Brain Bank for Aging Research (BBAR)

Director: Yuko Saito M.D. Ph.D.
*Secretary General: Shigeo Murayama M.D. Ph.D.**

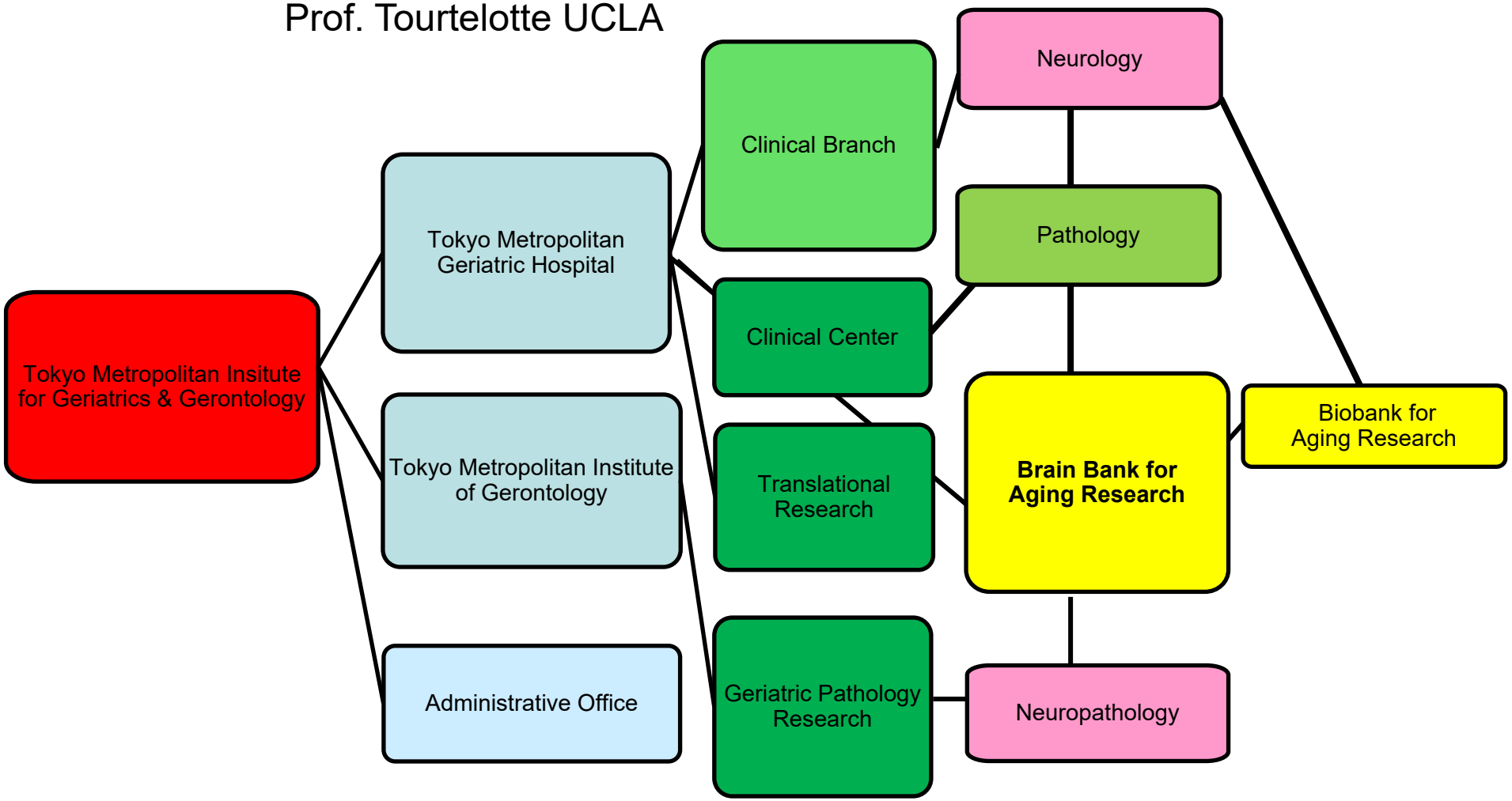
Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan

*Specially Appointed Professor, Brain Bank for Neurodevelopmental, Neurological and Psychiatric Disorders, United Graduate School of Child Development, Osaka University (cross appointment)

Brain Bank for Aging Research (BBAR)

Tokyo Metropolitan Institute for Geriatrics and Gerontology

Brain Bank is a movement conducted by patients, doctors and researchers, to conquer intractable neuro- psychiatric disorders.
Prof. Tourtelotte UCLA



Brain Bank for Aging Research (BBAR)

TMIGG

Resources consisting of consecutive autopsy cases from a general geriatric hospital & all Japan depository of rare neurological and developmental disorders (http://www.mci.gr.jp/BrainBank)

In House Cohort Resource

1. Paraffin blocks and glass slides (1972.5-)
   for Clinical, Radiological and Pathological Research 7418
   >2. Frozen neocortex and body tissues (1995.1-)
   for Molecular Research: 2,415
   >3. Frozen half brains (2001.7-)
   for Neuroscience Research: 1,102

All Japan Depository of Neurological and Psychiatric Disorders

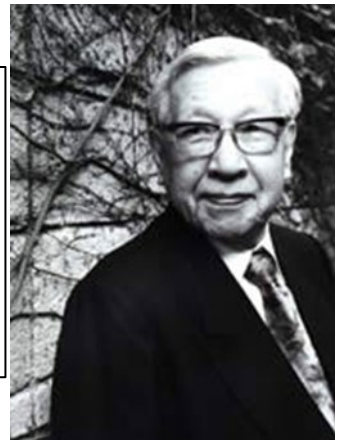
Brain Bank for Neurodevelopmental, Neurological and Psychiatric Disorders, Osaka University

Basic Concept of BBAR

1. Seamless cooperative management of the hospital and the research institute.
2. The longstanding mutual reliable relationship with the supporting cohort.
3. Establishment of the NIH- type PET Center.
4. Establishment of the Department of Neuropathology.

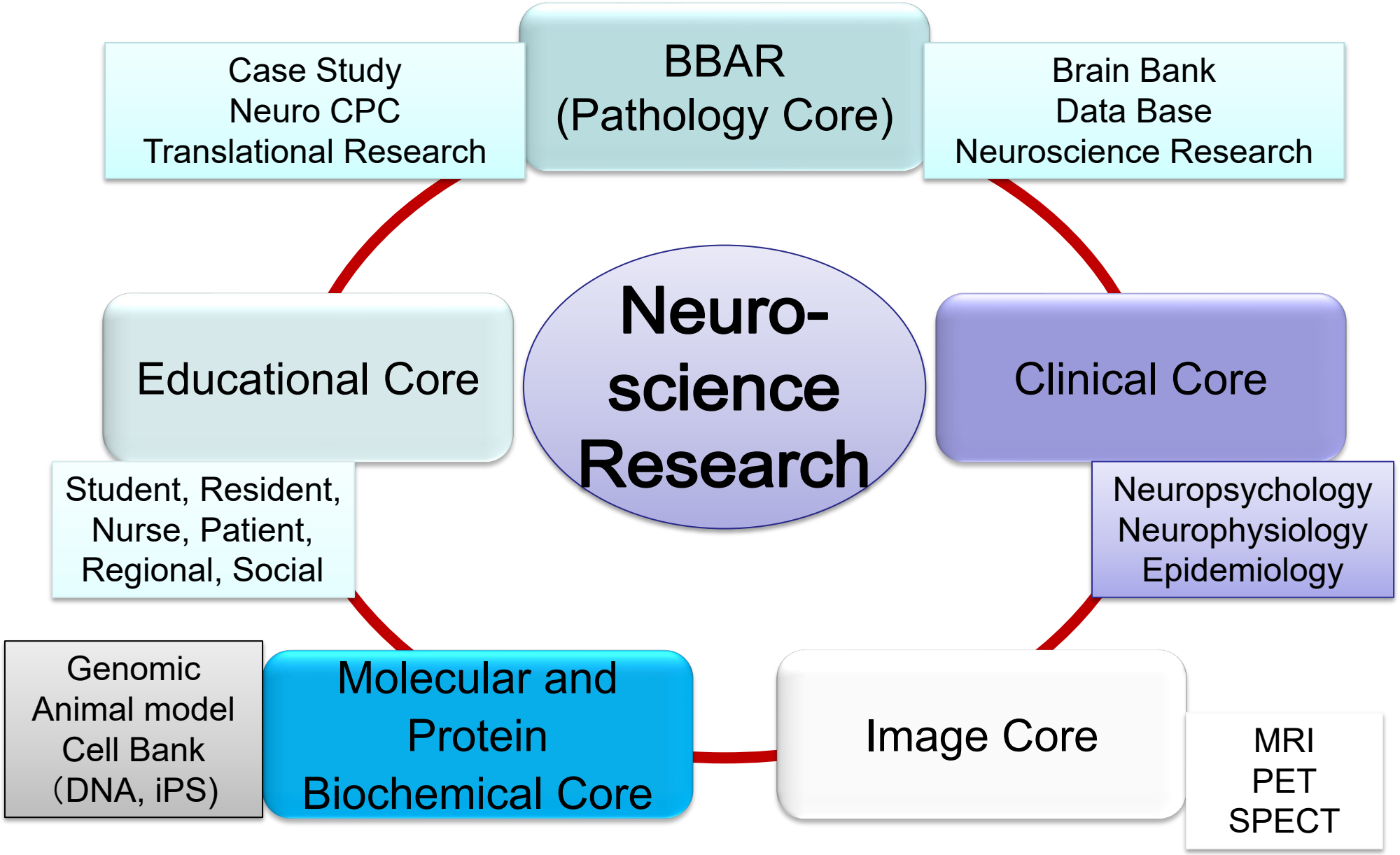
(Late Prof. Kazutomo Imahoari, reg. to BBAR in 2016）

5. Diagnosis of dementia and/ or parkinsonism with CSR surrogate baiomarkers> 3,600 cases (Dr. Iwata A).
6. Clinical, radiological and pathological data base of the consecutive autopsy cases.

