg06730721	19	1039831	p	<i>ABCA7</i>	TSS1500	island	0.00017999	0.45379528
cg26263477	19	1039863	p	<i>ABCA7</i>	TSS1500	island	-0.001005821	0.373346683
cg05504606	19	1039871	p	<i>ABCA7</i>	TSS1500	island	-0.011745041	0.068207296
cg26264438	19	1039942	p	<i>ABCA7</i>	TSS200	island	0.001548543	0.195717304
cg07726048	19	1039944	p	<i>ABCA7</i>	TSS200	island	0.00278492	0.122175098
cg21590311	19	1040077	p	<i>ABCA7</i>	TSS200	island	0.003282857	0.064198412
cg10749413	19	1041020	p	<i>ABCA7</i>	5'UTR	shore	-0.00253345	0.21414373
cg05989429	19	1041026	p	<i>ABCA7</i>	5'UTR	shore	-0.001579918	0.239462832
cg23027715	19	1045096	p	<i>ABCA7</i>	Body	shore	-0.002253812	0.362483171
cg02817925	19	1046325	p	<i>ABCA7</i>	Body	island	-0.000401564	0.444115291
cg06169110	19	1046615	p	<i>ABCA7</i>	Body	island	0.001359184	0.407259833
cg02253236	19	1046996	p	<i>ABCA7</i>	Body	island	0.001941582	0.270070625
cg02959678	19	1047604	p	<i>ABCA7</i>	Body	island	0.002095005	0.271380517
cg02807077	19	1049287	p	<i>ABCA7</i>	Body	shore	0.006115872	0.025896164
cg23657707	19	1050977	p	<i>ABCA7</i>	Body	island	0.001282284	0.234220846
cg10406526	19	1051079	p	<i>ABCA7</i>	Body	island	0.000652641	0.454813387
cg00874873	19	1051160	p	<i>ABCA7</i>	Body	island	9.32E-05	0.48522457
cg18529892	19	1052159	p	<i>ABCA7</i>	Body	shore	0.000285157	0.484054583
cg24145486	19	1054884	p	<i>ABCA7</i>	Body	shelf	0.002506596	0.24958472
cg02986791	19	1062178	p	<i>ABCA7</i>	Body	shore	0.00399009	0.284496958
cg21995147	19	1064017	p	<i>ABCA7</i>	Body	island	-0.00613838	0.148319753

cg12082025	19	1064218	p	<i>ABCA7</i>	Body	island	-0.010782148	0.277005066
cg26576206	19	1064938	p	<i>ABCA7</i>	Body	island	0.011564149	0.254780086
cg13761375	19	1065184	p	<i>ABCA7</i>	Body	island	0.001011592	0.366001791
cg11363615	8	41507621	p	<i>ANK1</i>	IGR	island	-0.004450573	0.18446204
cg21468634	8	41507844	p	<i>ANK1</i>	IGR	island	0.002183274	0.161299331
cg15649474	8	41507852	p	<i>ANK1</i>	IGR	island	0.002747945	0.052292338
cg25670429	8	41507937	p	<i>ANK1</i>	IGR	shore	0.002364873	0.157759376
cg20677018	8	41508391	p	<i>ANK1</i>	IGR	shore	0.001581652	0.315736368
cg07161603	8	41508618	p	<i>ANK1</i>	IGR	shore	-0.002310296	0.36098446
cg19945060	8	41508779	p	<i>ANK1</i>	IGR	shore	-0.001946652	0.356982275
cg21289397	8	41510988	p	<i>ANK1</i>	3'UTR	island	0.014195058	0.257695654
cg24739382	8	41511175	p	<i>ANK1</i>	3'UTR	island	0.007277427	0.32907607
cg07529534	8	41511314	p	<i>ANK1</i>	3'UTR	island	0.002608004	0.443163462
cg24931737	8	41511709	p	<i>ANK1</i>	3'UTR	shore	0.008739961	0.212838904
cg16140558	8	41514039	p	<i>ANK1</i>	3'UTR	shelf	0.004164877	0.237612713
cg12148515	8	41517301	p	<i>ANK1</i>	3'UTR	open sea	0.029189646	0.142472605
cg13603914	8	41518004	p	<i>ANK1</i>	3'UTR	open sea	0.007437259	0.120452283
cg10794439	8	41518051	p	<i>ANK1</i>	3'UTR	open sea	0.009695964	0.132856135
cg17886457	8	41518134	p	<i>ANK1</i>	3'UTR	open sea	0.001066058	0.446122347
cg10715527	8	41518139	p	<i>ANK1</i>	3'UTR	open sea	-0.010455028	0.306858204
cg04319844	8	41519026	p	<i>ANK1</i>	Body	open sea	-0.003617636	0.360259961
cg00328284	8	41519119	p	<i>ANK1</i>	Body	open sea	0.013667716	0.093711645
cg05066959	8	41519308	p	<i>ANK1</i>	Body	open sea	-0.003959589	0.267994153
cg11823178	8	41519399	p	<i>ANK1</i>	Body	open sea	0.001460177	0.323494916
cg12439423	8	41522721	p	<i>ANK1</i>	Body	open sea	0.001454951	0.411874729
cg25043378	8	41522857	p	<i>ANK1</i>	TSS200	open sea	0.008482586	0.258922545
cg01678292	8	41522873	p	<i>ANK1</i>	TSS200	open sea	-0.001910697	0.424271546
cg11479568	8	41522951	p	<i>ANK1</i>	TSS200	open sea	0.001564098	0.399662619
cg13432087	8	41523480	p	<i>ANK1</i>	TSS1500	open sea	-0.000391706	0.48554443
cg12003463	8	41523968	p	<i>ANK1</i>	TSS1500	open sea	0.001258111	0.454447344
cg11912315	8	41528946	p	<i>ANK1</i>	Body	open sea	0.008649238	0.268611002
cg05986168	8	41529109	p	<i>ANK1</i>	Body	open sea	0.023140221	0.009343593
cg19441908	8	41529140	p	<i>ANK1</i>	Body	open sea	0.008087102	0.15598381
cg17103638	8	41542140	p	<i>ANK1</i>	Body	open sea	-0.000975056	0.358605592
cg26697310	8	41542172	p	<i>ANK1</i>	Body	open sea	0.000171481	0.481554322
cg22532314	8	41546072	p	<i>ANK1</i>	Body	open sea	-0.004272786	0.387306899
cg09897002	8	41553955	p	<i>ANK1</i>	Body	open sea	0.001999383	0.303998403

cg09576978	8	41554080	p	<i>ANK1</i>	Body	open sea	0.003286312	0.233424382
cg08388995	8	41554149	p	<i>ANK1</i>	Body	open sea	0.002100339	0.290528088
cg14445914	8	41556933	p	<i>ANK1</i>	Body	shelf	0.006366526	0.100442234
cg11696388	8	41557540	p	<i>ANK1</i>	Body	shore	0.002224231	0.391249331
cg05234958	8	41557710	p	<i>ANK1</i>	Body	shore	0.002658832	0.292433943
cg08786207	8	41559303	p	<i>ANK1</i>	Body	island	-0.001950782	0.242319537
cg02712294	8	41559393	p	<i>ANK1</i>	Body	island	-0.005604845	0.155752791
cg07533533	8	41559593	p	<i>ANK1</i>	Body	island	0.011778219	0.158569847
cg20464175	8	41559903	p	<i>ANK1</i>	Body	shore	0.029513596	0.019342829
cg07680965	8	41563429	p	<i>ANK1</i>	Body	shelf	-0.009304953	0.224730719
cg13152952	8	41570554	p	<i>ANK1</i>	Body	open sea	-0.002824177	0.258629514
cg10601625	8	41570622	p	<i>ANK1</i>	Body	open sea	0.001390613	0.343883968
cg27260174	8	41576763	p	<i>ANK1</i>	Body	open sea	-0.0003045	0.478757541
cg18491744	8	41580834	p	<i>ANK1</i>	Body	shelf	0.027601145	0.122622391
cg04236786	8	41580903	p	<i>ANK1</i>	Body	shelf	0.012793139	0.090395875
cg13609385	8	41580932	p	<i>ANK1</i>	Body	shelf	0.014830467	0.213813265
cg05538980	8	41581845	p	<i>ANK1</i>	Body	shore	-0.00022215	0.471832455
cg27619646	8	41583018	p	<i>ANK1</i>	Body	shore	0.00203362	0.349350659
cg27650870	8	41583136	p	<i>ANK1</i>	Body	island	0.01137301	0.200560565
cg15706250	8	41583321	p	<i>ANK1</i>	Body	island	0.005011937	0.334310927
cg19537719	8	41583498	p	<i>ANK1</i>	Body	island	-0.00049486	0.456796338
cg18614735	8	41583523	p	<i>ANK1</i>	Body	island	0.006933331	0.241569434
cg03755522	8	41585237	p	<i>ANK1</i>	Body	shore	0.002651053	0.317757122
cg17182837	8	41585554	p	<i>ANK1</i>	Body	shelf	-0.002490254	0.391794856
cg10116189	8	41588560	p	<i>ANK1</i>	Body	open sea	0.003413594	0.11516337
cg20468415	8	41592973	p	<i>ANK1</i>	Body	open sea	-0.013446723	0.21137276
cg27016366	8	41604672	p	<i>ANK1</i>	Body	open sea	0.011411494	0.320580557
cg07889469	8	41624634	p	<i>ANK1</i>	Body	island	0.000922277	0.420095585
cg07162571	8	41624841	p	<i>ANK1</i>	Body	island	0.009344813	0.031787639
cg09125812	8	41625127	p	<i>ANK1</i>	Body	island	0.004973601	0.060696467
cg05522554	8	41625190	p	<i>ANK1</i>	Body	island	0.001483497	0.25406554
cg07235638	8	41625417	p	<i>ANK1</i>	Body	shore	0.001872695	0.26486281
cg24128389	8	41625579	p	<i>ANK1</i>	Body	shore	0.002388536	0.407968655
cg08521995	8	41628237	p	<i>ANK1</i>	Body	shelf	0.004325531	0.348577709
cg05885688	8	41628552	p	<i>ANK1</i>	Body	shelf	0.008481861	0.32981136
cg19442889	8	41639488	p	<i>ANK1</i>	Body	open sea	-0.000984897	0.316015351
cg17256609	8	41643375	p	<i>ANK1</i>	Body	open sea	-0.001566596	0.433599625

cg20263686	8	41643429	p	<i>ANK1</i>	Body	open sea	0.000872027	0.459022606
cg11059357	8	41649676	p	<i>ANK1</i>	Body	open sea	0.024789362	0.040425683
cg09997356	8	41651695	p	<i>ANK1</i>	Body	shelf	-0.000150713	0.471834265
cg26172342	8	41654331	p	<i>ANK1</i>	Body	shore	0.002374529	0.281903269
cg08923054	8	41654455	p	<i>ANK1</i>	Body	shore	0.00423139	0.146368771
cg14030674	8	41654557	p	<i>ANK1</i>	Body	shore	0.002838377	0.204417983
cg00176210	8	41654967	p	<i>ANK1</i>	Body	island	0.00642268	0.155408513
cg26326633	8	41655078	p	<i>ANK1</i>	1stExon	island	0.012883152	0.128494042
cg08194989	8	41655154	p	<i>ANK1</i>	TSS200	island	0.009509336	0.096388952
cg14904662	8	41655673	p	<i>ANK1</i>	TSS1500	island	0.002703537	0.373769821
cg25154801	8	41655826	p	<i>ANK1</i>	TSS1500	island	0.023108107	0.06730583
cg00783104	8	41655894	p	<i>ANK1</i>	TSS1500	island	0.026978682	0.105079444
cg04153489	8	41655983	p	<i>ANK1</i>	TSS1500	island	0.003916102	0.349377841
cg08894480	8	41659962	p	<i>ANK1</i>	Body	shelf	-0.017623122	0.123275056
cg02716401	8	41668188	p	<i>ANK1</i>	Body	open sea	0.008166447	0.175630941
cg03493932	8	41668449	p	<i>ANK1</i>	Body	open sea	-0.003786802	0.328302025
cg21132564	8	41675568	p	<i>ANK1</i>	Body	open sea	0.003507371	0.337710007
cg19997384	8	41685595	p	<i>ANK1</i>	Body	shore	0.002500937	0.428683478
cg12292531	8	41685719	p	<i>ANK1</i>	Body	shore	0.003977701	0.119621721
cg02172579	8	41685992	p	<i>ANK1</i>	Body	island	0.011705249	0.040837714
cg03596181	8	41686111	p	<i>ANK1</i>	Body	island	0.00416683	0.154082422
cg10470489	8	41686324	p	<i>ANK1</i>	Body	island	0.015051106	0.17668803
cg11207534	8	41686438	p	<i>ANK1</i>	Body	island	-0.005879258	0.306260825
cg16129172	8	41686467	p	<i>ANK1</i>	Body	island	0.007249574	0.177465188
cg12180191	8	41686706	p	<i>ANK1</i>	Body	shore	0.019221324	0.087529474
cg15133790	8	41689378	p	<i>ANK1</i>	Body	shelf	-0.013205464	0.25748516
cg14354820	8	41691767	p	<i>ANK1</i>	Body	open sea	0.008662453	0.341575475
cg22845790	8	41694003	p	<i>ANK1</i>	Body	open sea	0.009098118	0.129630967
cg27479267	8	41703005	p	<i>ANK1</i>	Body	open sea	0.006439856	0.380758931
cg21342785	8	41707516	p	<i>ANK1</i>	Body	open sea	-0.021838159	0.133240445
cg02231197	8	41730737	p	<i>ANK1</i>	Body	shelf	-0.001386048	0.40473386
cg21470142	8	41732895	p	<i>ANK1</i>	Body	shore	-0.00030653	0.483037819
cg08604534	8	41733475	p	<i>ANK1</i>	Body	shore	-0.000955811	0.391653024
cg25052664	8	41733652	p	<i>ANK1</i>	Body	island	0.020017611	0.128801778
cg24800880	8	41733711	p	<i>ANK1</i>	Body	island	-0.002255279	0.351559929
cg02392634	8	41733831	p	<i>ANK1</i>	Body	island	0.012009909	0.108970103
cg06812861	8	41739738	p	<i>ANK1</i>	Body	open sea	-0.021109286	0.116177268

cg22746182	8	41749867	p	<i>ANK1</i>	Body	shelf	-0.005121542	0.339682557
cg00583328	8	41753348	p	<i>ANK1</i>	Body	island	0.034643122	0.049902289
cg09405790	8	41753440	p	<i>ANK1</i>	Body	island	0.007104946	0.17443457
cg05166490	8	41754172	p	<i>ANK1</i>	1stExon	island	0.000355871	0.408897978
cg17331296	8	41754181	p	<i>ANK1</i>	1stExon	island	-0.000927651	0.386073746
cg19585816	8	41754742	p	<i>ANK1</i>	TSS1500	island	0.003786765	0.263731411
cg19891728	8	41754871	p	<i>ANK1</i>	TSS1500	island	0.000617664	0.397804689
cg20676100	8	41754928	p	<i>ANK1</i>	TSS1500	island	-0.003394838	0.119560359
cg01616178	8	41755140	p	<i>ANK1</i>	TSS1500	island	0.002141502	0.361210015
cg19844326	8	41755409	p	<i>ANK1</i>	TSS1500	shore	0.005524073	0.190423751
cg14123992	19	45407868	q	<i>APOE</i>	TSS1500	shelf	0.013610372	0.019681845
cg04406254	19	45407945	q	<i>APOE</i>	TSS1500	shelf	0.009598514	0.227117301
cg01032398	19	45408121	q	<i>APOE</i>	TSS1500	shelf	-0.007675741	0.02287373
cg12049787	19	45409080	q	<i>APOE</i>	1stExon	shelf	0.006881376	0.104293105
cg08955609	19	45409353	q	<i>APOE</i>	5'UTR	shelf	0.000681538	0.334164842
cg18768621	19	45409440	q	<i>APOE</i>	5'UTR	shelf	0.005887273	0.083864114
cg19514613	19	45409713	q	<i>APOE</i>	5'UTR	shelf	0.011238653	0.040187938
cg06750524	19	45409955	q	<i>APOE</i>	Body	shore	0.006783652	0.240673598
cg05501958	19	45411873	q	<i>APOE</i>	Body	island	-0.005043801	0.25576148
cg18799241	19	45412599	q	<i>APOE</i>	3'UTR	island	-0.000543906	0.459702989
cg21879725	19	45412647	q	<i>APOE</i>	3'UTR	shore	-0.005588893	0.078615636
cg13965133	21	27228125	q	<i>APP</i>	IGR	open sea	-0.005894199	0.33259425
cg21000999	21	27253974	q	<i>APP</i>	3'UTR	open sea	-0.003070302	0.435845125
ch.21.228978R	21	27297434	q	<i>APP</i>	Body	open sea	0.013018012	0.120404367
cg25314245	21	27354743	q	<i>APP</i>	Body	open sea	-0.00798937	0.137081747
cg24168308	21	27372387	q	<i>APP</i>	Body	open sea	0.002389075	0.29792489
cg11321156	21	27372396	q	<i>APP</i>	Body	open sea	-0.002706372	0.322585901
cg23269692	21	27372446	q	<i>APP</i>	Body	open sea	-0.003020086	0.284993369
cg18274664	21	27372461	q	<i>APP</i>	Body	open sea	-0.000123335	0.489541593
cg14414154	21	27538021	q	<i>APP</i>	Body	shelf	-0.006180272	0.3192913
cg01286133	21	27540106	q	<i>APP</i>	Body	shore	0.009328951	0.212475432
cg19788250	21	27540220	q	<i>APP</i>	Body	shore	0.005708015	0.20527451
cg18597421	21	27540728	q	<i>APP</i>	Body	shore	-0.001294782	0.444474004
cg12144476	21	27541894	q	<i>APP</i>	Body	island	0.001562089	0.273654794
cg10129201	21	27542749	q	<i>APP</i>	Body	island	-0.000900196	0.270797455
cg13169373	21	27542843	q	<i>APP</i>	Body	island	0.002840388	0.4173351
cg15407086	21	27543045	q	<i>APP</i>	1stExon	island	-0.004729246	0.065266044

cg03779431	21	27543124	q	<i>APP</i>	1stExon	island	0.001709356	0.146244138
cg08015776	21	27543229	q	<i>APP</i>	TSS200	island	0.001401846	0.177381019
cg27372898	21	27543410	q	<i>APP</i>	TSS1500	island	0.002734416	0.083217316
cg08866780	21	27543523	q	<i>APP</i>	TSS1500	island	-0.00082172	0.424669872
cg26153954	21	27543721	q	<i>APP</i>	TSS1500	shore	-0.001101875	0.43722838
cg19707128	2	127635279	q	<i>BINI</i>	IGR	open sea	0.002218409	0.446697581
cg03741475	2	127635614	q	<i>BINI</i>	IGR	open sea	0.004774612	0.172695159
cg24164996	2	127635644	q	<i>BINI</i>	IGR	open sea	-0.005703359	0.255953421
cg16909742	2	127635678	q	<i>BINI</i>	IGR	open sea	-0.003961273	0.27486291
cg01390061	2	127642574	q	<i>BINI</i>	IGR	shore	-0.012406344	0.152277897
cg04202002	2	127643360	q	<i>BINI</i>	IGR	shore	0.004357572	0.219422422
cg08535260	2	127643971	q	<i>BINI</i>	IGR	island	0.003646056	0.059326201
cg23460843	2	127644075	q	<i>BINI</i>	IGR	island	0.008812835	0.185415209
cg19738404	2	127644612	q	<i>BINI</i>	IGR	shore	0.008933026	0.299246814
cg05736424	2	127646592	q	<i>BINI</i>	IGR	shelf	-0.011810275	0.181863396
cg02304361	2	127699673	q	<i>BINI</i>	IGR	open sea	0.014917121	0.14275502
cg03089864	2	127705908	q	<i>BINI</i>	IGR	open sea	-0.018932696	0.172956087
cg17962090	2	127728910	q	<i>BINI</i>	IGR	shore	0.004219216	0.228971519
cg20663365	2	127729097	q	<i>BINI</i>	IGR	shore	0.022493209	0.056658865
cg08687025	2	127729123	q	<i>BINI</i>	IGR	shore	-0.016347916	0.187191045
cg22669787	2	127729597	q	<i>BINI</i>	IGR	shore	-0.000703346	0.401097536
cg17214616	2	127729681	q	<i>BINI</i>	IGR	island	-0.00342061	0.197348763
cg11527373	2	127729760	q	<i>BINI</i>	IGR	island	0.000415168	0.374268238
cg15442262	2	127729904	q	<i>BINI</i>	IGR	island	0.003250366	0.167253303
cg22009500	2	127729962	q	<i>BINI</i>	IGR	shore	0.012920872	0.113496932
cg16988616	2	127732268	q	<i>BINI</i>	IGR	shelf	0.003232627	0.382555202
cg03516358	2	127733882	q	<i>BINI</i>	IGR	shore	-0.007219232	0.048037307
cg14431024	2	127734416	q	<i>BINI</i>	IGR	island	-0.004041577	0.162895365
cg11657043	2	127734511	q	<i>BINI</i>	IGR	island	0.006716371	0.248131273
cg02767024	2	127734676	q	<i>BINI</i>	IGR	island	0.002314617	0.388418918
cg06006907	2	127734952	q	<i>BINI</i>	IGR	shore	0.004640283	0.207496292
cg27228272	2	127772338	q	<i>BINI</i>	IGR	open sea	0.005632243	0.379524943
cg22762545	2	127774099	q	<i>BINI</i>	IGR	open sea	0.001358385	0.370185694
cg26829670	2	127780459	q	<i>BINI</i>	IGR	shelf	-0.002989518	0.216148705
cg08563189	2	127780654	q	<i>BINI</i>	IGR	shore	0.002713131	0.350730482
cg19153828	2	127782651	q	<i>BINI</i>	IGR	island	-0.010099519	0.015487939
cg19590598	2	127782813	q	<i>BINI</i>	IGR	island	-0.004670791	0.071672561

cg03766620	2	127783082	q	<i>BINI</i>	IGR	island	0.000175142	0.461867412
cg22830113	2	127783168	q	<i>BINI</i>	IGR	island	-0.00199706	0.321600812
cg12632573	2	127783243	q	<i>BINI</i>	IGR	island	0.004561522	0.271268539
cg02139871	2	127783370	q	<i>BINI</i>	IGR	shore	0.001389648	0.397089529
cg21554034	2	127785512	q	<i>BINI</i>	IGR	shelf	-0.004672686	0.283973701
cg19954334	2	127791786	q	<i>BINI</i>	IGR	open sea	-0.006259297	0.212578718
cg22883290	2	127800646	q	<i>BINI</i>	IGR	open sea	-0.025612666	0.15606573
cg05942551	2	127801137	q	<i>BINI</i>	IGR	open sea	0.002840389	0.201369211
cg00824156	2	127801271	q	<i>BINI</i>	IGR	open sea	0.002872364	0.292383681
cg22768700	2	127805770	q	<i>BINI</i>	3'UTR	open sea	0.000752163	0.402810345
cg02116471	2	127805855	q	<i>BINI</i>	3'UTR	open sea	0.002054093	0.337958069
cg18981277	2	127805910	q	<i>BINI</i>	3'UTR	open sea	0.004930982	0.182631358
cg24587400	2	127811805	q	<i>BINI</i>	Body	open sea	-0.016696681	0.167282146
cg01441308	2	127811853	q	<i>BINI</i>	Body	open sea	-0.009219978	0.259456314
cg22376361	2	127815133	q	<i>BINI</i>	Body	shelf	0.002586364	0.155007447
cg06912356	2	127815206	q	<i>BINI</i>	Body	shelf	-0.000606715	0.371699287
cg05603944	2	127817030	q	<i>BINI</i>	Body	shore	0.001905983	0.312449409
cg15356320	2	127818000	q	<i>BINI</i>	Body	island	0.013537865	0.145338254
cg08663425	2	127818046	q	<i>BINI</i>	Body	island	-0.000160598	0.495531539
cg13293246	2	127818101	q	<i>BINI</i>	Body	island	0.008236263	0.111537696
cg21427464	2	127818226	q	<i>BINI</i>	Body	island	0.014305595	0.03318228
cg05842548	2	127821711	q	<i>BINI</i>	Body	shelf	0.007436553	0.25336363
cg06021088	2	127822551	q	<i>BINI</i>	Body	open sea	0.001856563	0.438485846
cg24998649	2	127825935	q	<i>BINI</i>	Body	open sea	0.007446347	0.233670164
cg26467631	2	127826083	q	<i>BINI</i>	Body	open sea	0.006346979	0.049595879
cg05157961	2	127826149	q	<i>BINI</i>	Body	open sea	-0.001174346	0.324357298
cg27405400	2	127839539	q	<i>BINI</i>	Body	open sea	0.014673865	0.013780782
cg04019522	2	127852450	q	<i>BINI</i>	Body	open sea	0.008370651	0.263461205
cg00436254	2	127862614	q	<i>BINI</i>	Body	shore	0.000339899	0.488875727
cg00091827	2	127863656	q	<i>BINI</i>	Body	island	-0.001592246	0.295534474
cg07661177	2	127864026	q	<i>BINI</i>	Body	island	0.000213069	0.470167127
cg04095651	2	127864359	q	<i>BINI</i>	Body	island	0.001930955	0.283227841
cg23667267	2	127864762	q	<i>BINI</i>	1stExon	island	0.000159781	0.48283482
cg10353870	2	127864778	q	<i>BINI</i>	1stExon	island	-0.002311261	0.093474913
cg22364819	2	127864926	q	<i>BINI</i>	TSS200	island	0.002340398	0.032449986
cg23599640	2	127864941	q	<i>BINI</i>	TSS200	island	0.001547711	0.275335278
cg14478610	2	127864964	q	<i>BINI</i>	TSS200	island	0.001574955	0.181286337

cg02446627	2	127865197	q	<i>BIN1</i>	TSS1500	island	0.001029669	0.374303948
cg07774478	2	127865245	q	<i>BIN1</i>	TSS1500	island	0.003744745	0.329628393
cg02161262	2	127865248	q	<i>BIN1</i>	TSS1500	island	-0.002463426	0.294543297
cg25228746	2	127865379	q	<i>BIN1</i>	TSS1500	shore	-0.004498821	0.026644802
cg08168897	2	127865431	q	<i>BIN1</i>	TSS1500	shore	-0.006173267	0.323560221
cg06223080	2	127868745	q	<i>BIN1</i>	IGR	shelf	0.007611822	0.338596183
cg24331301	10	73156377	q	<i>CDH23</i>	TSS1500	island	-0.004556098	0.322302753
cg15323528	10	73156427	q	<i>CDH23</i>	TSS1500	island	0.013485901	0.170426915
cg01000831	10	73156460	q	<i>CDH23</i>	TSS1500	island	-0.004397375	0.270650874
cg09796583	10	73156647	q	<i>CDH23</i>	TSS200	island	-0.003581955	0.355063041
cg18901116	10	73156858	q	<i>CDH23</i>	1stExon	island	0.000665519	0.435155583
cg25798987	10	73157222	q	<i>CDH23</i>	5'UTR	island	-0.002505748	0.163513924
cg22839123	10	73157611	q	<i>CDH23</i>	5'UTR	island	-0.000748018	0.38166625
cg24094513	10	73157911	q	<i>CDH23</i>	5'UTR	island	0.005585426	0.140066542
cg01160241	10	73157953	q	<i>CDH23</i>	5'UTR	island	0.000743128	0.434995942
cg18608017	10	73158072	q	<i>CDH23</i>	5'UTR	shore	0.009477919	0.224569293
cg27017382	10	73160237	q	<i>CDH23</i>	5'UTR	shelf	0.000888628	0.345189005
cg00234046	10	73169245	q	<i>CDH23</i>	5'UTR	open sea	-1.14E-05	0.497918356
cg07835953	10	73202938	q	<i>CDH23</i>	Body	open sea	0.00198415	0.302306077
cg07975680	10	73225789	q	<i>CDH23</i>	Body	open sea	0.005949765	0.176283325
cg10684627	10	73288563	q	<i>CDH23</i>	Body	open sea	-0.006040322	0.225513013
cg09728120	10	73300441	q	<i>CDH23</i>	Body	open sea	-0.006459754	0.070166423
cg04457572	10	73303234	q	<i>CDH23</i>	Body	open sea	-0.000521705	0.412840391
cg09501025	10	73312955	q	<i>CDH23</i>	Body	open sea	-0.004493351	0.202277216
cg18947261	10	73321439	q	<i>CDH23</i>	Body	open sea	0.000802956	0.420342267
cg15077792	10	73324481	q	<i>CDH23</i>	Body	open sea	0.000194958	0.491868346
cg12830671	10	73335297	q	<i>CDH23</i>	Body	open sea	-0.000267849	0.476353521
cg22630628	10	73337125	q	<i>CDH23</i>	Body	open sea	-0.00116943	0.426243773
cg24124069	10	73369502	q	<i>CDH23</i>	Body	open sea	-0.000293471	0.480562954
cg18645316	10	73381995	q	<i>CDH23</i>	Body	open sea	-0.000801658	0.480362589
cg13714026	10	73385503	q	<i>CDH23</i>	Body	open sea	-0.011262067	0.292144508
cg20283498	10	73387917	q	<i>CDH23</i>	Body	open sea	0.002027256	0.294304647
cg22763136	10	73395000	q	<i>CDH23</i>	Body	open sea	0.007254555	0.186489328
cg00462411	10	73401422	q	<i>CDH23</i>	Body	open sea	-0.00827624	0.247257031
cg23867673	10	73404170	q	<i>CDH23</i>	Body	open sea	0.004361369	0.366373108
cg04161859	10	73404657	q	<i>CDH23</i>	Body	open sea	0.000991899	0.479264295
cg05523505	10	73405460	q	<i>CDH23</i>	Body	open sea	-0.000409468	0.468173582