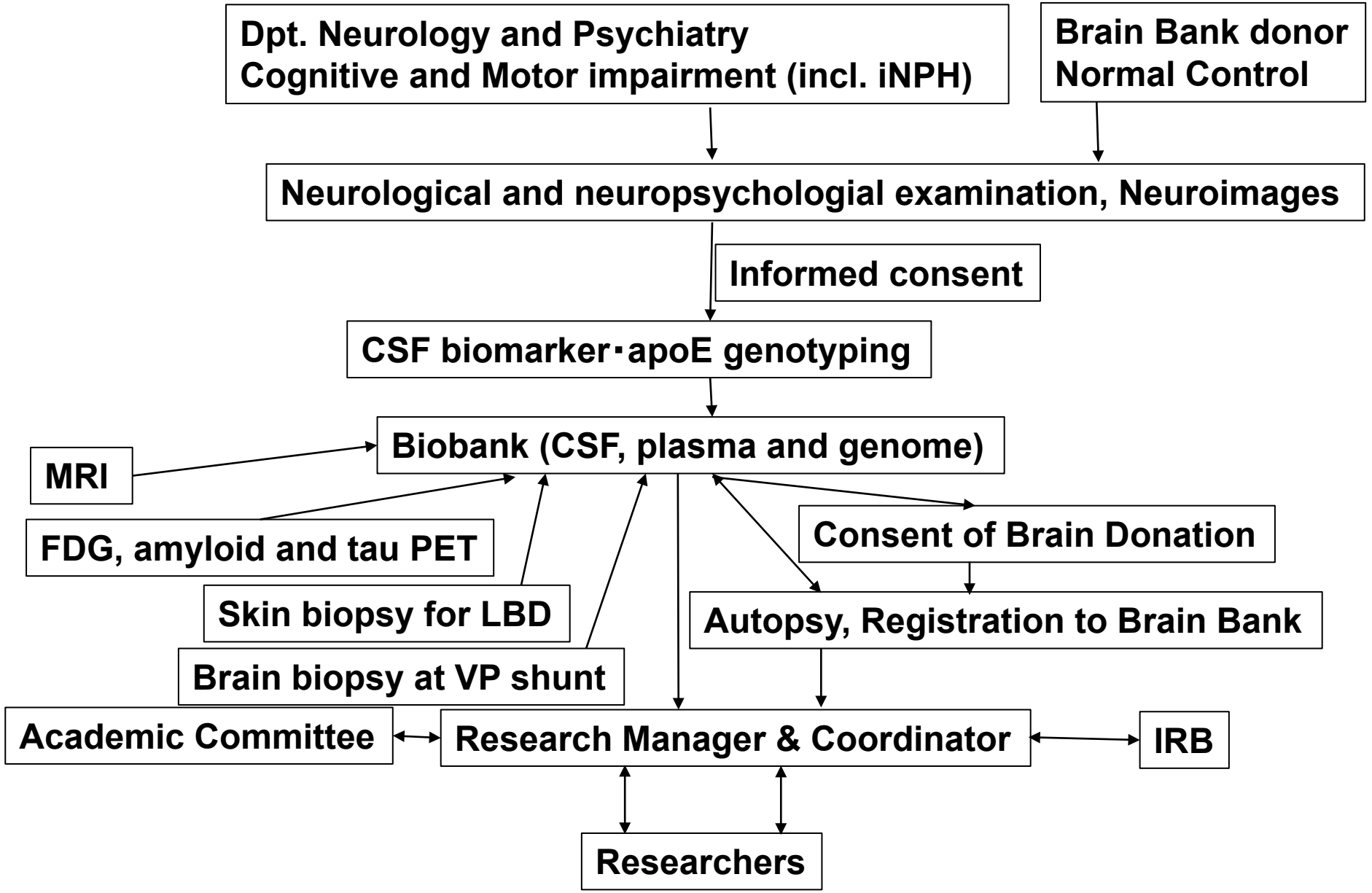


Late Emeritus Prof.
Kazutomo Imahori
The Univ. Tokyo
Registered to BBAR
2016

Basic Scheme of BBAR



BBAR Resource Built



BBAR Clinical Project

Prospective longitudinal clinical studies of dementia and parkinsonism, confirmed by final neuropathological findings

- Neuropsychiatric & neuropsychological examinations
- Voxel based morphometry with MRI
- CSF and blood biomarker (tau, ptau, Abeta 1-42, HVA, 5HIAA)
- SPECT: Brain Tc- ECD, Heart MIBG and DAT
- PET: FDG, PIB, Tau, Dopamine (P2I, Raclopride), THK5351

Grants in Aid from Tokyo Metropolitan Government,
Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labor and Welfare, and Japanese Agency for Medical Research and Development

BBAR Research Project

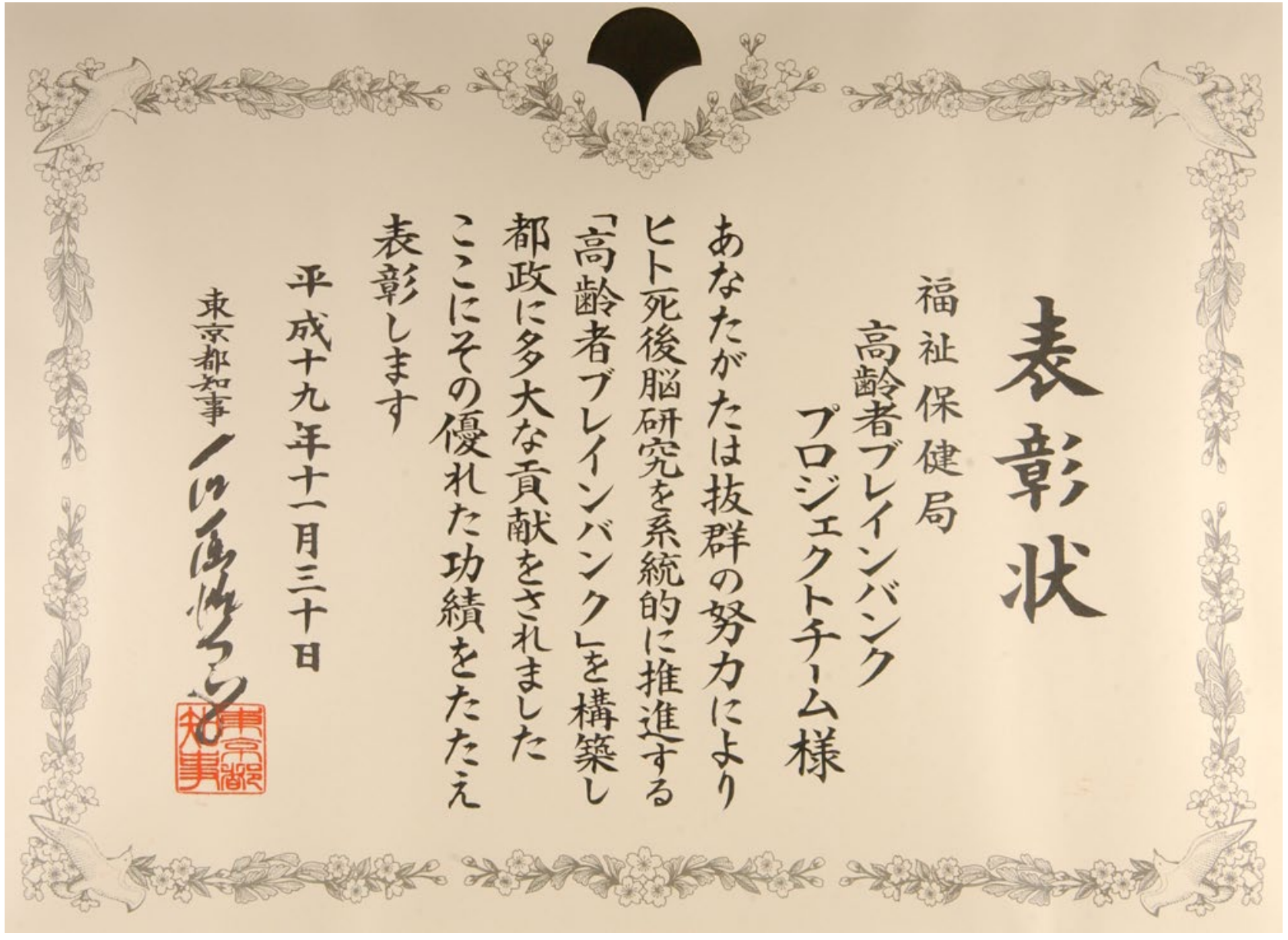
Cross- sectional Pathological Studies

- Dynamic Neuropathology
  = to elucidate the correlation between the longitudinally acquired in vivo clinical and radiological findings and postmortem pathological findings
- Molecular Neuropathology
  = to clarify the molecular basis of each pathological process
- Epidemiological Neuropathology
  = to study a large number of unbiased samples, actively correlated with the former two methods

BBAR Resource Center

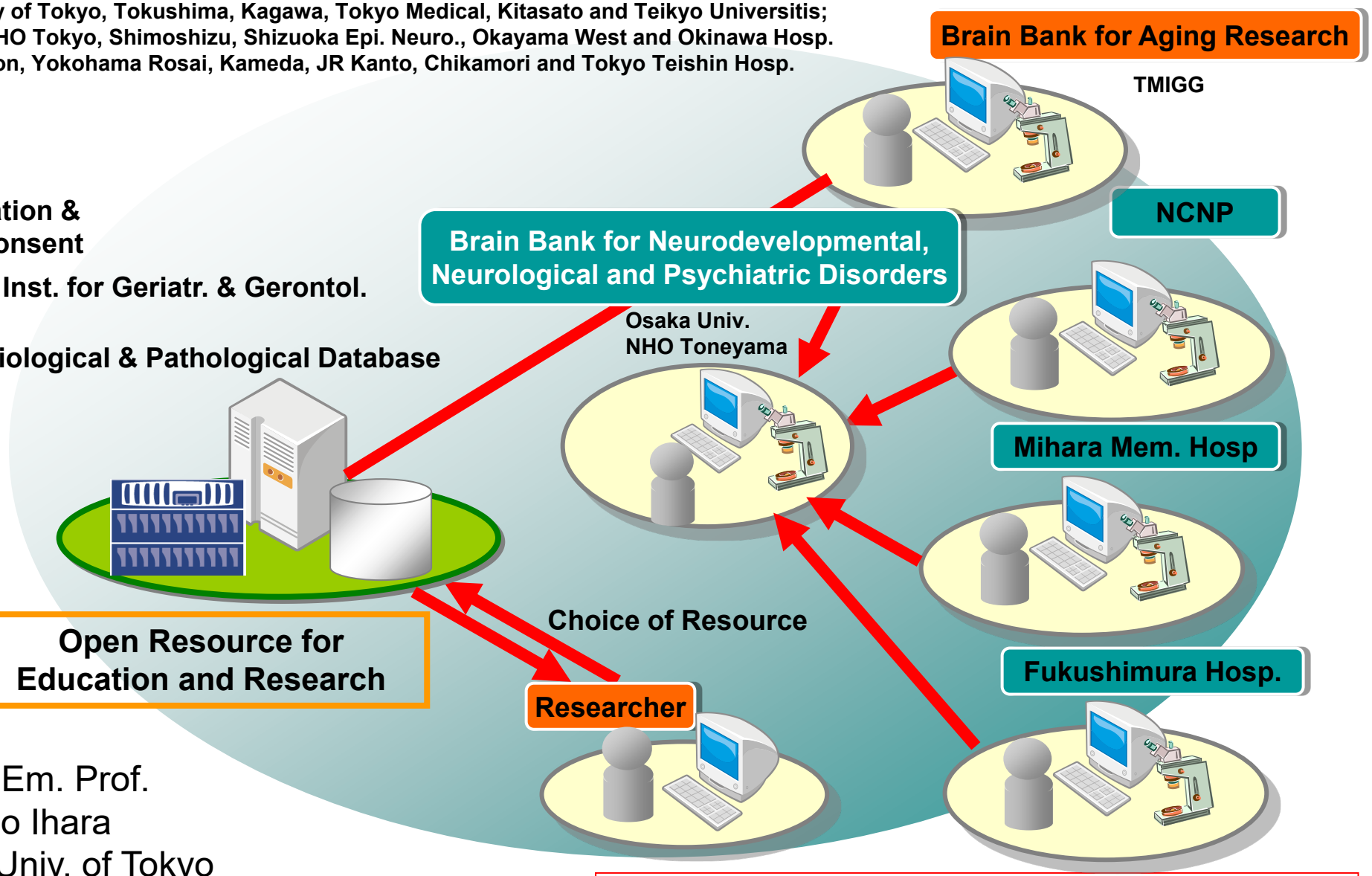
- A fulltime brain bank coordinator.
- All BBAR records stored in hospital digital clinical chart system with Brain Bank ID.
- BBAR Resource Center:
  24 deep freezers, including one
  for a national prion back- up bank
- >7000 cases- paraffin blocks
- BBAR Data Center: a virtual slide system for educational output.
- BBAR Network Conference Room:
  internet conference with Osaka U and Toneyama

Tokyo Metropolitan Mayor's Award 2007
The Brain Bank for Aging Research Project



Japanese Brain Bank Network for Neuroscience Research

University of Tokyo, Tokushima, Kagawa, Tokyo Medical, Kitasato and Teikyo Universitis;
NCGM, NHO Tokyo, Shimoshizu, Shizuoka Epi. Neuro., Okayama West and Okinawa Hosp.
Toranomon, Yokohama Rosai, Kameda, JR Kanto, Chikamori and Tokyo Teishin Hosp.



Late Em. Prof.
Yasuo Ihara
The Univ. of Tokyo
registered to BBAR 2023

Brain Bank Committee, Jap. Soc. Neuropath.

Japanese Brain Bank Net （JBBN)
2017- 2021

AMED Comprehensive Brain
PI: Yuko Saito

Jpn Soc. Biol. Psychitr., Jpn Soc. Dementia Res., Jpn Soc. Neurol., JSNP, Jpn. Soc. Pathology

National Center of Neurology and Psychiatry (Saito)

Psychiatric
- Fukushima Pre. Univ. Brain Bank (Yabe)
- Nagoya Univ. Psychi. Consortium (Iritani)
- Okayama Univ. Psych. (Terada)
- Matsuzawa Hosp (Oshima)

Aging and Dementia
- The Brain Bank for Aging Research, Tokyo Metro. Geriatr. Hosp. & Inst. Gerontol., co-funded by NCGG (Murayama)

Neurological
- Brain Research Institute, Niigata U (Prof. Kakita) [Genome (Ikeuchi)]
- Aging Res. Inst. Aichi Medical Univ. (Yoshida)

Shared Data Base

AD: 1000
PD: 250
Schizo 200

JBBN

Statistical advisor (Tanaka)

Academic Committee

Application

Biobank (Goto)

Research Mnagement Center

IRB (each institute)

Researcher

IRB (each institute)

@NCNP

Ethical advisor (Inoue)

Executive Committee

(Evaluation and Advise)

Outside Advisory Board

2006 Joint Ethical Guideline by Japanese Society of Neuropathology and Japanese Society of Biological Psychiatry

（Cooperation）

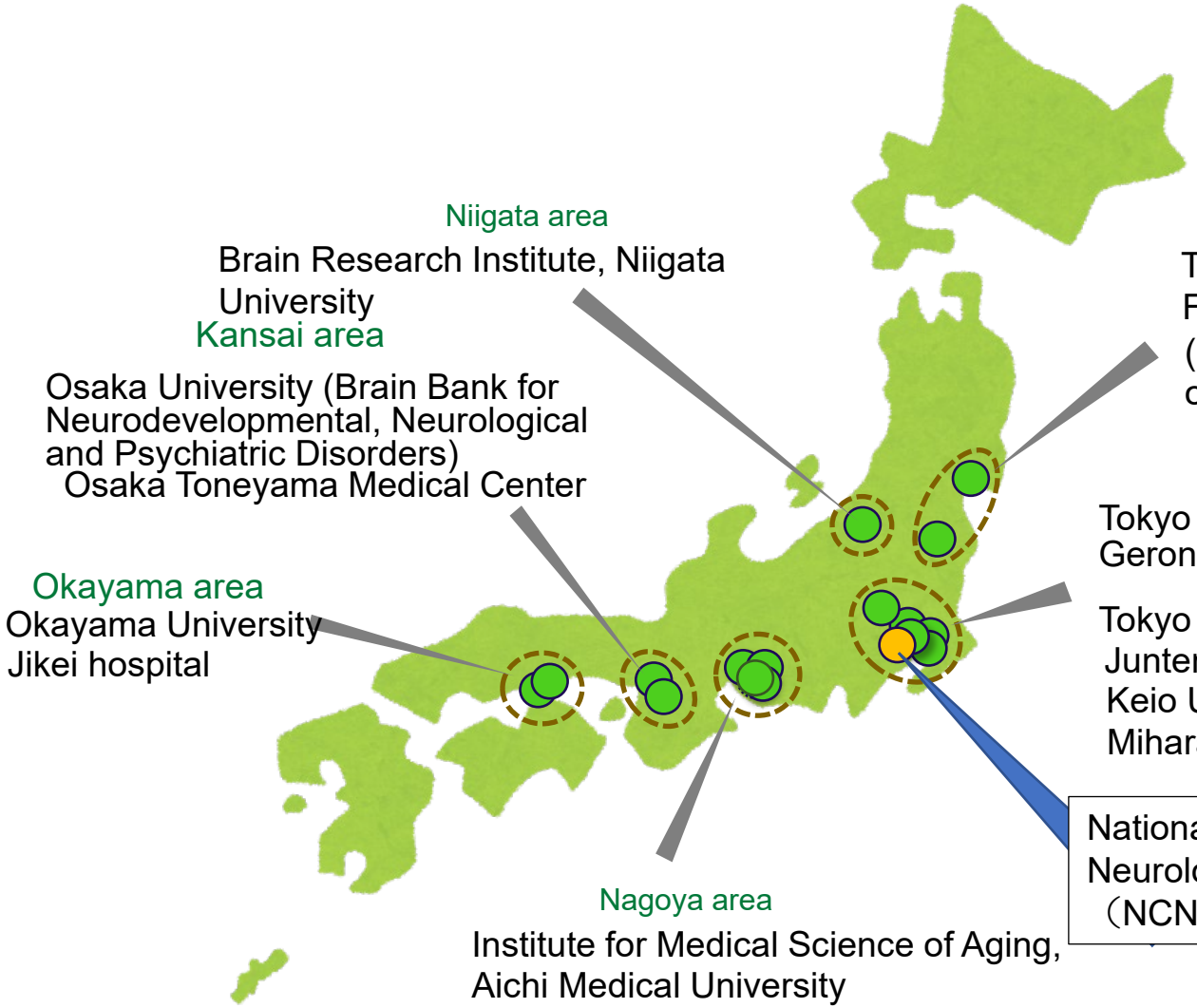
（Evaluation, Standardization, Qulity Control）

Brain Bank Committee, JSNP

Late Emeritus Professor
Ichiro Kanazawa
The Univ. of Tokyo
registered to BBAR 2016

Japan Brain Bank Net, Second

AMED 2022- 2026 Psychiatric brains



Niigata area

Brain Research Institute, Niigata University

Kansai area

Osaka University (Brain Bank for Neurodevelopmental, Neurological and Psychiatric Disorders)