cg04567334	10	73408185	q	<i>CDH23</i>	Body	open sea	0.007681571	0.170052862
cg09598552	10	73417893	q	<i>CDH23</i>	Body	open sea	0.00296708	0.275338395
cg03028769	10	73421791	q	<i>CDH23</i>	Body	open sea	0.002445703	0.236596507
cg23104184	10	73437334	q	<i>CDH23</i>	Body	open sea	0.013709747	0.134454028
cg22545027	10	73437363	q	<i>CDH23</i>	Body	open sea	0.015015566	0.070508817
cg03033796	10	73445156	q	<i>CDH23</i>	Body	open sea	-0.008444133	0.274744066
cg17019070	10	73466639	q	<i>CDH23</i>	Body	open sea	0.001319579	0.264480363
cg10505163	10	73466728	q	<i>CDH23</i>	Body	open sea	-0.001055615	0.270868044
cg18235465	10	73471634	q	<i>C10orf105</i>	3'UTR	open sea	-0.005547154	0.397251501
cg21369812	10	73471699	q	<i>C10orf105</i>	3'UTR	open sea	0.003569057	0.140647223
cg07571519	10	73472315	q	<i>C10orf105</i>	3'UTR	open sea	-0.000335184	0.463130246
cg24457649	10	73472344	q	<i>C10orf105</i>	3'UTR	open sea	-0.001080156	0.428549995
cg15763670	10	73473235	q	<i>C10orf105</i>	3'UTR	open sea	0.038462792	0.014807087
cg19988181	10	73478985	q	<i>C10orf105</i>	5'UTR	open sea	-0.003171909	0.174591525
cg08734090	10	73479514	q	<i>C10orf105</i>	1stExon	open sea	-0.003477327	0.291464684
cg20390554	10	73479696	q	<i>C10orf105</i>	5'UTR	open sea	-0.002032633	0.340288884
cg09637449	10	73479754	q	<i>C10orf105</i>	5'UTR	open sea	-0.004466277	0.16315138
cg03456651	10	73479833	q	<i>C10orf105</i>	5'UTR	open sea	-6.92E-05	0.494542955
cg18668540	10	73479848	q	<i>C10orf105</i>	5'UTR	open sea	-0.002681092	0.194356036
cg05848785	10	73480942	q	<i>C10orf105</i>	5'UTR	open sea	0.00022297	0.472527778
cg13740185	10	73486801	q	<i>C10orf105</i>	5'UTR	open sea	-0.012858	0.170337592
cg00418663	10	73491922	q	<i>C10orf105</i>	5'UTR	open sea	-0.009377814	0.231376763
cg22991379	10	73491943	q	<i>C10orf105</i>	5'UTR	open sea	-0.000130974	0.496020405
cg05979232	10	73496014	q	<i>C10orf105</i>	5'UTR	open sea	-0.003540451	0.192542749
cg10750182	10	73497514	q	<i>C10orf105</i>	5'UTR	open sea	-0.000387536	0.476344861
cg19429405	10	73497609	q	<i>C10orf105</i>	TSS200	open sea	-0.006096814	0.360376047
cg23056923	10	73497629	q	<i>C10orf105</i>	TSS200	open sea	0.000735981	0.435214166
cg17422176	10	73497772	q	<i>C10orf105</i>	TSS200	open sea	-0.044581961	0.127242358
cg26091131	10	73498624	q	<i>C10orf105</i>	TSS1500	open sea	-0.001349482	0.431841057
cg24938210	10	73498640	q	<i>C10orf105</i>	TSS1500	open sea	0.002000031	0.392109379
cg01470340	10	73498766	q	<i>C10orf105</i>	TSS1500	open sea	-0.006232057	0.064574586
cg04304802	10	73499965	q	<i>CDH23</i>	Body	open sea	0.013445501	0.052331706
cg07676145	10	73506646	q	<i>CDH23</i>	Body	open sea	-0.010803137	0.163999849
cg05440642	10	73507806	q	<i>C10orf54</i>	3'UTR	open sea	0.004033171	0.367515589
cg04179740	10	73516760	q	<i>CDH23</i>	Body	open sea	-0.002940851	0.426839182
cg19227382	10	73521606	q	<i>CDH23</i>	Body	open sea	-2.64E-05	0.496218557
cg23968456	10	73521631	q	<i>CDH23</i>	Body	open sea	-0.001084731	0.230733219

cg09895190	10	73521645	q	<i>CDH23</i>	Body	open sea	0.001617691	0.399063501
cg14916175	10	73529624	q	<i>CDH23</i>	Body	shelf	0.005967547	0.345945983
cg06768251	10	73533035	q	<i>CDH23</i>	Body	shore	0.01999422	0.030866303
cg13954090	10	73533106	q	<i>CDH23</i>	Body	island	0.009050512	0.024008956
cg13957721	10	73533304	q	<i>C10orf54</i>	5'UTR	island	0.00146201	0.323738576
cg12568633	10	73533407	q	<i>CDH23</i>	Body	island	-0.002859682	0.354268177
cg04083751	10	73533414	q	<i>CDH23</i>	Body	island	-0.002973927	0.12572102
cg09810750	10	73533449	q	<i>CDH23</i>	Body	island	-0.00011539	0.490623406
cg14522427	10	73533468	q	<i>CDH23</i>	Body	island	-0.001667088	0.390922052
cg17411913	10	73533483	q	<i>CDH23</i>	Body	island	-0.005631296	0.194285045
cg06655361	10	73533561	q	<i>C10orf54</i>	TSS1500	shore	0.003306516	0.400397482
cg24499627	10	73533891	q	<i>C10orf54</i>	TSS1500	shore	-0.000613228	0.47722149
cg23282441	10	73533927	q	<i>C10orf54</i>	TSS1500	shore	-0.007789545	0.25358891
cg06372475	10	73534286	q	<i>C10orf54</i>	TSS1500	shore	0.002985424	0.331174436
cg11633461	10	73534338	q	<i>C10orf54</i>	TSS1500	shore	0.003249155	0.272633712
cg24772501	10	73537481	q	<i>CDH23</i>	Body	shelf	0.004227834	0.190122759
cg22877524	10	73553138	q	<i>CDH23</i>	Body	open sea	0.001521436	0.333408203
cg24980638	10	73553196	q	<i>CDH23</i>	Body	open sea	0.004484623	0.258387879
cg07658681	10	73553201	q	<i>CDH23</i>	Body	open sea	0.002547517	0.401084036
cg19906973	10	73562723	q	<i>CDH23</i>	Body	shelf	0.000758081	0.420424289
cg09229668	10	73565440	q	<i>CDH23</i>	Body	shore	0.003099854	0.24479105
cg17485681	10	73565625	q	<i>CDH23</i>	Body	island	0.008037739	0.138382874
cg08293528	10	73565688	q	<i>CDH23</i>	Body	island	0.007050243	0.333525786
cg23983208	10	73565812	q	<i>CDH23</i>	Body	island	0.013246551	0.136982556
cg17641566	10	73565966	q	<i>CDH23</i>	Body	shore	-0.003519586	0.37981238
cg23284338	10	73569605	q	<i>CDH23</i>	Body	shelf	-0.00442148	0.143038667
cg26134646	10	73569677	q	<i>CDH23</i>	Body	shelf	0.001463355	0.207969712
cg00613914	10	73569753	q	<i>CDH23</i>	Body	shelf	0.004677139	0.079896139
cg23119049	10	73572537	q	<i>CDH23</i>	Body	open sea	0.014437694	0.137338972
cg05864024	10	73574855	q	<i>CDH23</i>	Body	open sea	0.002322233	0.359882804
cg02851751	10	73574918	q	<i>CDH23</i>	Body	open sea	-0.001015181	0.443455665
cg19612504	10	73574943	q	<i>CDH23</i>	Body	open sea	-0.001035576	0.421306949
cg02180979	10	73575440	q	<i>CDH23</i>	3'UTR	open sea	0.00075451	0.463684039
cg05196905	21	47877665	q	<i>DIP2A</i>	TSS1500	shore	0.033161994	0.012917904
cg25539589	21	47877758	q	<i>DIP2A</i>	TSS1500	shore	0.003201054	0.112706542
cg26629188	21	47878281	q	<i>DIP2A</i>	TSS1500	island	0.003574192	0.269585057
cg19247551	21	47878552	q	<i>DIP2A</i>	TSS1500	island	0.001083408	0.152128148

cg15775835	21	47878727	q	<i>DIP2A</i>	TSS200	island	0.000405419	0.380968216
cg12533308	21	47878746	q	<i>DIP2A</i>	TSS200	island	-0.00129319	0.292710785
cg11752103	21	47878969	q	<i>DIP2A</i>	1stExon	island	0.001823564	0.14256677
cg03599110	21	47879272	q	<i>DIP2A</i>	Body	island	-0.002781754	0.348502597
cg13784482	21	47881507	q	<i>DIP2A</i>	Body	shore	0.004683273	0.266251852
cg12149795	21	47882121	q	<i>DIP2A</i>	Body	shelf	0.008729639	0.282499671
cg09493818	21	47917455	q	<i>DIP2A</i>	Body	shore	0.003105588	0.409117523
cg16004390	21	47918542	q	<i>DIP2A</i>	Body	island	-0.00423865	0.231948409
cg10573553	21	47918580	q	<i>DIP2A</i>	Body	island	-0.000515383	0.44475564
cg26155719	21	47918693	q	<i>DIP2A</i>	Body	island	0.003976046	0.286015506
cg16636721	21	47920571	q	<i>DIP2A</i>	Body	shore	0.00957486	0.30681487
cg03173479	21	47965968	q	<i>DIP2A</i>	Body	open sea	0.001465824	0.295131842
cg10605724	21	47966967	q	<i>DIP2A</i>	Body	open sea	0.005161047	0.192653554
cg07389144	21	47969887	q	<i>DIP2A</i>	Body	open sea	0.01071332	0.172266714
cg09371744	21	47987607	q	<i>DIP2A</i>	3'UTR	open sea	-0.011454094	0.295600043
cg14479617	3	119542274	q	<i>GSK3B</i>	3'UTR	open sea	0.001962751	0.452297553
cg15970035	3	119626443	q	<i>GSK3B</i>	Body	open sea	0.00091831	0.461536471
cg12090885	3	119632116	q	<i>GSK3B</i>	Body	open sea	0.010846822	0.070503316
ch.3.2338385R	3	119681371	q	<i>GSK3B</i>	Body	open sea	0.013233193	0.07078593
cg02636004	3	119747339	q	<i>GSK3B</i>	Body	open sea	-0.00246576	0.312529647
cg13474301	3	119748151	q	<i>GSK3B</i>	Body	open sea	-0.003946219	0.400301916
cg12956472	3	119791225	q	<i>GSK3B</i>	Body	open sea	-0.001441162	0.459953109
cg13250001	3	119810597	q	<i>GSK3B</i>	Body	shelf	0.007447043	0.232864296
cg19519393	3	119811892	q	<i>GSK3B</i>	Body	shore	0.006780995	0.33707332
cg10347998	3	119812602	q	<i>GSK3B</i>	1stExon	shore	0.001123757	0.238657454
cg25319031	3	119813310	q	<i>GSK3B</i>	TSS200	island	0.000971106	0.318980655
cg12698784	3	119813316	q	<i>GSK3B</i>	TSS200	island	-0.000599285	0.319745972
cg14472315	3	119813523	q	<i>GSK3B</i>	TSS1500	island	0.004060803	0.073198924
cg08227698	3	119813564	q	<i>GSK3B</i>	TSS1500	island	-0.002510282	0.284134318
cg14449845	3	119813927	q	<i>GSK3B</i>	TSS1500	island	-0.004447735	0.191906015
cg12733004	3	119814122	q	<i>GSK3B</i>	TSS1500	island	0.000305658	0.439850565
cg11789444	3	119814398	q	<i>GSK3B</i>	TSS1500	island	0.000388358	0.441613326
cg05300996	3	119814693	q	<i>GSK3B</i>	TSS1500	shore	0.002581774	0.216795815
cg11117266	17	43971461	q	<i>MAPT</i>	TSS1500	island	0.000680276	0.403060224
cg16520312	17	43971471	q	<i>MAPT</i>	TSS1500	island	0.001926543	0.27118258
cg07163735	17	43971906	q	<i>MAPT</i>	1stExon	island	0.000825867	0.411577136
cg20099416	17	43971919	q	<i>MAPT</i>	1stExon	island	0.004379638	0.036571534

cg21327887	17	43971928	q	<i>MAPT</i>	1stExon	island	0.002346723	0.136737836
cg12989733	17	43972306	q	<i>MAPT</i>	5'UTR	island	0.000586791	0.357243645
cg00891649	17	43972573	q	<i>MAPT</i>	5'UTR	island	0.000706321	0.465368101
cg19670923	17	43972806	q	<i>MAPT</i>	5'UTR	island	0.003377618	0.05884016
cg02804087	17	43972969	q	<i>MAPT</i>	5'UTR	island	0.002369872	0.061687447
cg18368019	17	43972978	q	<i>MAPT</i>	5'UTR	island	0.002251602	0.065977721
cg10725121	17	43973146	q	<i>MAPT</i>	5'UTR	island	-0.002219882	0.163988615
cg13137533	17	43973292	q	<i>MAPT</i>	5'UTR	island	-0.002530707	0.261099103
cg09478742	17	43973311	q	<i>MAPT</i>	5'UTR	island	-0.002703457	0.255003308
cg11489262	17	43973426	q	<i>MAPT</i>	5'UTR	island	0.016099632	0.0206586
cg10780632	17	43973522	q	<i>MAPT</i>	5'UTR	island	-0.005081071	0.179479501
cg19156875	17	43974446	q	<i>MAPT</i>	5'UTR	island	0.007777036	0.19369867
cg26606256	17	43974804	q	<i>MAPT</i>	5'UTR	island	3.33E-05	0.497967578
cg14202850	17	43974869	q	<i>MAPT</i>	5'UTR	island	0.008472044	0.229298085
cg11909912	17	43974919	q	<i>MAPT</i>	5'UTR	island	-0.000414697	0.472359905
cg04382470	17	43974975	q	<i>MAPT</i>	5'UTR	island	0.004588558	0.249117462
cg10224600	17	43975063	q	<i>MAPT</i>	5'UTR	shore	0.000695913	0.468109682
cg27457921	17	43976811	q	<i>MAPT</i>	5'UTR	shore	0.018811566	0.019737516
cg19108736	17	43977403	q	<i>MAPT</i>	5'UTR	shelf	0.00267914	0.427097119
cg20888521	17	43977917	q	<i>MAPT</i>	5'UTR	shelf	0.012128968	0.161082822
cg22291189	17	43978251	q	<i>MAPT</i>	5'UTR	shelf	0.008087593	0.121342401
cg26019600	17	43978704	q	<i>MAPT</i>	5'UTR	shelf	0.008779302	0.294771647
cg12633764	17	43978756	q	<i>MAPT</i>	5'UTR	shelf	0.003488564	0.297590242
cg26413900	17	43985654	q	<i>MAPT</i>	5'UTR	open sea	-0.003683986	0.430889311
cg16573346	17	44020278	q	<i>MAPT</i>	5'UTR	open sea	0.00482126	0.260972649
cg15323584	17	44022846	q	<i>MAPT</i>	5'UTR	shelf	0.004967362	0.250550155
cg00699617	17	44026428	q	<i>MAPT</i>	5'UTR	shore	0.01265718	0.193901445
cg26163368	17	44026652	q	<i>MAPT</i>	5'UTR	island	0.006604262	0.254676152
cg17569492	17	44026659	q	<i>MAPT</i>	5'UTR	island	0.024856213	0.031323104
cg05772917	17	44027251	q	<i>MAPT</i>	5'UTR	shore	0.004024611	0.419754673
cg01640727	17	44029468	q	<i>MAPT</i>	5'UTR	shelf	0.015190567	0.123658873
cg03836283	17	44058856	q	<i>MAPT</i>	Body	shore	0.00140378	0.425020086
cg00846647	17	44060252	q	<i>MAPT</i>	Body	island	-0.00153479	0.420142743
cg19276540	17	44060353	q	<i>MAPT</i>	Body	island	-0.000178597	0.47081144
cg20265358	17	44060424	q	<i>MAPT</i>	Body	island	0.006425394	0.125183385
cg00438222	17	44060502	q	<i>MAPT</i>	Body	island	0.000801136	0.391785485
cg22128613	17	44061117	q	<i>MAPT</i>	Body	shore	0.002759966	0.24679588