Osaka Toneyama Medical Center

Okayama area

Okayama University

Jikei hospital

Nagoya area

Institute for Medical Science of Aging, Aichi Medical University

Nagoya University Hospital

Seishinkai Okehazama Hospital

Moriyama Hospital

Tohoku area

Tohoku University

Fukushima Medical University

(Postmortem Brain and DNA Bank of Fukushima for Psychiatric Research)

Kanto area

Tokyo Metropolitan Institute for Geriatrics and Gerontology (Brain Bank for Aging Research)

Tokyo Metropolitan Matsuzawa Hospital Institute

Juntendo University

Keio University

Mihara Memorial Hospital

National Center of Neurology and Psychiatry （NCNP Brain Bank）

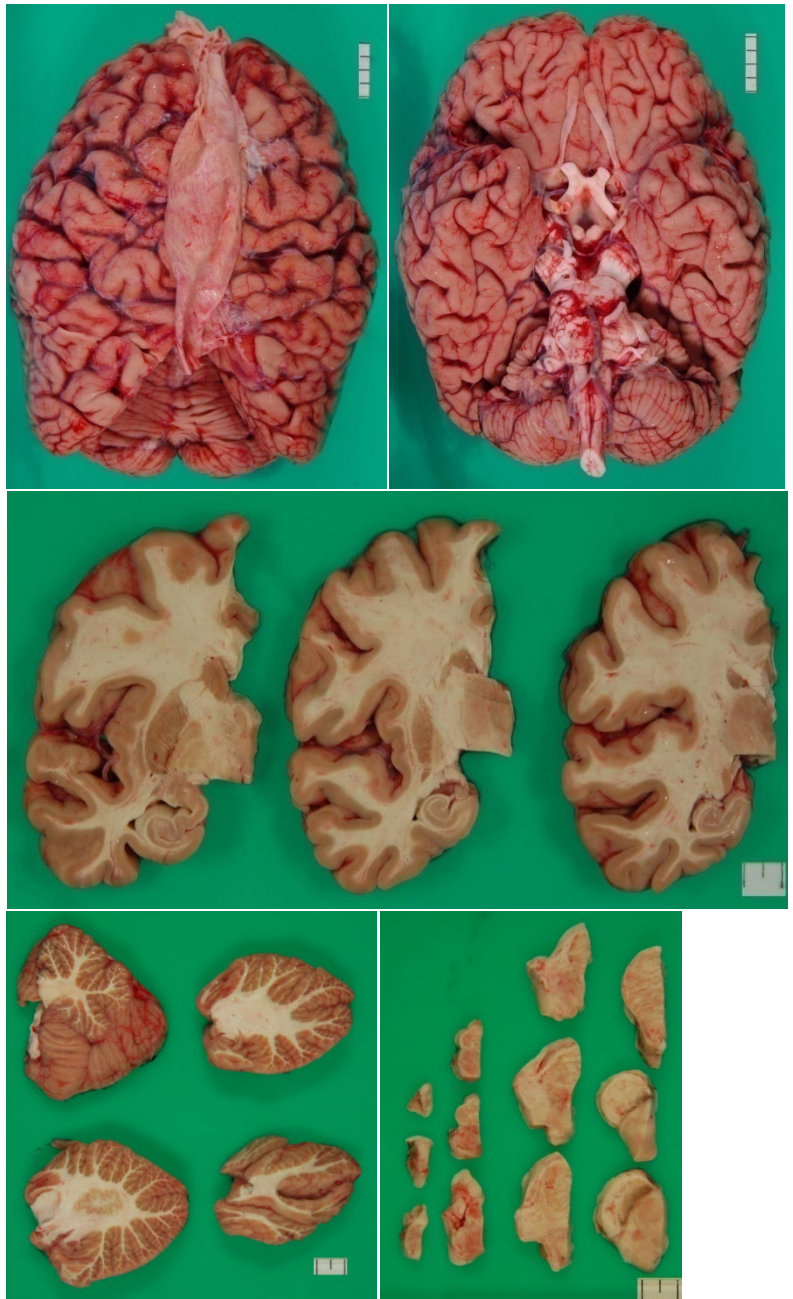
JSNP Brain Bank Committee (1986-)

Chair: Murayama S (Osaka U)

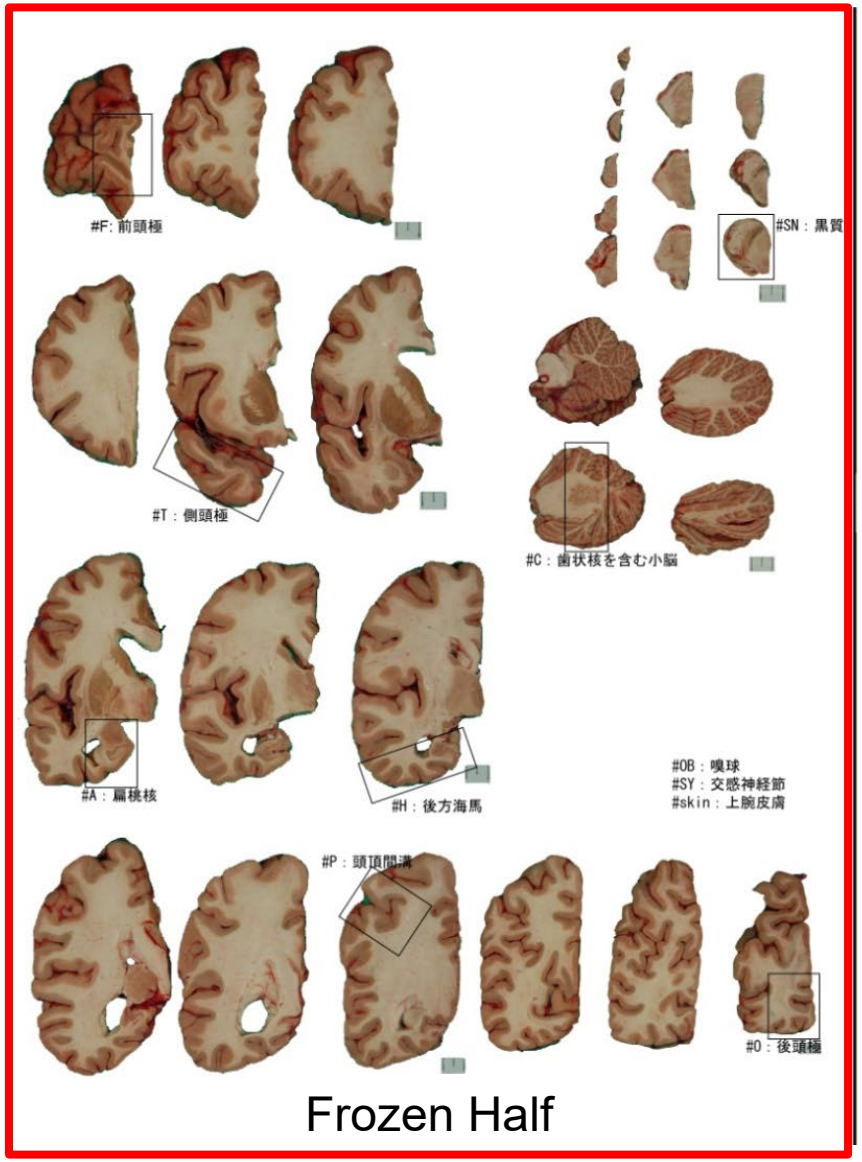
- Adachi T (NP, Tottori U)
- Beck G (Neu Osaka U)
- Furuta T (Pat
- Hasegawa M (Bio Ch TMIMR)
- Inoue, K.（Neu NHO Toneyama)
- Ikeuchi, K. (Genome Niigata U)
- Inoue Y (Ethis IMSUT)
- Iritani S (Psy Nagoya U)
- Ito K (NP Kyoto Pr U)
- Izumi Y (Neu Tokushima U)
- Kaneda D (Neu Fukushimura)
- Kawakami I (Psy Juntendo)
- Komori T (NP TMNH)
- Kowa H（Neu Kobe U）
- Kunii Y (Psy Tohoku U)
- Tanigawa K (Pat Hokkaido U)
- Matsumoto T (Forensic Osaka U)
- Nishida N (Forensic Toyama U)
- Nishimura H（Pat Kawasaki U)
- Oshima K（Psy Matsuzawa H.）
- Saito Y (NP TMIGG)
- Shimizu H (NP Niigata U)
- Suzuki H. (Pat NPO Sendai)
- Takao M (Lab NCNP)
- Taniguchi M（Neu Juntendo U）
- Tokumaru A (Rad TMIGG)
- Miki Y (NP Hirosaki U)
- Yamada M (NP Shinshu U)
- Yokota O (Psy Okayama U)
- Yoshida M (NP Aichi M U)

Autopsy of Brains

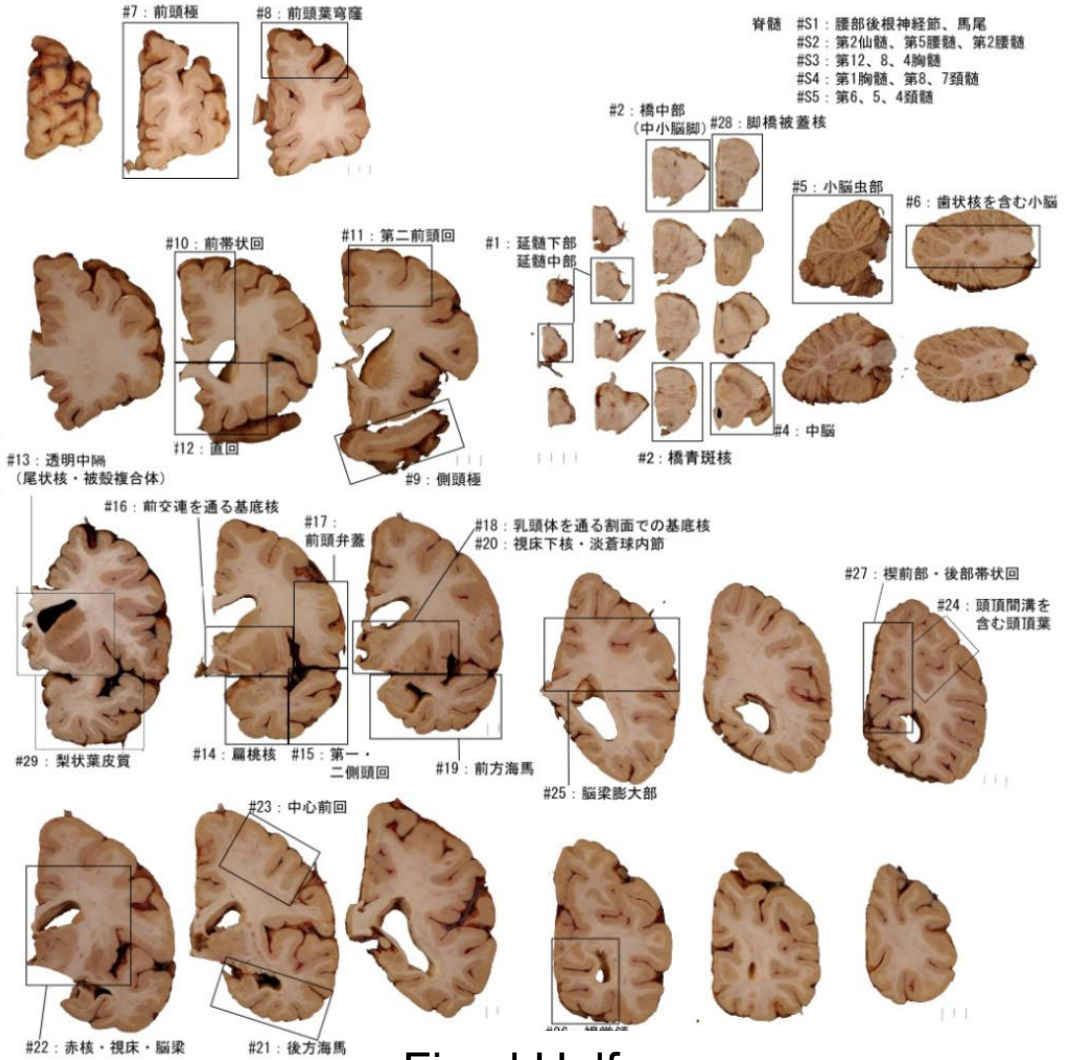
- Each case is handled by an attending brain bank doctor (neuropathologist) and a technician (specially trained), in collaboration with an attending general pathologist and two pathology technicians.
- The attending brain bank doctor determines the frozen side.
- The doctor forms 8mm-thick serial coronal slices of the brain, 5mm- thick serial sagittal slices of the cerebellum and 5mm- thick axial slices of the brain stem.
- The technician takes photos and freezes tissues immediately.



BBAR Protocol (www.mci.gr.jp)



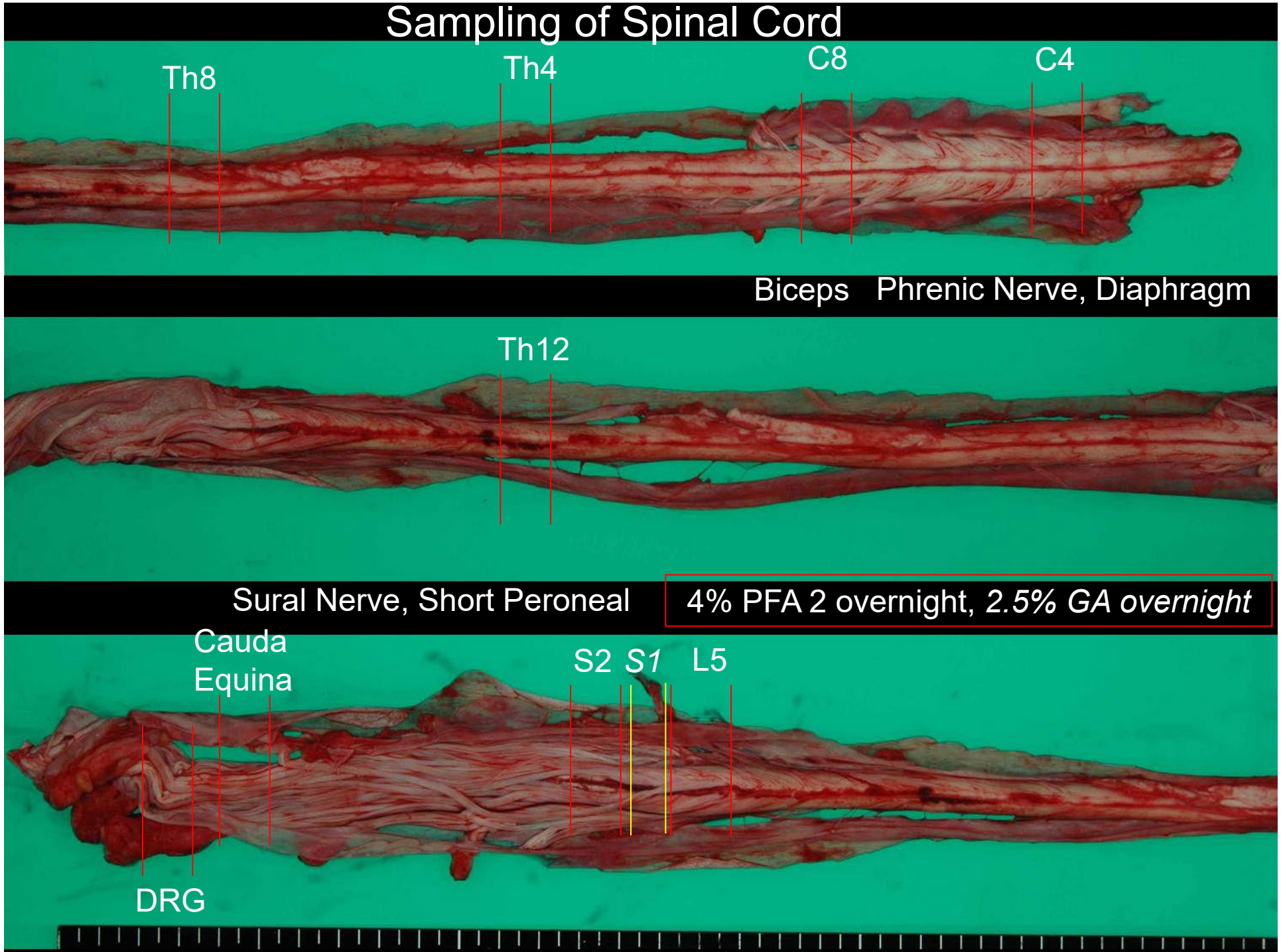
Frozen Half



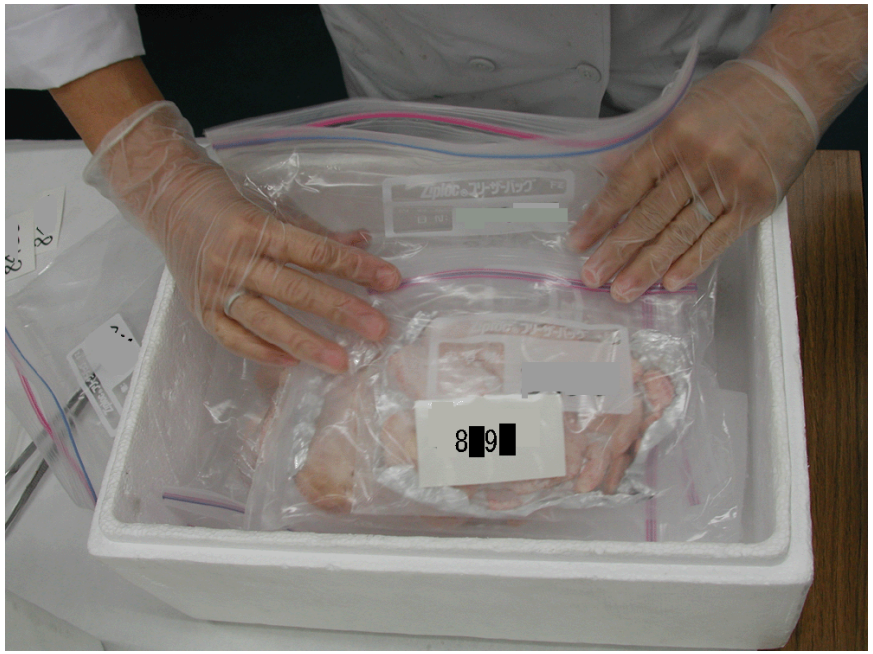
Fixed Half

8 areas: 4% paraformaldehyde over 2 nights
(McGeer's method @ British Columbia)

Sampling of Spinal Cord




a copper plate chilled in refrigerator on sliced dry ice




REVCO
REVCO

BBAR Resource (Frozen)

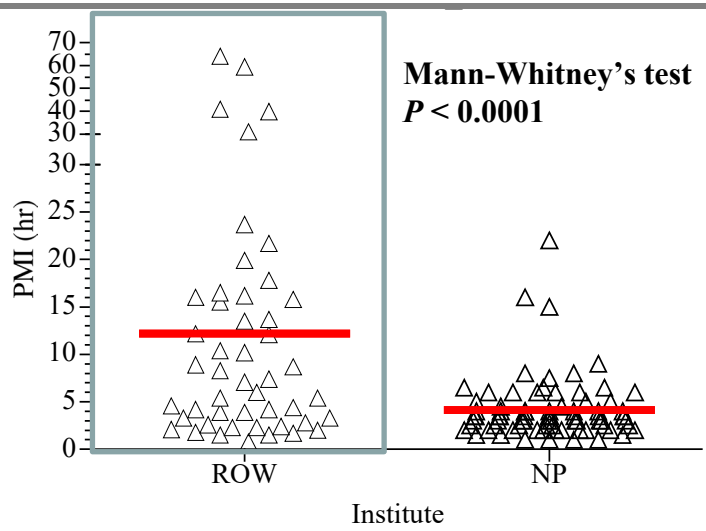
- Half brain after sampling small pieces of tissues for weak fixation.
- Entire spinal cord, after sampling the segments for pathological evaluation.
- Peripheral autonomic nervous system: sympathetic ganglia, esophago- columnar junction, heart, skin and olfactory plate.
- Skeletal muscle: biceps brachii (for the study of sarcopenia)
- General organs: small pieces of liver, kidney, lung, esophagus
- Serum (stored in the hospital laboratory).