cg21953146	17	44061258	q	<i>MAPT</i>	Body	shore	0.006275857	0.286376301
cg26979107	17	44061355	q	<i>MAPT</i>	Body	shore	-0.002282469	0.299146658
cg19495068	17	44061467	q	<i>MAPT</i>	Body	shore	0.00220096	0.407751937
cg01934064	17	44064242	q	<i>MAPT</i>	Body	shelf	0.00131111	0.390547073
cg16656794	17	44068842	q	<i>MAPT</i>	Body	open sea	6.26E-05	0.493963111
cg00480298	17	44068857	q	<i>MAPT</i>	Body	open sea	0.011949771	0.178017152
cg05721485	17	44071124	q	<i>MAPT</i>	Body	open sea	0.017532332	0.091236818
cg12604352	17	44073915	q	<i>MAPT</i>	Body	open sea	0.008844467	0.262624401
cg12727978	17	44075500	q	<i>MAPT</i>	Body	open sea	-0.000740711	0.433160045
cg24677220	17	44075684	q	<i>MAPT</i>	Body	open sea	0.008350911	0.035849638
cg14431592	17	44076415	q	<i>STH</i>	TSS200	open sea	-0.008062941	0.209919014
cg15682851	17	44076429	q	<i>STH</i>	TSS200	open sea	-0.005728146	0.281493931
cg01098886	17	44076726	q	<i>MAPT</i>	Body	open sea	-0.006579559	0.354964312
cg13400969	17	44087762	q	<i>MAPT</i>	Body	open sea	-0.012028073	0.174431475
cg20840174	17	44087784	q	<i>MAPT</i>	Body	open sea	0.004136896	0.374278902
cg07368061	17	44090862	q	<i>MAPT</i>	Body	open sea	0.005234941	0.402268029
cg15690475	17	44101453	q	<i>MAPT</i>	Body	open sea	-0.014338538	0.098674978
cg24612059	17	44101462	q	<i>MAPT</i>	Body	open sea	-0.012210508	0.124489134
cg05533539	17	44104521	q	<i>MAPT</i>	3'UTR	open sea	0.012789297	0.171627353
cg09764761	17	44105544	q	<i>MAPT</i>	3'UTR	open sea	0.000220186	0.493343883
cg05872255	14	73592157	q	<i>PSEN1</i>	IGR	open sea	0.010554702	0.130716029
cg09970967	14	73602752	q	<i>PSEN1</i>	TSS1500	shore	-0.000894964	0.466118889
cg26124115	14	73602899	q	<i>PSEN1</i>	TSS1500	island	-0.002844604	0.136415812
cg11490446	14	73602923	q	<i>PSEN1</i>	TSS1500	island	-0.000580511	0.427771662
cg13173405	14	73602951	q	<i>PSEN1</i>	TSS200	island	0.001289393	0.403256357
cg11143091	14	73603203	q	<i>PSEN1</i>	1stExon	island	0.001548308	0.255744529
cg26376566	14	73603660	q	<i>PSEN1</i>	5'UTR	island	0.007960539	0.327587189
cg12162778	14	73603844	q	<i>PSEN1</i>	5'UTR	shore	0.004372837	0.324760238
cg23501468	14	73606606	q	<i>PSEN1</i>	5'UTR	shelf	-0.004686003	0.366180909
cg10734940	14	73668083	q	<i>PSEN1</i>	Body	open sea	0.004467083	0.158606112
cg10426062	14	73677854	q	<i>PSEN1</i>	Body	open sea	0.010648083	0.200379239
cg05385100	14	73689196	q	<i>PSEN1</i>	3'UTR	open sea	0.003326107	0.372193275
cg06540458	1	226951747	q	<i>PSEN2</i>	IGR	open sea	0.019687566	0.12925639
cg21879716	1	226967207	q	<i>PSEN2</i>	IGR	open sea	-0.001101802	0.42171192
cg03547355	1	227003060	q	<i>PSEN2</i>	IGR	open sea	0.002303232	0.466329302
cg14422093	1	227009245	q	<i>PSEN2</i>	IGR	open sea	0.006926346	0.222288302
cg08654091	1	227015418	q	<i>PSEN2</i>	IGR	open sea	0.019154506	0.133540391

cg16985288	1	227015456	q	<i>PSEN2</i>	IGR	open sea	0.007788674	0.337451454
cg20484086	1	227015727	q	<i>PSEN2</i>	IGR	open sea	0.014330611	0.172290849
cg13870041	1	227015885	q	<i>PSEN2</i>	IGR	open sea	0.008781004	0.041373382
cg23950691	1	227015916	q	<i>PSEN2</i>	IGR	open sea	0.003821691	0.190790221
cg13935266	1	227015922	q	<i>PSEN2</i>	IGR	open sea	0.001995265	0.340851626
cg13223182	1	227015944	q	<i>PSEN2</i>	IGR	open sea	-0.001012799	0.375719125
cg22223430	1	227015971	q	<i>PSEN2</i>	IGR	open sea	0.008658978	0.04366096
cg01784507	1	227016024	q	<i>PSEN2</i>	IGR	open sea	0.036204731	0.030061738
cg12761965	1	227051345	q	<i>PSEN2</i>	IGR	open sea	0.007216079	0.210366461
cg18395233	1	227054129	q	<i>PSEN2</i>	IGR	shelf	0.007943971	0.084169296
cg10879712	1	227056896	q	<i>PSEN2</i>	TSS1500	shore	0.001170394	0.409926335
cg00479101	1	227058070	q	<i>PSEN2</i>	TSS1500	island	-0.00304471	0.170207454
cg03307360	1	227058426	q	<i>PSEN2</i>	5'UTR	island	0.004020812	0.076070407
cg21417192	1	227058595	q	<i>PSEN2</i>	5'UTR	island	0.000532828	0.394111636
cg03338380	1	227058754	q	<i>PSEN2</i>	5'UTR	island	-0.001015001	0.224050263
cg26656022	1	227058905	q	<i>PSEN2</i>	5'UTR	island	-0.002295916	0.221911991
cg05134019	1	227059463	q	<i>PSEN2</i>	5'UTR	shore	-0.002154485	0.253213633
cg23220071	1	227061009	q	<i>PSEN2</i>	5'UTR	shelf	0.007552277	0.360336149
cg08708961	1	227070630	q	<i>PSEN2</i>	Body	open sea	0.000680894	0.467932806
cg18027831	1	227083489	q	<i>PSEN2</i>	3'UTR	open sea	-0.007585419	0.248974151
cg09769084	1	227091160	q	<i>PSEN2</i>	IGR	open sea	0.00184865	0.342560167
cg01359015	17	74467334	q	<i>RHBDF2</i>	3'UTR	shore	0.000639268	0.435843412
cg08104579	17	74467662	q	<i>RHBDF2</i>	3'UTR	shore	0.00358963	0.221896359
cg18493449	17	74467972	q	<i>RHBDF2</i>	Body	island	-0.001915956	0.379187917
cg21280422	17	74468141	q	<i>RHBDF2</i>	Body	island	0.001783257	0.325822674
cg16607945	17	74468491	q	<i>RHBDF2</i>	Body	shore	-0.000215832	0.473529522
cg04577809	17	74469369	q	<i>RHBDF2</i>	Body	shore	0.001582421	0.264980752
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cg17289057	17	74473006	q	<i>RHBDF2</i>	Body	shelf	0.002083195	0.093534665
cg06097533	17	74473066	q	<i>RHBDF2</i>	Body	shelf	-0.003130113	0.143211891
cg08008636	17	74475050	q	<i>RHBDF2</i>	Body	shore	0.001662275	0.299243964
cg05810363	17	74475270	q	<i>RHBDF2</i>	Body	island	0.001086669	0.262102608
cg13076843	17	74475294	q	<i>RHBDF2</i>	Body	island	0.003099262	0.168950432
cg12309456	17	74475402	q	<i>RHBDF2</i>	Body	island	0.001472824	0.267312914
cg20690125	17	74476978	q	<i>RHBDF2</i>	Body	shore	0.023679497	0.101706327
cg21486834	17	74477542	q	<i>RHBDF2</i>	Body	shelf	0.006366226	0.116671896
cg09123026	17	74480528	q	<i>RHBDF2</i>	5'UTR	open sea	-0.001567315	0.280961119

cg26737223	17	74488855	q	<i>RHBDF2</i>	5'UTR	open sea	0.005580949	0.192429814
cg12900649	17	74494213	q	<i>RHBDF2</i>	5'UTR	shelf	0.021498136	0.093759764
cg24757533	17	74494286	q	<i>RHBDF2</i>	5'UTR	shelf	0.02518894	0.057606087
cg25826360	17	74496953	q	<i>RHBDF2</i>	5'UTR	shore	-0.013416461	0.18141556
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cg25038060	17	74497306	q	<i>RHBDF2</i>	5'UTR	island	-0.002594961	0.180201437
cg12565681	17	74497418	q	<i>RHBDF2</i>	5'UTR	island	-0.001266218	0.287469639
cg21028211	17	74497614	q	<i>RHBDF2</i>	TSS200	island	-0.001369047	0.396321956
cg11539992	17	74497631	q	<i>RHBDF2</i>	TSS200	island	-0.000661802	0.417863122
cg09458299	17	74497653	q	<i>RHBDF2</i>	TSS200	shore	0.017965883	0.038117901
cg00634714	17	74497851	q	<i>RHBDF2</i>	TSS1500	shore	0.029681675	0.008024954
cg20690922	17	74498083	q	<i>RHBDF2</i>	TSS1500	shore	0.001473825	0.35510093
cg01217876	17	74498163	q	<i>RHBDF2</i>	TSS1500	shore	0.003815653	0.2513997
cg23877786	16	89626662	q	<i>RPL13</i>	TSS1500	island	0.000196517	0.438514396
cg05547654	16	89626678	q	<i>RPL13</i>	TSS1500	island	0.001554316	0.156085848
cg26585801	16	89626715	q	<i>RPL13</i>	TSS1500	island	-9.47E-05	0.483631873
cg02897623	16	89626761	q	<i>RPL13</i>	TSS1500	island	0.00595191	0.020355857
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cg07868478	16	89627303	q	<i>RPL13</i>	5'UTR	island	-0.000265421	0.436280942
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cg09411121	16	89627813	q	<i>RPL13</i>	Body	island	0.005698609	0.038714181
cg01035068	16	89627855	q	<i>RPL13</i>	Body	island	0.002093929	0.171835297
cg01995548	16	89628799	q	<i>RPL13</i>	Body	shore	0.002982648	0.414687092
cg02732508	16	89628853	q	<i>RPL13</i>	Body	shore	-0.008748374	0.292219278
cg07344397	16	89629499	q	<i>RPL13</i>	3'UTR	shore	0.013092918	0.164126483
cg08838752	17	1659924	p	<i>SERPINF1</i>	IGR	shelf	0.00219743	0.255033794
cg08547211	17	1664077	p	<i>SERPINF1</i>	TSS1500	open sea	0.004631378	0.251327877
cg22234345	17	1664329	p	<i>SERPINF1</i>	TSS1500	open sea	-0.003044954	0.310206448
cg00844277	17	1664339	p	<i>SERPINF1</i>	TSS1500	open sea	-0.011972835	0.04160007
cg24214470	17	1665119	p	<i>SERPINF1</i>	TSS200	open sea	-0.004309583	0.424251801
cg22513955	17	1665123	p	<i>SERPINF1</i>	TSS200	open sea	-0.008684244	0.338616416
cg27102649	17	1665172	p	<i>SERPINF1</i>	TSS200	open sea	-0.006415735	0.327418463
cg11692409	17	1665181	p	<i>SERPINF1</i>	TSS200	open sea	-0.011446183	0.29323126
cg22242539	17	1665220	p	<i>SERPINF1</i>	TSS200	open sea	0.001406409	0.471106742

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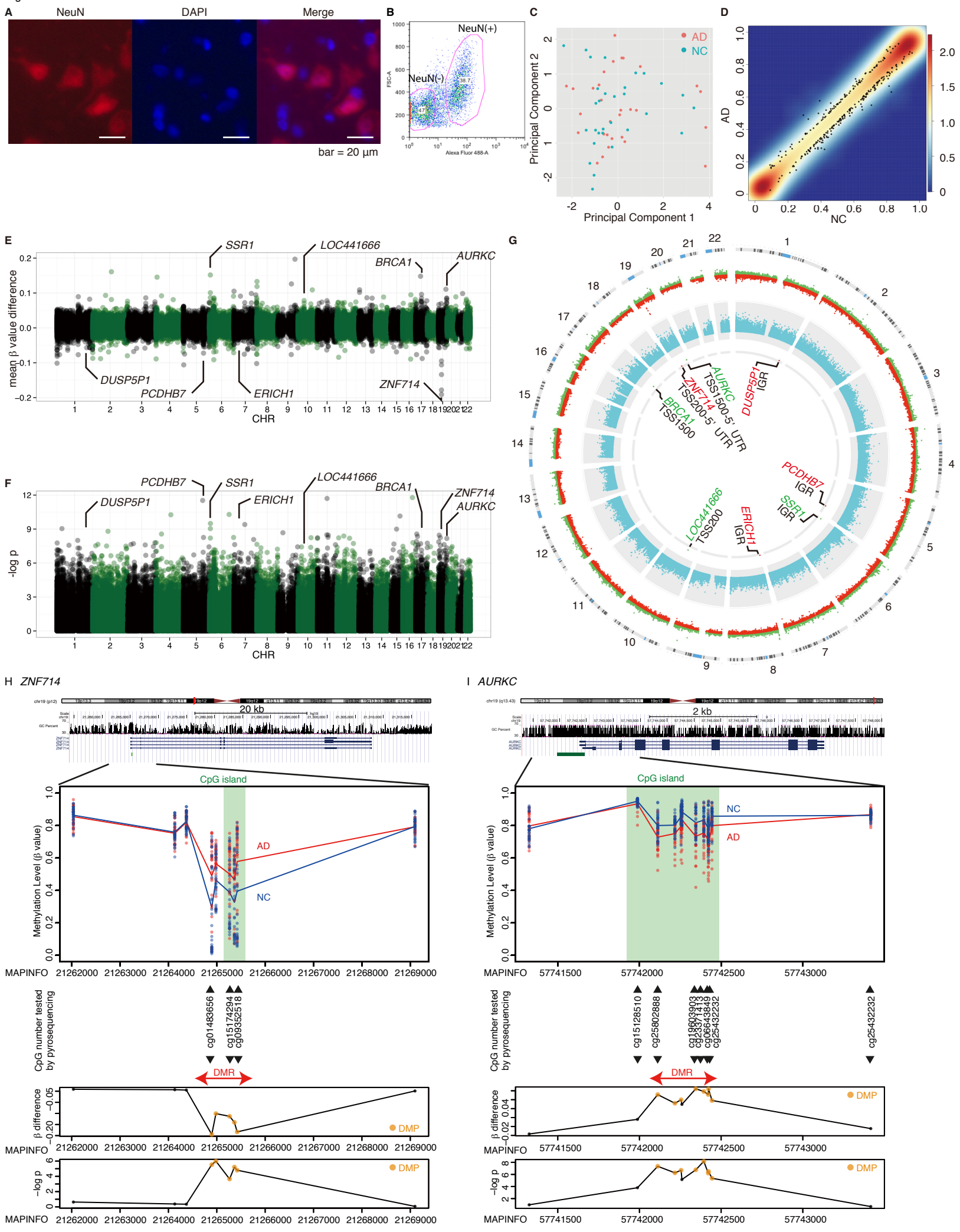
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cg25158320	17	1665262	p	<i>SERPINF1</i>	1stExon	open sea	-0.005748118	0.378052098
cg06940127	17	1665303	p	<i>SERPINF1</i>	1stExon	open sea	0.004470772	0.381107243
cg00777079	17	1666607	p	<i>SERPINF1</i>	5'UTR	open sea	0.000317959	0.494182452
cg07438421	17	1675235	p	<i>SERPINF1</i>	Body	open sea	0.008007864	0.136369766
cg17141696	17	1680805	p	<i>SERPINF1</i>	3'UTR	open sea	-0.005373523	0.349224791
cg07804577	17	1645462	p	<i>SERPINF2</i>	TSS1500	open sea	-0.001928056	0.306426633
cg07433905	17	1645859	p	<i>SERPINF2</i>	TSS1500	open sea	-0.001807963	0.44481848
cg06387669	17	1646196	p	<i>SERPINF2</i>	1stExon	open sea	-0.023320151	0.159247426
cg04780454	17	1647819	p	<i>SERPINF2</i>	5'UTR	open sea	0.027788267	0.02359298
cg25803583	17	1648622	p	<i>SERPINF2</i>	Body	open sea	0.000637018	0.382218983
cg14208859	17	1653873	p	<i>SERPINF2</i>	Body	shelf	0.002903475	0.132594647
cg10516117	17	1656147	p	<i>SERPINF2</i>	Body	shore	0.004313767	0.334613397
cg13027184	17	1657448	p	<i>SERPINF2</i>	Body	island	0.005624985	0.209656001
cg23226397	17	1657480	p	<i>SERPINF2</i>	Body	island	0.001173381	0.390514208
cg17514665	17	1657533	p	<i>SERPINF2</i>	Body	island	0.001182215	0.317764251
cg18278729	17	1657676	p	<i>SERPINF2</i>	Body	island	0.018457067	0.038733449
cg20162822	17	1658265	p	<i>SERPINF2</i>	3'UTR	shore	0.005494672	0.350173228
cg21458932	17	1658296	p	<i>SERPINF2</i>	3'UTR	shore	0.015088016	0.183139727



Figure S1



**Figure S1**

Neuron-specific methylome screening reveals differentially methylated genes in AD brains. (A)

NeuN, DAPI staining, and their merged images of the representative starting material for FACS

separation. (B) Representative flow cytogram with NeuN antibody. (C) Principal component

analysis of 30 AD (red) and 30 NC (blue) based on methylation levels of MVP (most variable

probe) 1000. Neuronal DNA was extracted from the temporal lobe of the brain samples. The first

and second principal components are plotted. (D) Distribution of mean  $\beta$ -values of 30 AD and 30

NC depicted as a density plot. Black dots represent differentially methylated probes (one-sided

Student's *t*-test  $P < 0.05$ , mean  $\beta$  difference  $> 0.05$ ). Density of each point was depicted with color

scale ranging from blue to red. (E, F) Manhattan plots of the  $\beta$ -value differences (E) and the

statistical significance using a  $-\log(P)$  scale (F). Gene names related to DMRs are shown. (G)

Circos plot of the genome wide DNA methylation landscape of inferior temporal gyrus neuronal

DNA from 30 AD and 30 NC samples. The outermost ring represents chromosome ideograms,

annotated with chromosome numbers, with the p-ter to q-ter orientation in a clockwise direction.

Blue bars represent centromeres within each chromosome. Hypermethylated CpGs in AD samples

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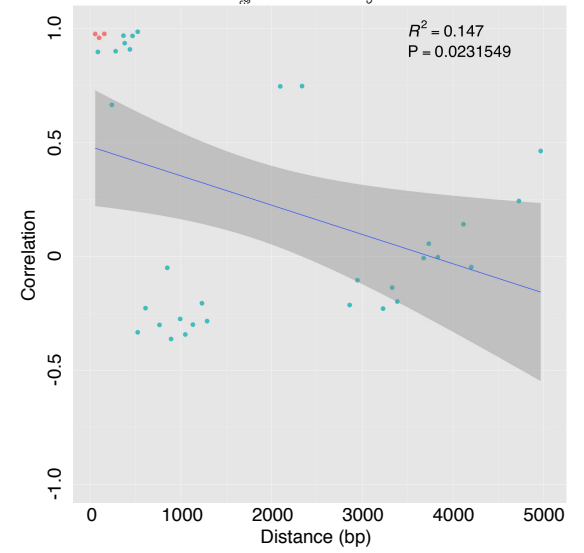
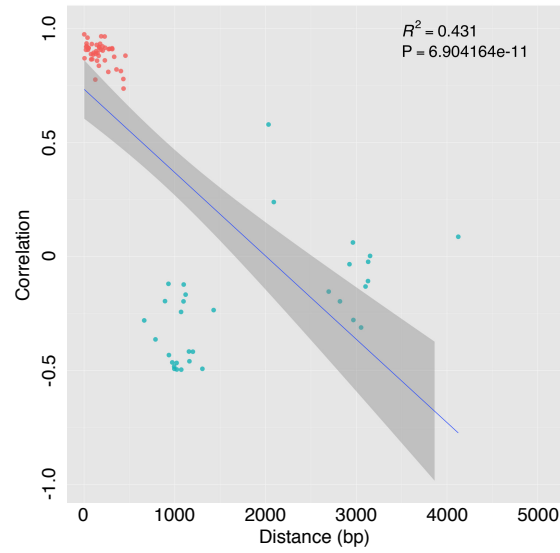
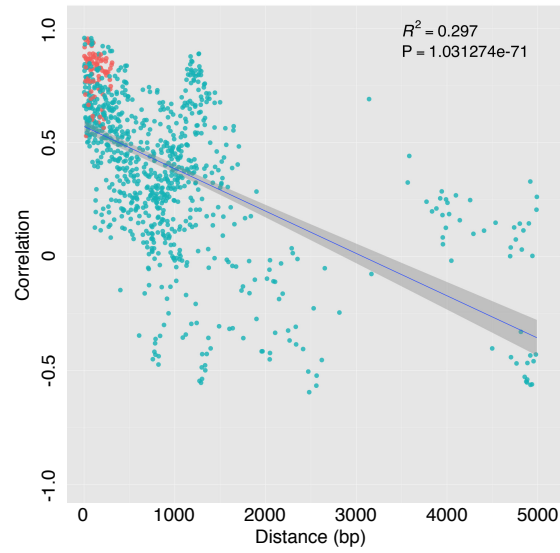
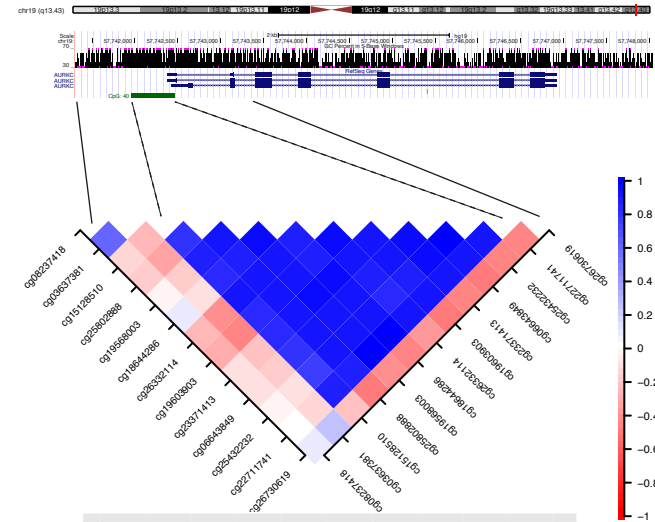
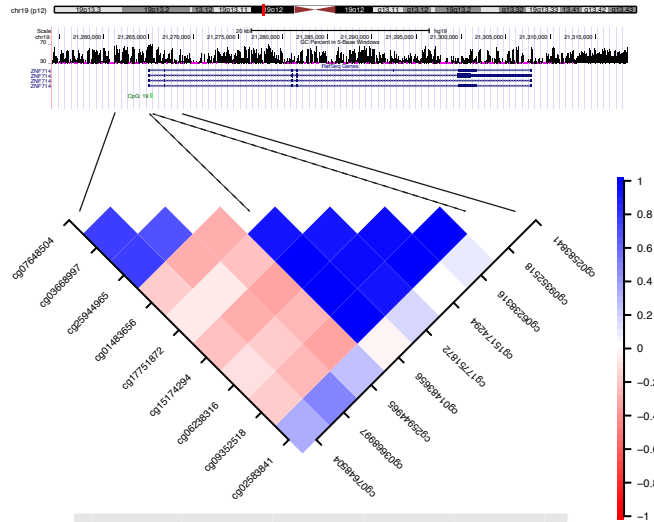
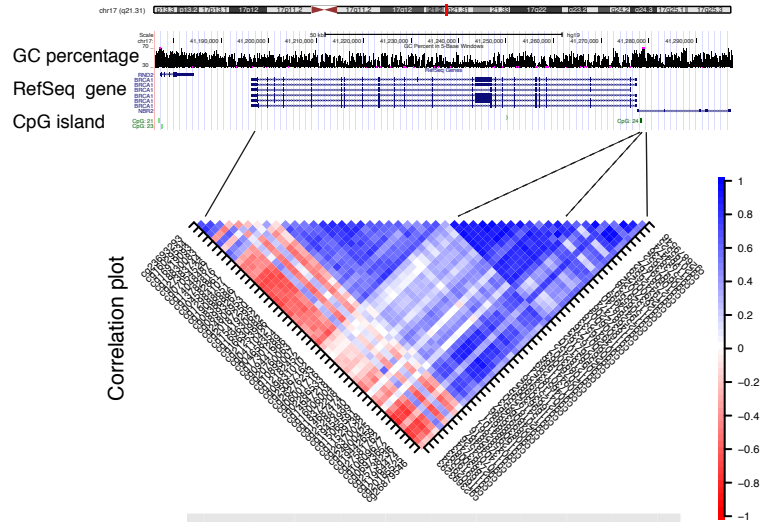
are shown with red dots, whereas hypomethylated CpGs are green, with the height of the dots representing the mean  $\beta$ -value difference. The blue dots correspond to the significance level of the  $\beta$ -value difference using a  $-\log(P)$  scale. The innermost circle shows differentially methylated regions (DMRs) annotated with RefSeq gene symbols; genes related to hypermethylated DMRs are shown in red, and hypomethylated DMRs in green. DMR positions are shown in black. IGR, intergenic region; TSS, transcription start site; UTR, untranslated region. (H, I) Details of differentially methylated regions associated with *ZNF714* (H) and *AURKC* (I). The uppermost panel shows genomic structures from the UCSC genome browser including chromosomal ideogram, GC content (vertical bars), RefSeq gene map (blue lines and bars), and CpG islands (green bars). The second panel depicts  $\beta$ -values of each sample at each CpG site. Dots are  $\beta$ -values from each sample and solid lines are mean  $\beta$ -values of each group. Light green areas correspond to CpG islands. CG identifiers listed are the sites where methylation levels were validated using an additional pyrosequencing assay. The last two panels show  $\beta$ -value differences (upper,  $\beta_{NC} - \beta_{AD}$ ) and significance levels on a  $-\log(P)$  scale at each CpG site. Orange dots represent differentially methylated probes (DMPs) discovered by Infinium screening.

Figure S2

A *BRCA1*

B *ZNF714*

C *AURKC*



**Figure S2**

Methylation level of CpGs found in *BRCA1* (A), *ZNF714* (B), and *AURKC* (C) show correlation.

Pearson correlation among neighboring CpGs were calculated using the same data sets in figure S1.

The uppermost panel shows genomic structure from UCSC genome browser including chromosomal ideogram, GC percentage (vertical bars), RefSeq gene map (blue lines and bars), and CpG islands (green bars). The second panel depicts Pearson correlation between neighboring CpGs.

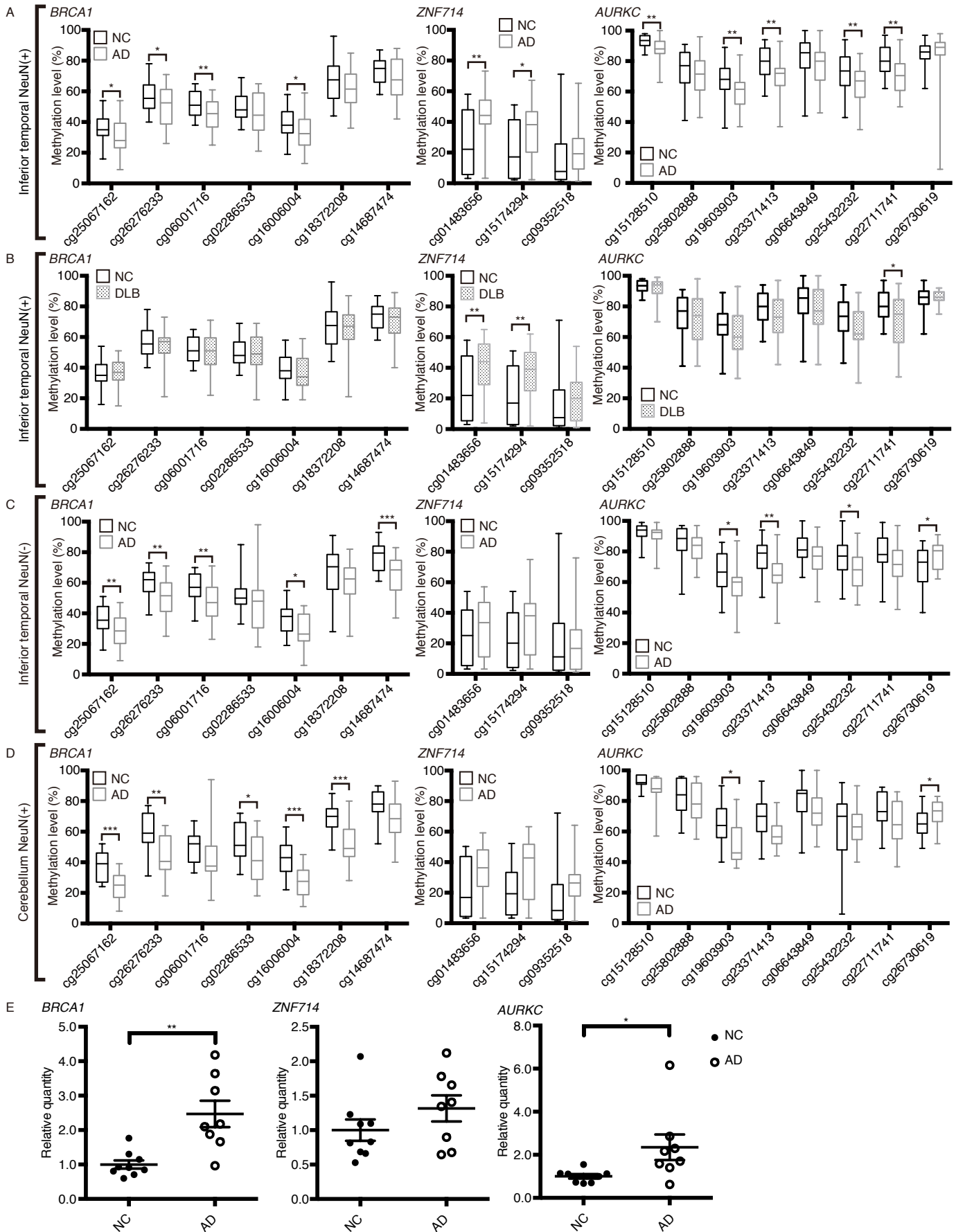
Each block represents pairwise Pearson correlation between CpGs, annotated by CpG identifiers.