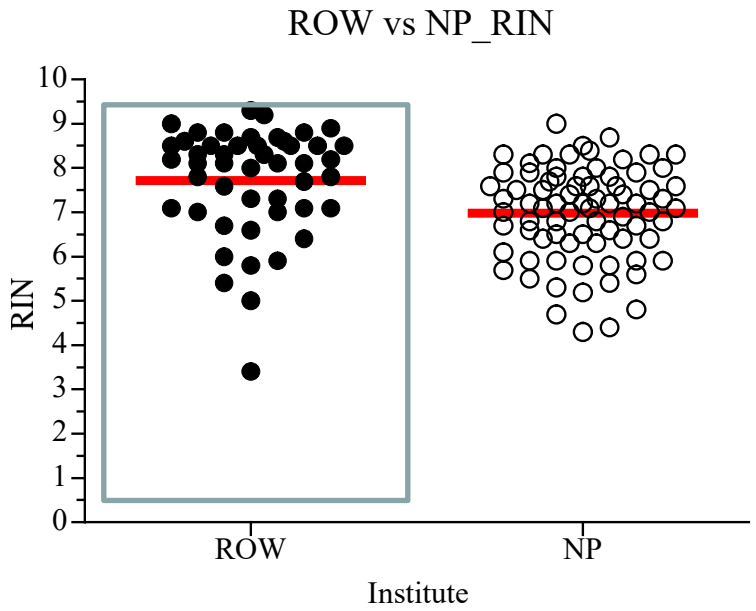
Total RNA Quality Check (Dpt. Mol. Biol. Niigata Univ. BRI)

DNA & RNA Back Up

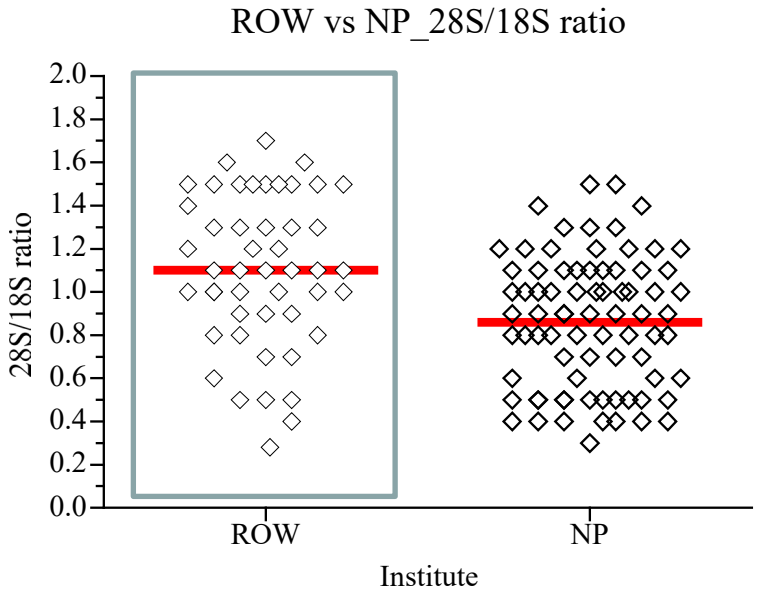
BBAR (N=48: ROW) vs Control (N=78: NP)

RNA Quality of BBAR is better than rapid autopsy control, probably due to a very short cooling interval (interval between death and transfer to a refrigerator).





Mann-Whitney's test, *P* < 0.0001



Mann-Whitney's test, *P* = 0.0002

BBAR Resource (Fixed)

- 4% paraformaldehyde over two nights, one half for paraffin embedding and another half preserved in 20% sucrose PBS+0.1% NaN3

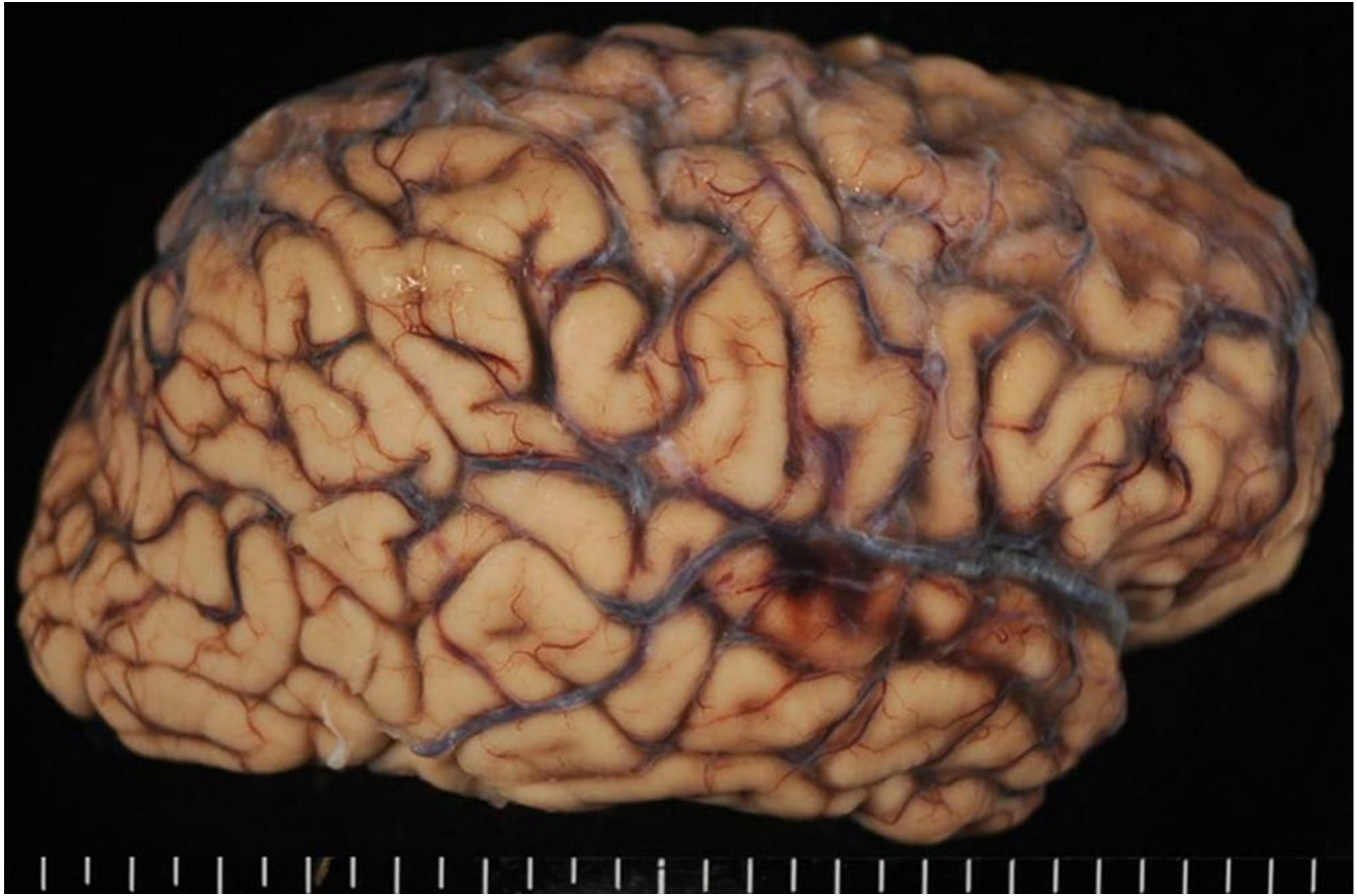
- Brain: frontal, temporal and occipital poles, intraparietal sulcus, anterior amygdala, posterior hippocampus, midbrain, dentate nucleus, olfactory bulb
- Spinal Cord: C4/8, T4/8/12, L5, S2
- Peripheral ANS: sympathetic ganglia, esophago- columnar junction, anterior wall of the left ventricle of the heart, skin, olfactory plate, biceps brachii

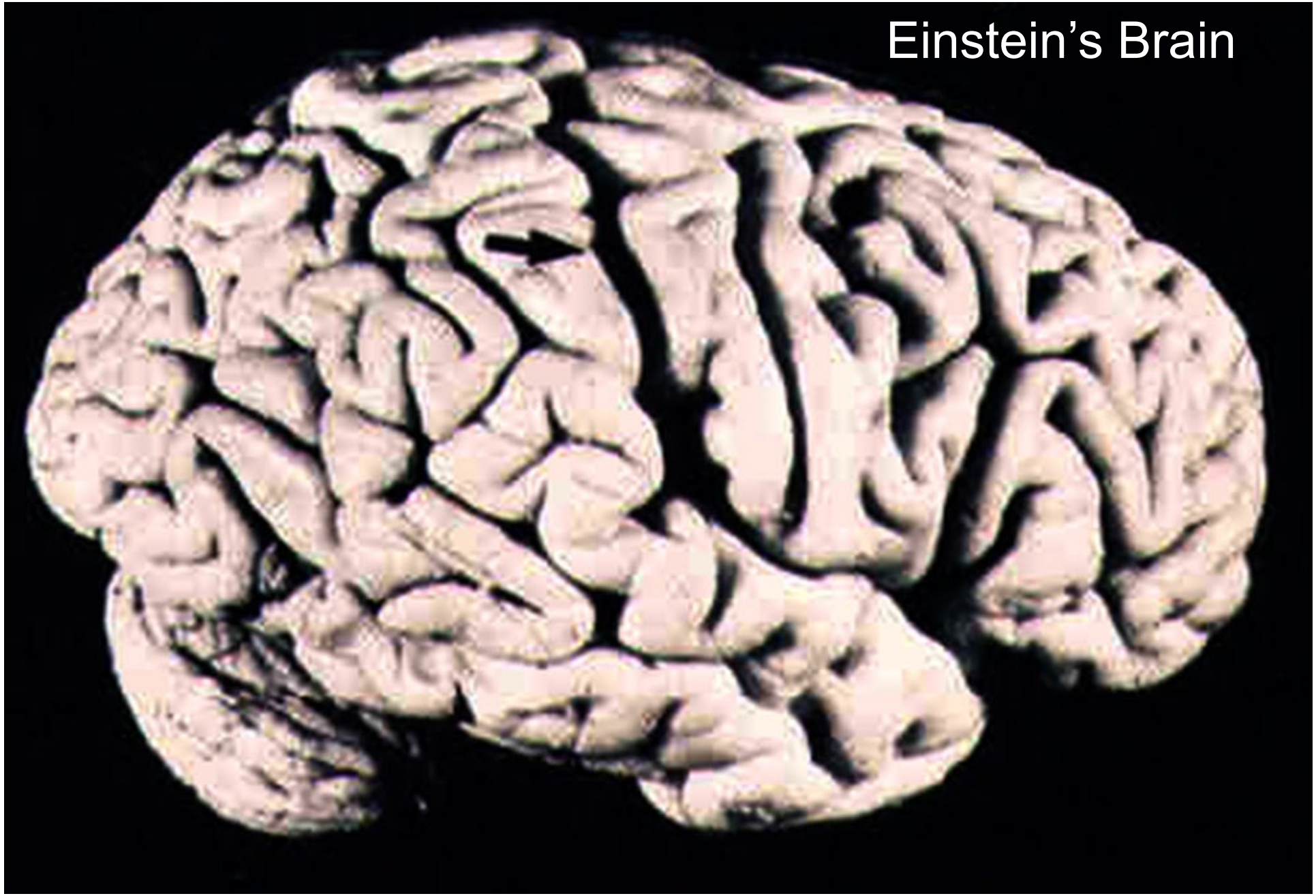
- 20% buffered formalin for 7-13 days

- Half brain, body organs

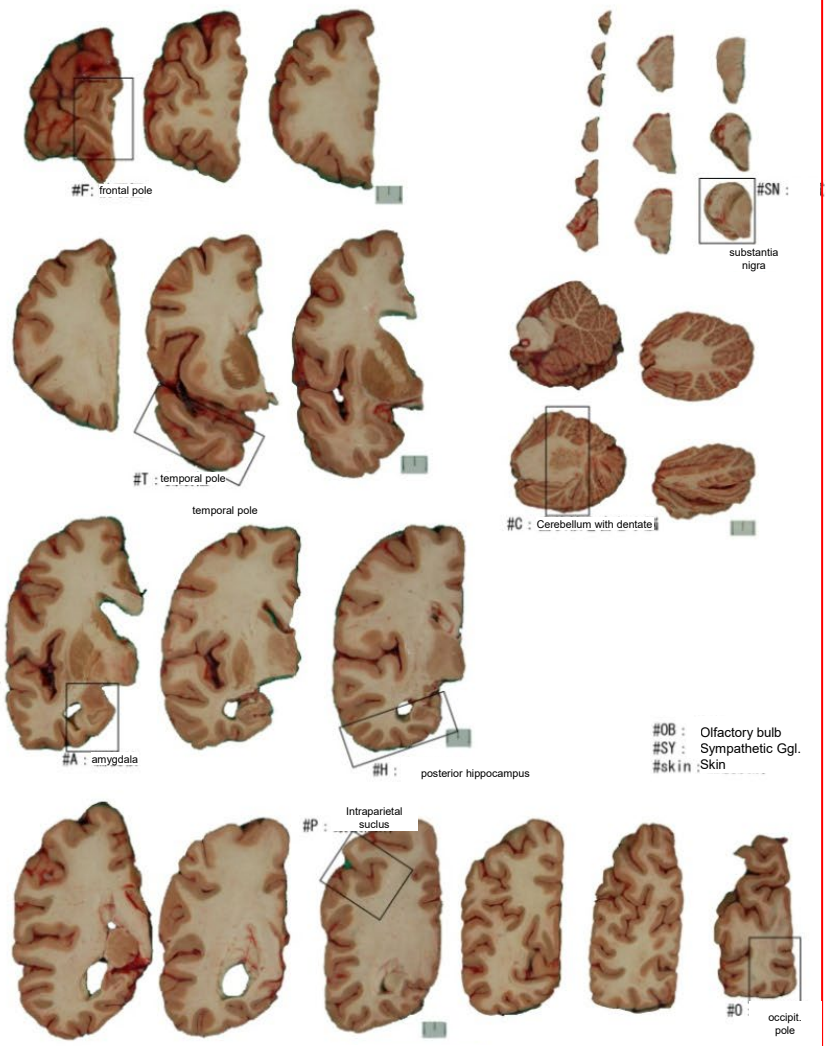
Brain Cutting (1972.5.1-)

Neurology, Neuropathology, Psychiatry, Pathology, Rehabilitation,
connected to Osaka U and Toneyama via internet