Lines connected with the gene structure depicted above, at the location of the corresponding CpGs.

Broken lines indicate CpG islands. The third panel shows the relationship between correlation and distance between neighboring CpGs related to each gene. Green color indicates that both CpGs calculated are within the same CpG island. Correlation is depicted with color scale ranging from -1

(blue) to 1 (red).  $R^2$  and P values are shown in the panels.

Figure S3



**Figure S3**

Pyrosequencing confirmation of *BRCA1*, *ZNF714*, and *AURKC* CpG methylation level from various samples and their expression analysis from bulk brain mRNA.

(A) Pyrosequencing validation of differentially methylated probes detected in methylation array

analysis. Significance was tested by *t*-test. Black open bar = NC (n = 28), gray open bar = AD (n =

30). (B) Pyrosequencing of dementia with Lewy body (DLB) inferior temporal gyrus samples.

Black open bar = NC (n = 28), gray solid bar=DLB (n = 21). (C) Pyrosequencing results of non-

neuronal DNA from inferior temporal gyrus. Black open bar=NC (n = 24), gray open bar = AD (n =

4). (D) Pyrosequencing results of neuronal DNA from cerebellum samples. Black open bar = NC (n

= 15), gray open bar = AD (n = 14). (E) Quantitative PCR of DMR-associated genes; *BRCA1*,

*ZNF714*, and *AURKC*. Messenger RNA was extracted from the temporal lobe of each brain

samples. Expression levels relative to *GAPDH* are normalized to NC = 1.0. Each sample was

analyzed in quadruplicate, and samples with more than two outliers were filtered out. Each dot

represents the mean value of an individual sample. Error bars represent mean  $\pm$  SEM. n = 8. Solid

circle=NC, open circle=AD. Mean  $\pm$  SEM; *BRCA1*: 1.00  $\pm$  0.12 in NC vs. 2.47  $\pm$  0.38 in AD,

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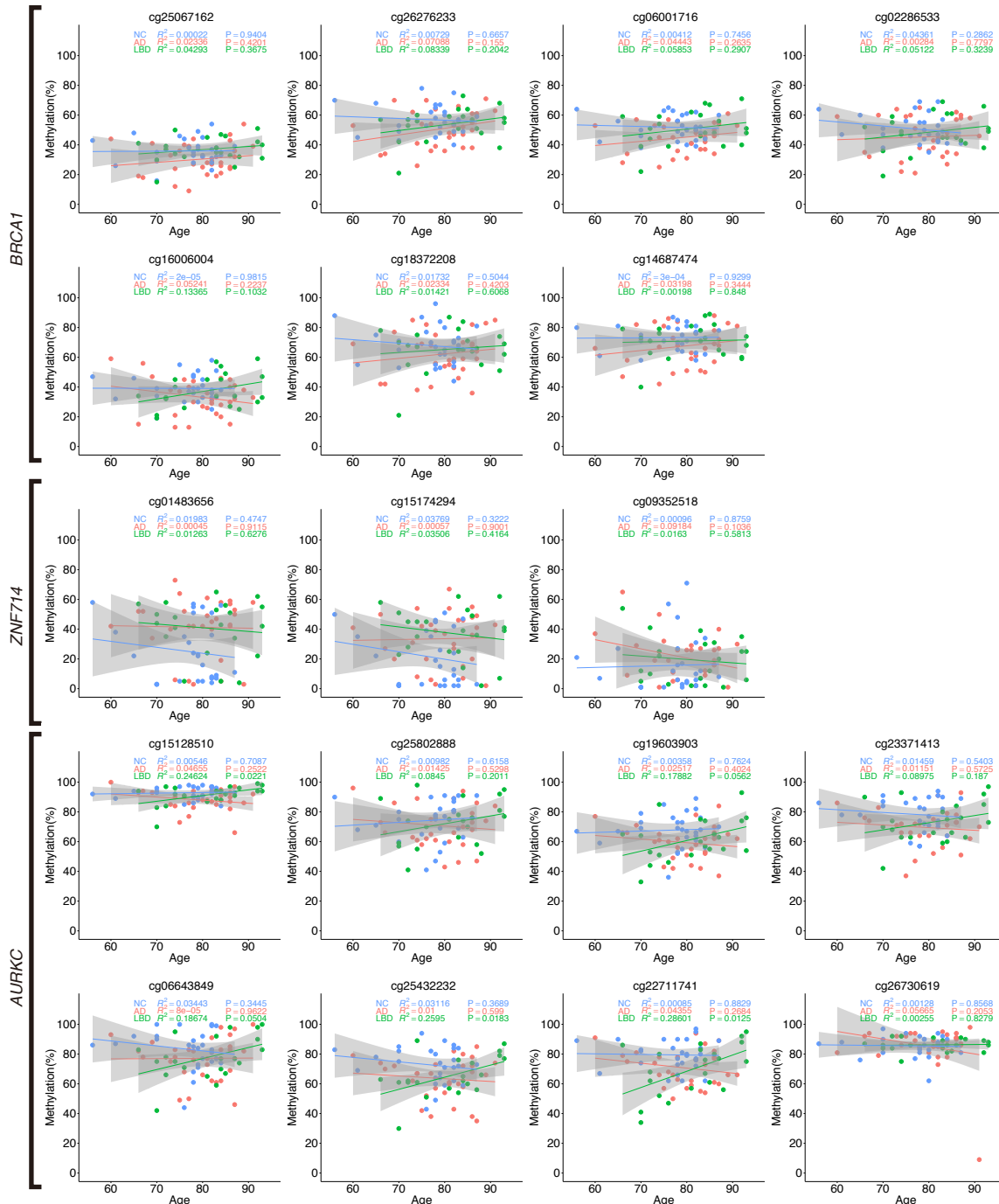
*ZNF714*:  $1.00 \pm 0.15$  in NC vs.  $1.32 \pm 0.19$  in AD, *AURKC*:  $1.00 \pm 0.10$  in NC vs.  $2.69 \pm 0.69$  in

AD.

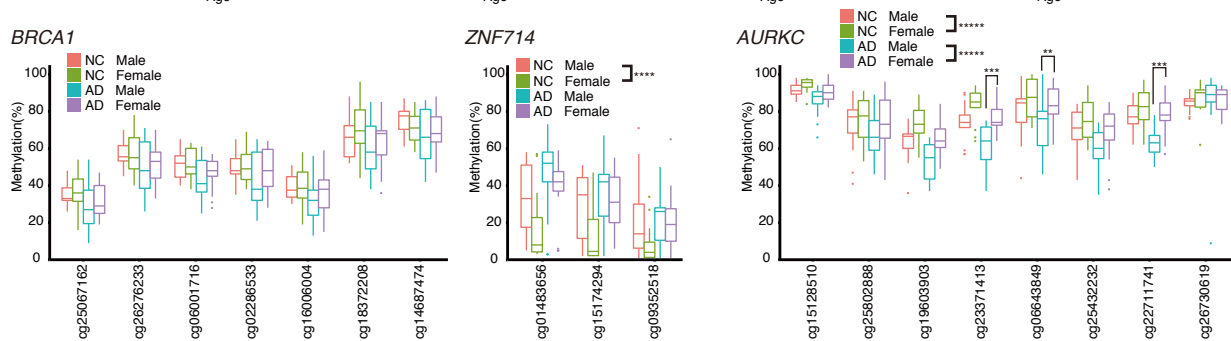


Figure S4

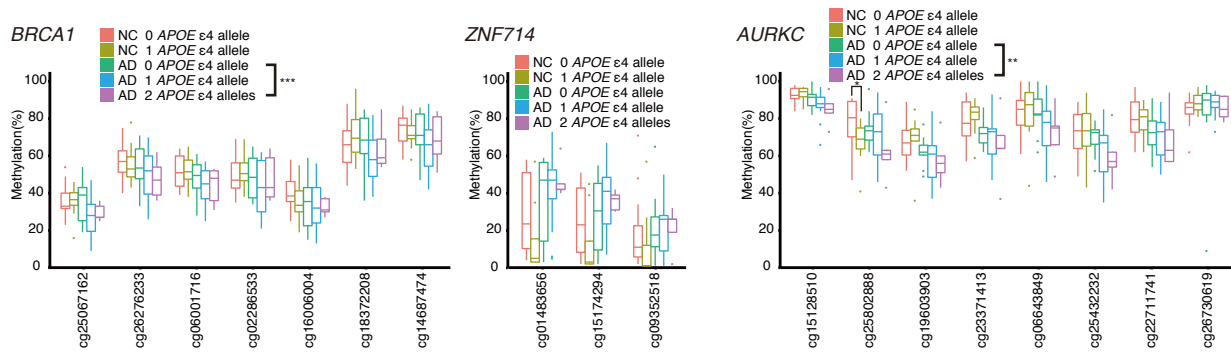
A



B



C



**Figure S4**

Relationship between pyrosequenced methylation level of each DMP and age at death, sex, and the number of *APOE*  $\epsilon 4$  alleles.

(A) Correlation plots of pyrosequenced methylation level of each DMP and age at death for *BRCA1*, *ZNF714*, and *AURKC*. Dots represent individual data and lines are their regression. Blue = NC, red = AD and green = DLB. Gray bands represent a 95% confidence interval of each linear regression. Pearson's product-moment correlation coefficient ( $r$ ) between methylation level and age at death of the subjects and subsequent significance were shown in each graph. ns: not significant, \* $P < 0.05$ .

(B, C) Comparison of each DMP's methylation levels by sex differences (B) and the number of *APOE*  $\epsilon 4$  alleles (C). (B) Orange, green, blue, and purple represent NC male, NC female, AD male, and AD female, respectively. Significance was determined using Two-way ANOVA followed by *post hoc* Sidak method. (C) Orange, light green, green, blue, and purple represent NC without *APOE*  $\epsilon 4$  allele, NC with one *APOE*  $\epsilon 4$  allele, AD without *APOE*  $\epsilon 4$  allele, AD with one *APOE*  $\epsilon 4$  allele, and AD with two *APOE*  $\epsilon 4$  alleles, respectively. Boxes extend from the 25th–75th percentiles and the lines in the boxes are the median. The whiskers were defined by Tukey's boxplot method. Significance was determined for NC and AD using Two-way ANOVA followed

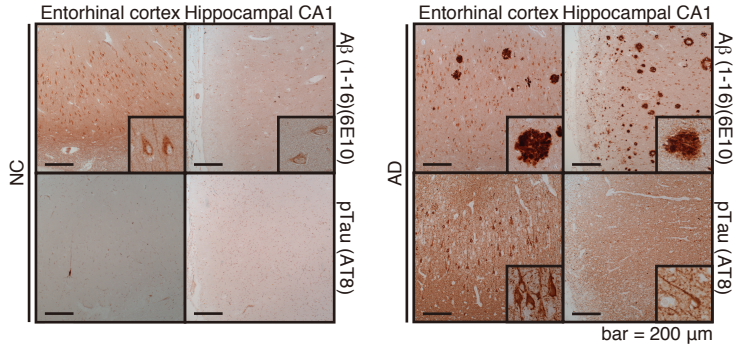
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by *post hoc* Tukey (for NC) or Sidak method (for AD).  $R^2$  and P values are shown in the panels.

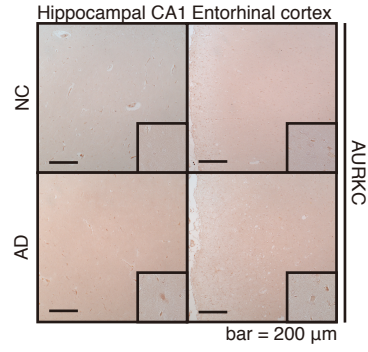
(A)-(C) The data set analyzed here were identical to that of SI Appendix Fig. S3.

Figure S5

A Advanced stage AD



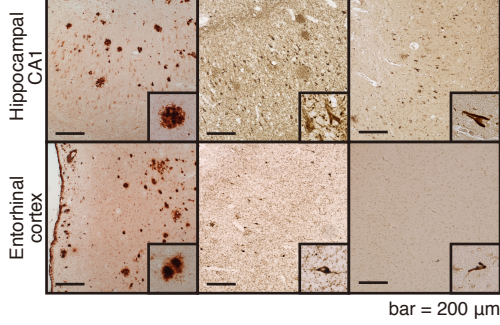
B Advanced stage AD



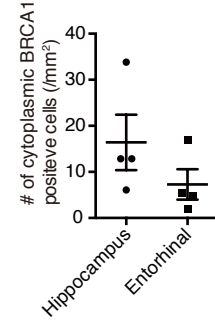
C Early stage AD



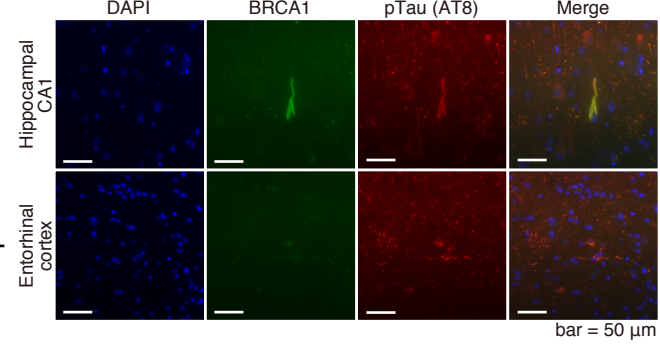
D Early stage AD



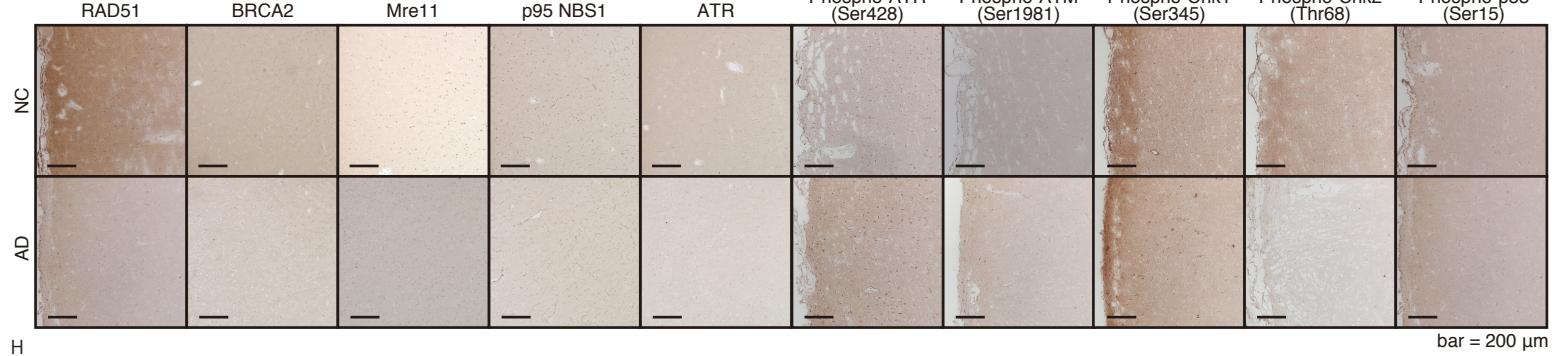
E



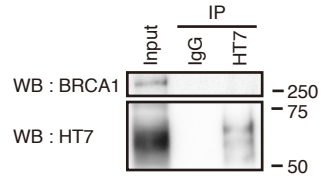
F Early stage AD



G Advanced stage AD



H



**Figure S5**

Pathological changes in advanced and early stage AD.

(A, B) Immunohistochemical images of the entorhinal cortex and hippocampal CA1 from NC or advanced stage brains AD by anti-A $\beta$  (1-16) anti-pTau (A), and anti-AURKC (B) antibodies.

Representative immunohistochemical images are shown from a total of n = 6. (C) Large scale coronal section at the hippocampal level of the representative early stage AD brain stained by anti-pTau antibody. (D) Immunohistochemical images of subjects harboring early stage AD pathology

by A $\beta$ , pTau and BRCA1 antibodies. n=4. (E) Quantification of panel D. Mean  $\pm$  SEM;  $16.41 \pm$

$6.02 / \text{mm}^2$  in the hippocampus,  $7.27 \pm 3.30 / \text{mm}^2$  in the entorhinal cortex. (F) Immunofluorescence

images of early stage AD brains co-labeled with DAPI, anti-BRCA1, anti-pTau antibodies.

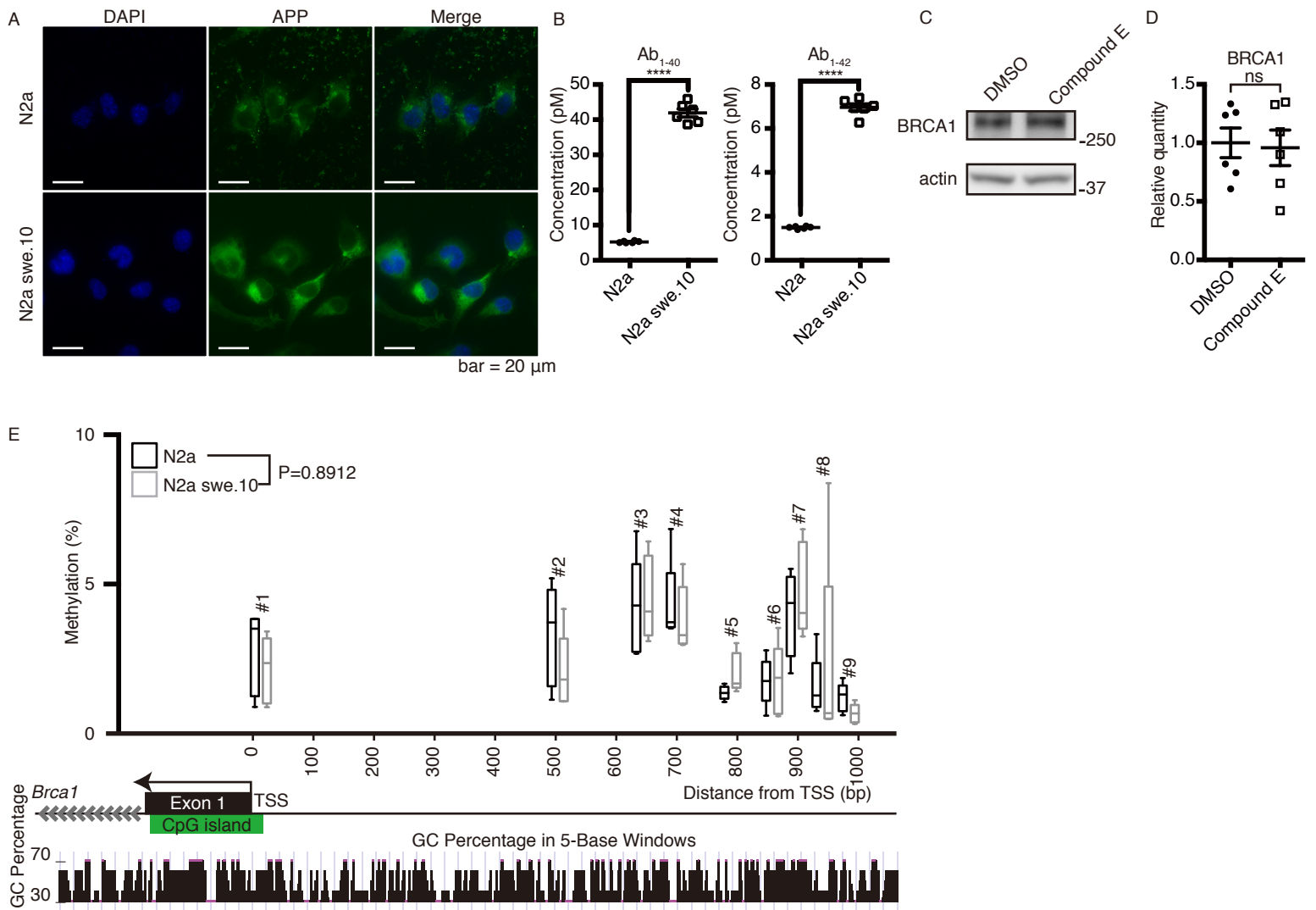
Representative images from n = 4. (G) Immunohistochemical images of inferior temporal gyrus

samples from NC or advanced stage AD brains by antibodies against various DNA repair proteins.

Representative images are shown from a total of n = 3 samples of AD and NC. (H)

Immunoprecipitation of soluble tau from postmortem brain detected by anti-BRCA1.

Figure S6



**Figure S6**

APP expression and methylation level analysis of *Brcal* promoter region in N2a and N2a swe.10.

(A) Immunofluorescence images of N2a and N2a swe.10 cells co-labeled with DAPI and anti-APP

antibody. (B) Concentrations of A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> in the culture media supernatant was measured by

ELISA. n = 6 independent wells. Mean  $\pm$  SEM; A $\beta$ <sub>40</sub>: 5.37  $\pm$  0.11 pM in N2a cells vs. 42.09  $\pm$  1.14

pM in N2a swe.10 cells, A $\beta$ <sub>42</sub>: 1.54  $\pm$  0.02 pM in N2a cells vs. 7.02  $\pm$  0.16 pM in N2a swe.10 cells.

(C) Western blot of N2a cells treated with DMSO or Compound E by anti-mouse BRCA1 or anti-

actin antibodies. (D) Quantitative measurement of panel C. n=6. Relative expression level was

normalized to DMSO = 1.0. Mean  $\pm$  SEM; BRCA1: 1.00  $\pm$  0.13 in DMSO and 0.96  $\pm$  0.15 in

Compound E. (E) Pyrosequencing analysis of the *Brcal* promoter region in N2a and swe.10 cells.

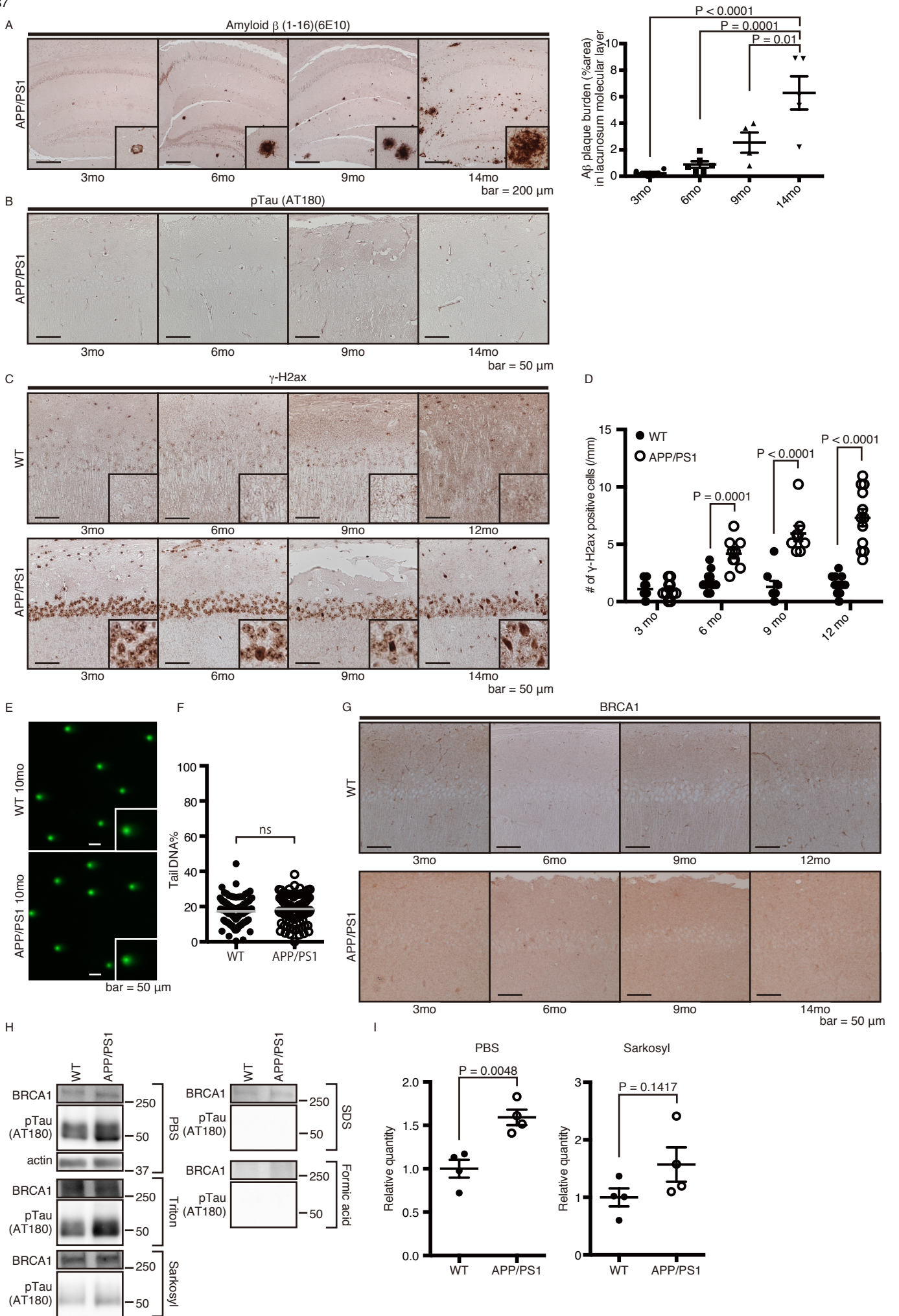
Boxes extend from the 25th–75th percentiles and the lines in the boxes represent the median. The

whiskers show the minimum and maximum values. Statistical significance was determined using

two-way ANOVA. The lower panel shows the structure of *Brcal* gene and its CpG island.



Figure S7





**Figure S7**

Evaluation of BRCA1 expression and DNA DSBs in APP/PS1 mice.

(A, B) Representative immunohistochemical images of A $\beta$  (A) and pTau (B) from APP/PS1

transgenic mice. n = 4 – 6 visual fields from 4 – 6 animals for APP/PS1 mice. Insets are higher

magnifications for A $\beta$  plaques. Quantification of A $\beta$  plaque (%area) is shown at the right side of the

panel. A $\beta$  plaque (%area) mean  $\pm$  SEM; 0.24  $\pm$  0.09 % in 3mo, 0.88  $\pm$  0.25 % in 6mo, 2.54  $\pm$  0.76

% in 9mo and 6.29  $\pm$  1.25 % in 14mo. (C) Representative immunohistochemical images are shown

for  $\gamma$ -H2ax staining. (D) Quantitation of multiple  $\gamma$ -H2ax foci positive cells in panel C experiments.

n = 8 – 16 visual fields from 4 – 7 animals for WT mice. n = 8 – 13 visual fields from 4 – 6 animals

for APP/PS1 mice. Error bars represent mean  $\pm$  SEM. Statistical significance was determined using

the Holm-Sidak method. Mean  $\pm$  SEM; WT: 1.10  $\pm$  0.25 / mm in 3mo, 1.73  $\pm$  0.20 / mm in 6mo,

1.28  $\pm$  0.51 / mm in 9mo and 1.37  $\pm$  0.20 / mm in 12mo, APP/PS1: 1.12  $\pm$  0.20 / mm in 3mo, 4.16  $\pm$

0.39 / mm in 6mo, 5.93  $\pm$  0.67 / mm in 9mo and 7.30  $\pm$  0.74 / mm in 14mo. (E) Comet assay of the

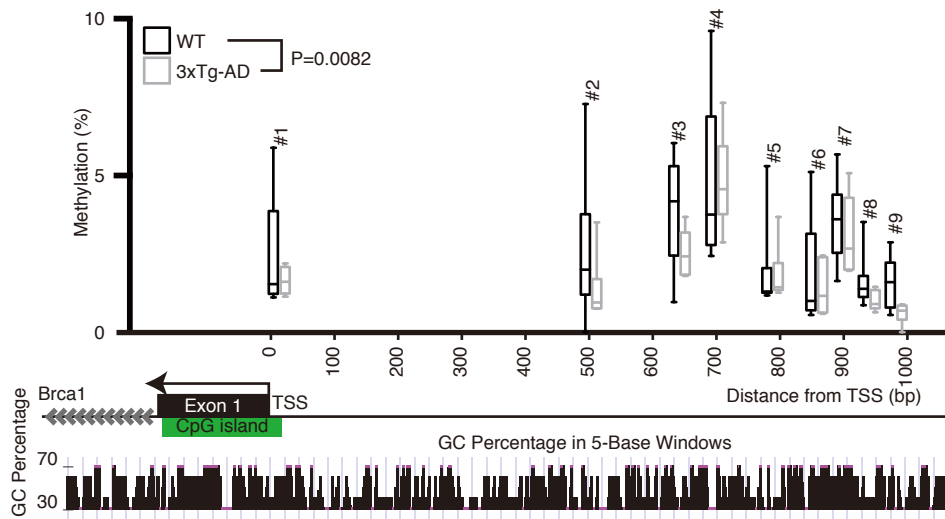
hippocampus from wild type and APP/PS1 mice. Representative microscopic images are shown

from a total of n = 140 cells of the hippocampus from wild type and APP/PS1 mice. Insets are

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magnified nuclei. (F) Quantification of tail DNA% measured for each cell, and analyzed semi-automatically by CASPLab software. Solid circles are wild type and open circles are APP/PS1 mice. Statistical significance was determined using *t*-test. Mean  $\pm$  SEM;  $17.25 \pm 0.55$  in WT vs.  $18.64 \pm 0.56$  in APP/PS1. (G) Representative immunohistochemical images are shown for BRCA1 from 4 – 7 animals for WT mice and 4 – 6 animals for APP/PS1 mice. (H) Expression of BRCA1 in the cortical regions from APP/PS1 mice at 12 mo of age. The samples were treated with 1% Triton X-100, 2% Sarkosyl, 0.1% SDS, and 70% formic acid in a serial manner, each time saving the centrifuged supernatant as soluble fractions for each detergent.  $n = 2$  mice at 12 mo of age. Representative blot is shown. (I) Statistical analysis of panel H experiments for PBS and Sarkosyl fractions.  $n = 4$ . Relative quantity against actin expression level was normalized to WT = 1.0. Mean  $\pm$  SEM; PBS:  $1.00 \pm 0.10$  in WT vs.  $1.59 \pm 0.09$  in APP/PS1, Sarkosyl:  $1.00 \pm 0.16$  WT vs.  $1.57 \pm 0.30$  in APP/PS1.

Figure S8



**Figure S8**

Methylation level of the *Brcal* promoter region in 3×Tg-AD and wild type mice.

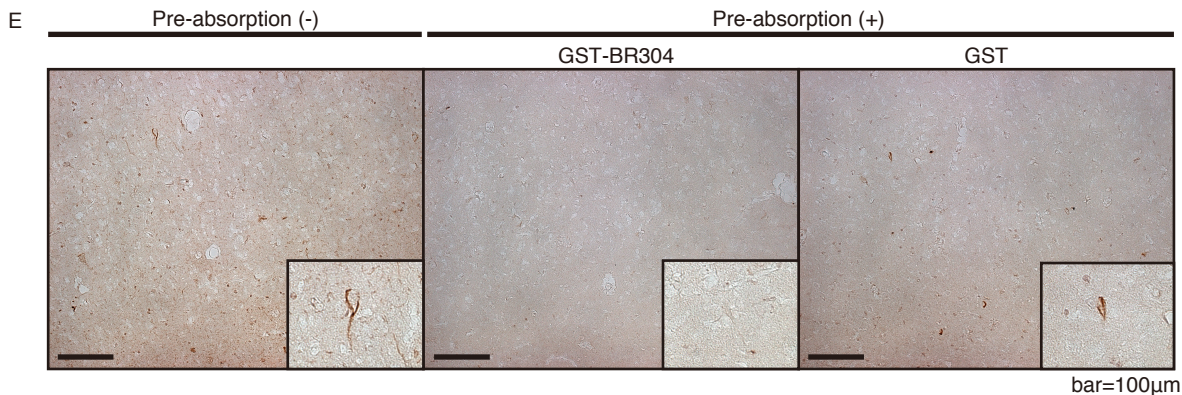
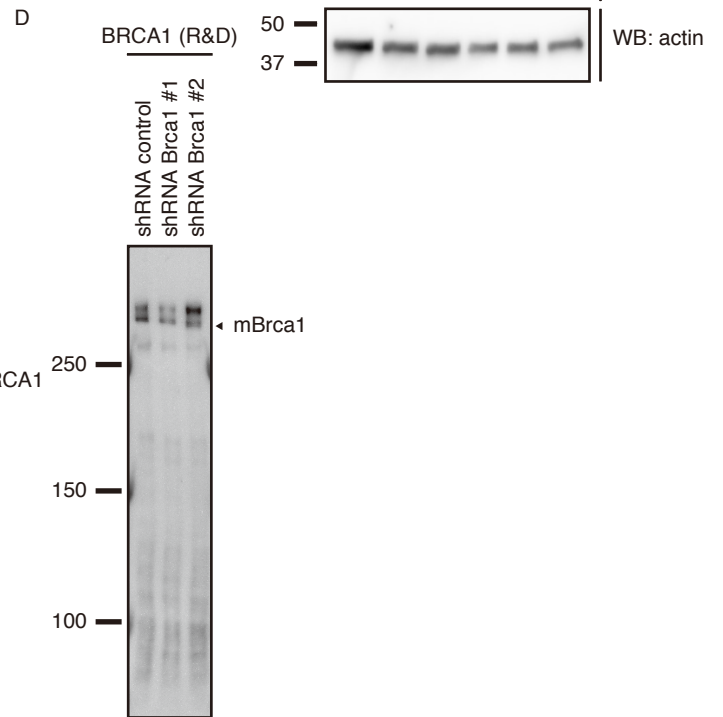
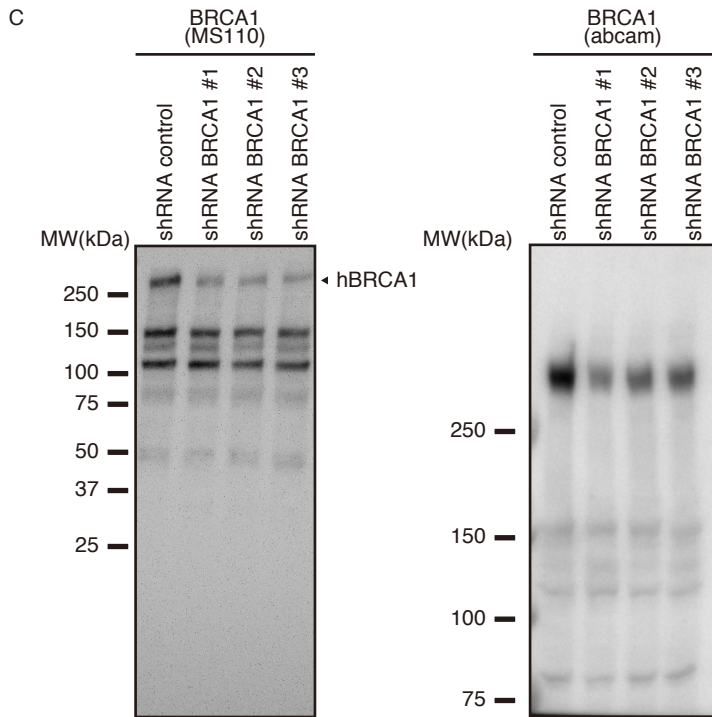
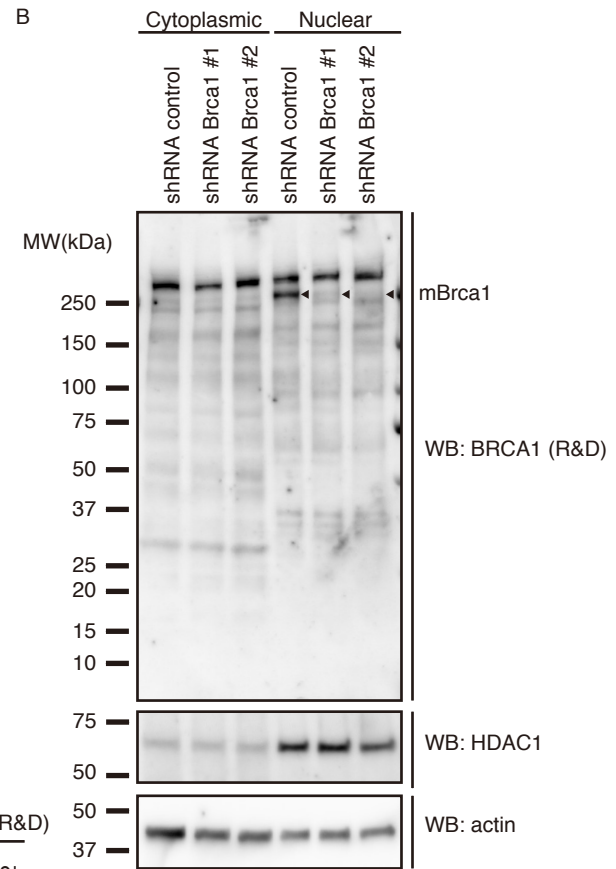
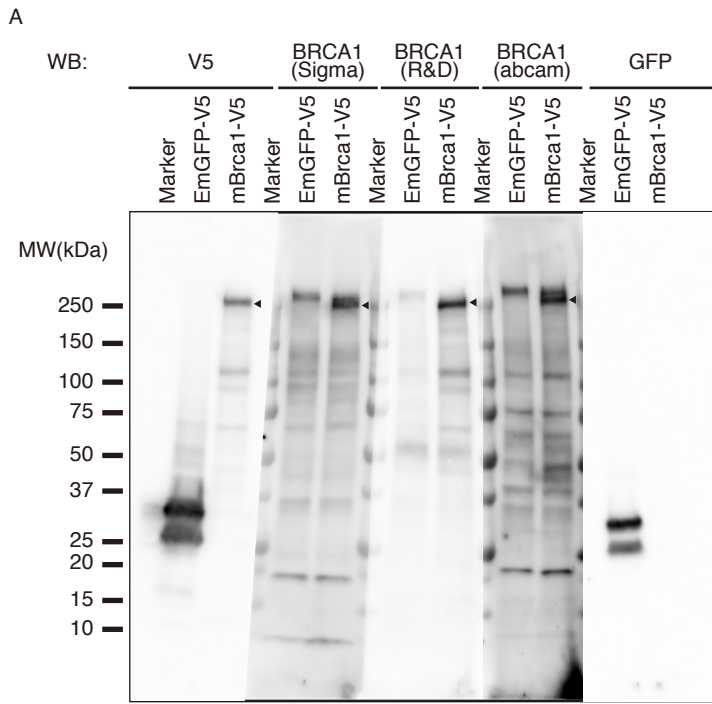
Boxes extend from the 25th–75th percentiles and the lines in the boxes represent the median. The

whiskers show the minimum and maximum values. Statistical significance was determined using

two-way ANOVA,  $P = 0.0082$ . WT mice ( $n = 9$ ),  $7.71 \pm 1.10$  months old; 3×Tg-AD ( $n = 6$ ),  $8.46, \pm$

1.43 months old.

Figure S9



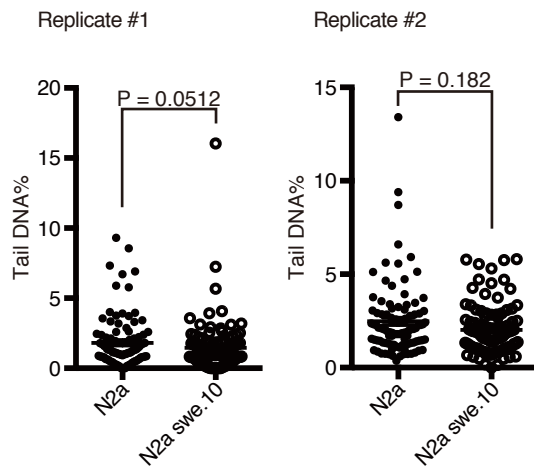
**Figure S9**

Validation of anti-BRCA1 antibodies in its detectability of human and murine BRCA1.

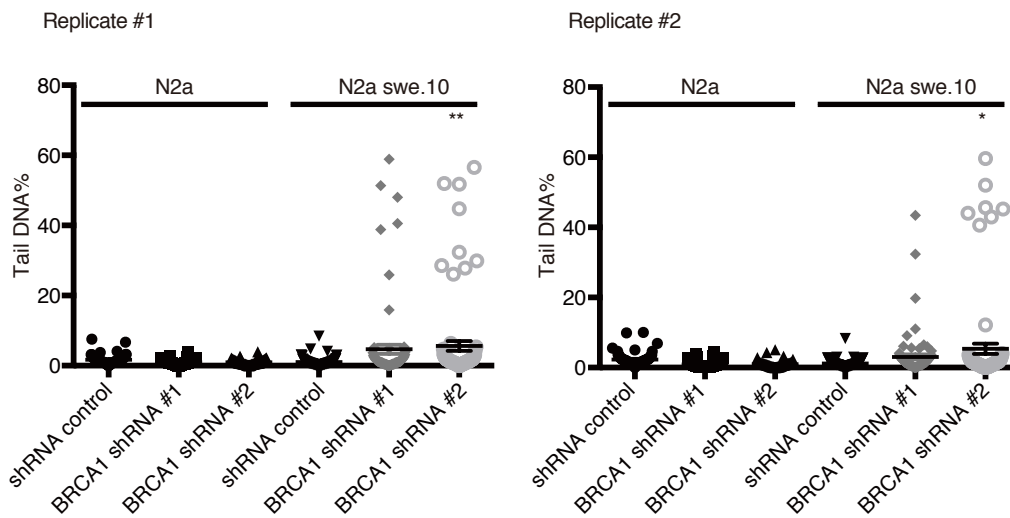
(A) Western blot of 293FT cells transiently transfected V5-tagged murine Brca1 or EmGFP detected by using various anti-BRCA1 antibodies. (B) N2a cells were infected with lentivirus containing various shRNAs. After harvest, cells were fractionated to cytoplasmic and nuclear fraction using hypotonic buffer and detergents. (C) HeLa cells were infected with lentivirus containing various shRNAs. Total cellular lysate was subjected to western blot. The arrowheads indicate human BRCA1. (D) Knock-down of murine Brca1 in primary cortical culture from 3×Tg-AD mice. (E) Antigen pre-absorption assay with GST-tagged N-terminal segment of BRCA1 (residues 1-304) (GST-BR304). Anti-human BRCA1 antibody (MS110) was pre-absorbed with GST-BR304, and subjected to immunostaining. Serial sections were stained with the same antibody without absorption or with absorption with GST. Insets are magnified view of the neuronal cells.

Figure S10

A Biological replicates for Fig. 4C, D



B Biological replicates for Fig. 4E, F



**Figure S10**

Biological replicates for comet assays in Figure 4

Comet assays were performed independently in 2 biological replicates for Figure 4C, D (A) and

Figure 4E, F (B).  $n = 100$  cells (A) or 80 cells (B) for each cell line. Statistical significance was

determined by unpaired Student *t*-test (A) or the Turkey's method (B). Mean  $\pm$  SEM were as

follows.

(A) Replicate #1:  $1.81 \pm 0.18$  % in N2a cells vs.  $1.46 \pm 0.19$  % in N2a swe.10 cells

Replicate #2:  $2.48 \pm 0.19$  % in N2a cells vs.  $2.02 \pm 0.13$  % in N2a swe.10 cells

(B) Replicate #1: N2a:  $1.70 \pm 0.14$  % in shRNA control,  $0.98 \pm 0.08$  % in shRNA #1,  $0.99 \pm 0.08$  %

in shRNA #2, N2a swe.10:  $1.03 \pm 0.14$  % in shRNA control,  $4.67 \pm 1.32$  % in shRNA #1,  $5.65 \pm$

$1.41$  % in shRNA #2

Replicate #2: N2a:  $2.27 \pm 0.19$  % in shRNA control,  $0.91 \pm 0.10$  % in shRNA #1,  $0.95 \pm 0.10$  % in

shRNA #2, N2a swe.10:  $1.17 \pm 0.13$  % in shRNA control,  $3.05 \pm 0.71$  % in shRNA #1,  $5.39 \pm 1.48$

% in shRNA #2