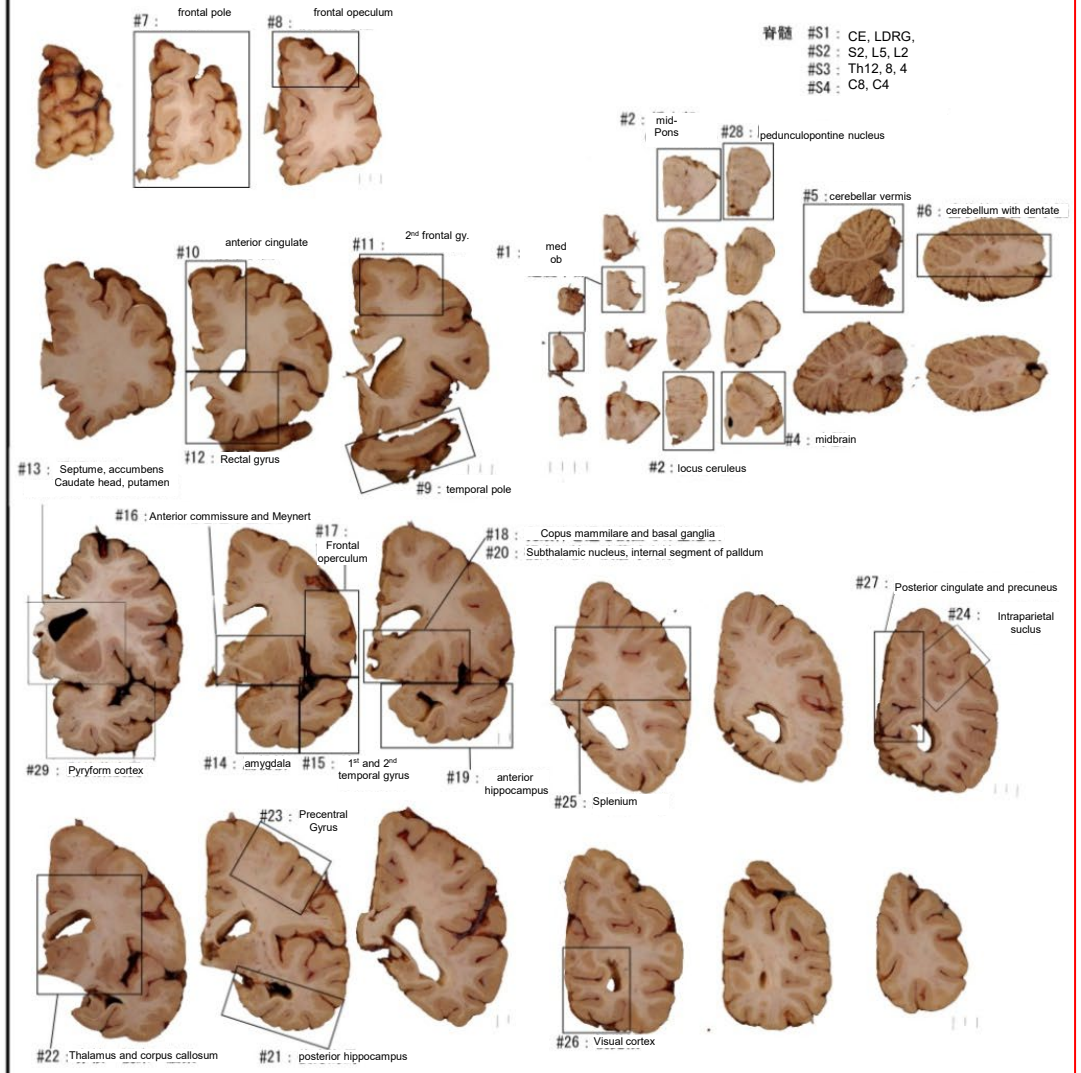

Einstein’s Brain

BBAR Protocol: Fixed Side



Frozen Half

Brain: 29 areas; Spinal Cord: 9 segments



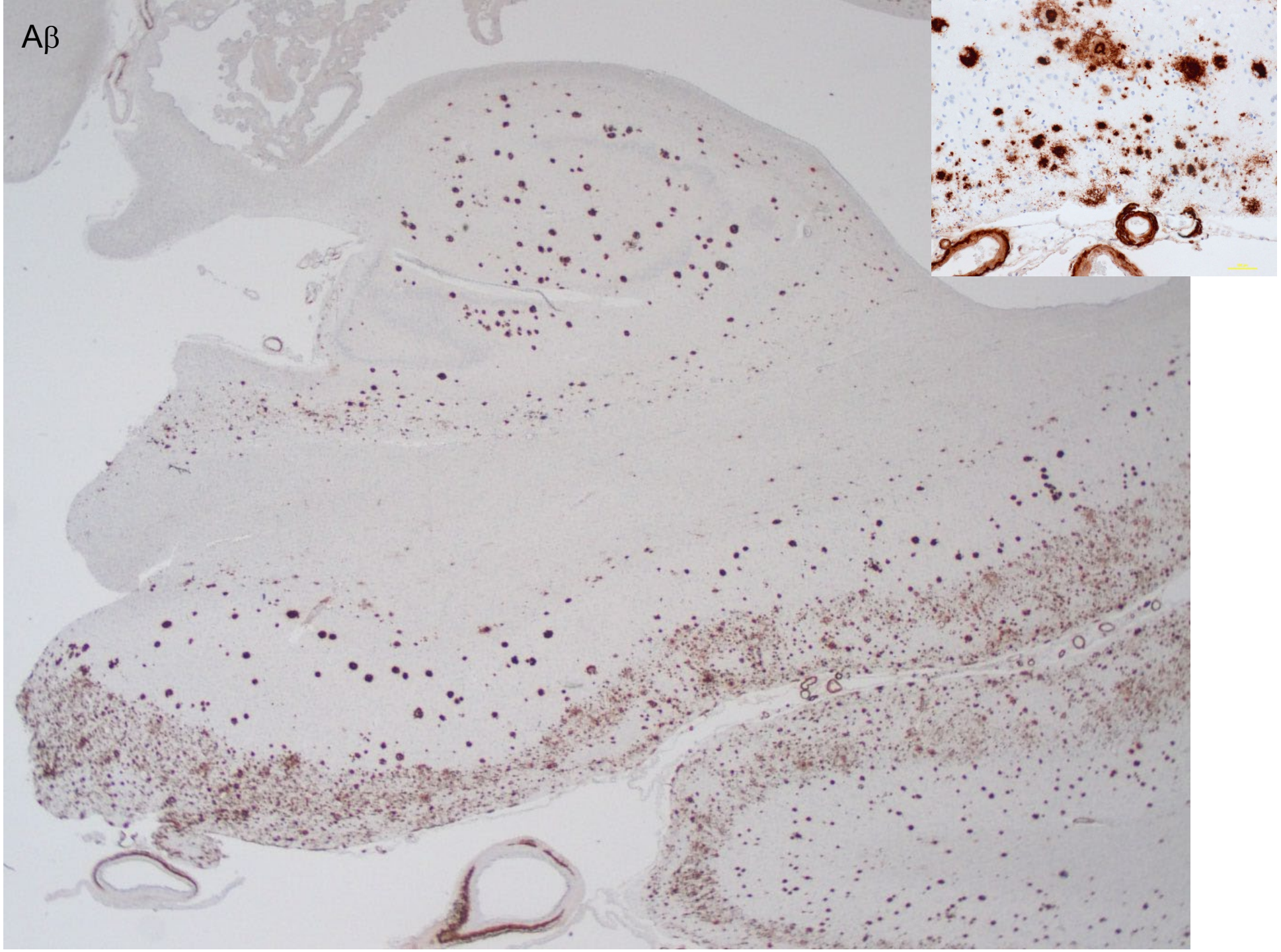
Fixed Half

Staining

Routine: H.E., K.B.
Special: Gallyas-Braak, methenamine silver,
Elastica Masson, Congo red, thioflavin S
Immunohistochemistry with automatic stainer（Ventana）

Epitope	Antibody	Clone
Aβ11-28aa	12B2 (IBL)	monoclonal
phosphorylated tau	AT8 (Innogene)	monoclonal
3R/ 4R tau	RD3/ RD4	monoclonal
phosphorylated α- synuclein	psyn64 (Wako)	monoclonal
Ubiquitin	Sigma	polyclonal
Phosphorylated TDP43	PSer409/410	monoclonal
FUS/ TLS	Sigma	polyclonal

Ventana NX20 autoimmunostainer: BBAR, NCNP, MMH and Osaka Area


Aβ

CNS Screening ← tau → Lewy TDP ← Aβ →

Y−9□7□	PT	NFT	GT	NT	NP	AG		AT		Psyn		TDP −43	DP		CP		A/V		CCAA	
						R	L	TSA	BLA	R	L		R	L	R	L	R	L	R	L
Sympathetic ganglion										o										
Dorsal root ganglion																				
Spinal cord																				
Sacral anterior horn																				
Sacral posterior horn																				
Intermediate zone (Sacral)										o	o									
Lumbar anterior horn												o								
Lumbar posterior horn																				
Lumbar anterior column																				
Lumbar lateral column										o	o									
Lumbar posterior column																				
Thoracic anterior horn																				
Thoratic posterior horn																				
Intermediolateral N. (Thoracic)										o										
Cervical anterior horn	o			o																
Cervical posterior horn																				
Medulla oblongata																				
Dorsal motor N. of vagus										o										
Hypoglossal N.																				
Inferior olivary N.																				
Pons																				
Pontine N.																				
Locus ceruleus										o										
Subceruleus																				
Pedunculopontine N.																				
Midbrain																				
Oculomotor N.																				
Edinger･Westphal N.																				
Pars compacta of SN	o			o						o	o									
Periaqueductal gray matter																				
Cerebellum																				
Cerebellar cortex													o		o		o			
Cerebellar white matter																				
Dentate N.																				
Interbrain / Basal ganglia																				
Broca's diagonal band																				
Hypothalamus																				
Nucleus basalis of Meynert	o			o																
Accumbens N.																				
Caudate N.																				
Putamen													o		o					
Ext. globus pallidus																				
Int. globus pallidus																				
Claustrum																				
Subthalamic N.																				
Thalamus																				
Allocortex (Rhinencephalon/Limbic)																				
Olfactory bulb periphery										o										
Anterior olfactory N.										o										
Piriform cortex (frontal)																				
Piriform cortex (temporal)																				
Amygdala	o	o		o		o	o	o	o	o			o		o					
Uncus / Ambient gyrus	o	o		o		o	o					o								
Dentate gyrus	o	o	o	o																
Hippocampus CA4	o	o	o	o																
Hippocampus CA3	o	o	o	o																
Hippocampus CA2	o	o	o	o						o										
Hippocampus CA1	o	o	o	o								o	o		o					
Subiculum	o	o	o	o		o	o					o								
Presubiculum																				
Entorhinal	o	o	o	o								o								
Transentrhinal	1	1	o	1						o										
Insular cortex																				
Anterior cingulate gyrus																				
Temporal pole (medial)																				
Cerebral neocortex (isocortex)																				
Temporal pole (lateral)																				
T4	o	o	o	o																
T2	o	o	o	o									o		o		o			
Fronatal pole													o		o		o			
F2																				
Supramarginal gyrus													o		o		o			
Visual association cortex																				
Striate area													o		o		o		o	
Primary motor cortex																				

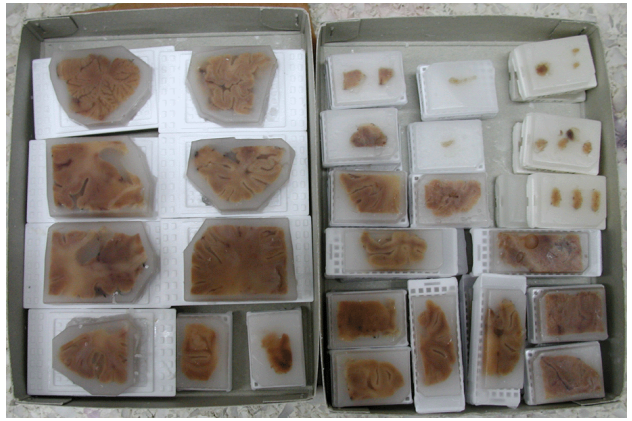
BBAR Degenerative Pathology Database

BBAR	Y96XX									
A/G	CDR	PMI	NFT	AT8	SP	CERAD	Thal	LB	LB score	DLB 3rd
93M	3	11:22	4/3	3/3	2	2	5	4	4	Limbic (amygdala predominant)
Grain	AA	AT	UD	TDP	ApoE	RIN				NPD
0.5/ 0.5	1C	1	3	T1M1S0	3/3	8.1				AD, LBD, CVDE

A/G age/ gender
CDR (clinical dementia rating): 0-3
PMI: postmortem interval
NFT (tangle: Braak Stage): 0-6
AT8 (tangle: AT8 Stage) 0-6
SP (senile plaque: Braak Stage): 0-3
CERAD 0-3 (0- C)
Thal (amyloid Thal Stage) 0-5
Lewy (Lewy body, BBAR Stage): 0-5
DLB score (DLB 1st Consensus Guideline)
DLB 3rd (DLB 3rd Consensus Guideline)
Grain (argyrophilic grain, Saito Stage): 0-3
AA (amyloid angiopathy, BBAR Stage): 0-3
AT (astrocytic tangle): 0-3
UD (ubiquitinated dots): 0-3
TDP (TDP-43 proteinopathy, temporal, medulla and spinal) 0-3
ApoE (apoE genotyping)
RIN (RNA intergrity number)
NPD: neuropathologic diagnosis (AD: Alzheimer disease; LBD: Lewy body disease; CVDE: embolic infarct)

BBAR Protocol: Histological Examination.

Internationally Standardized
Neuropathological Diagnostic Method



Paraffin block of >7,000 cases
easily accessible

Library

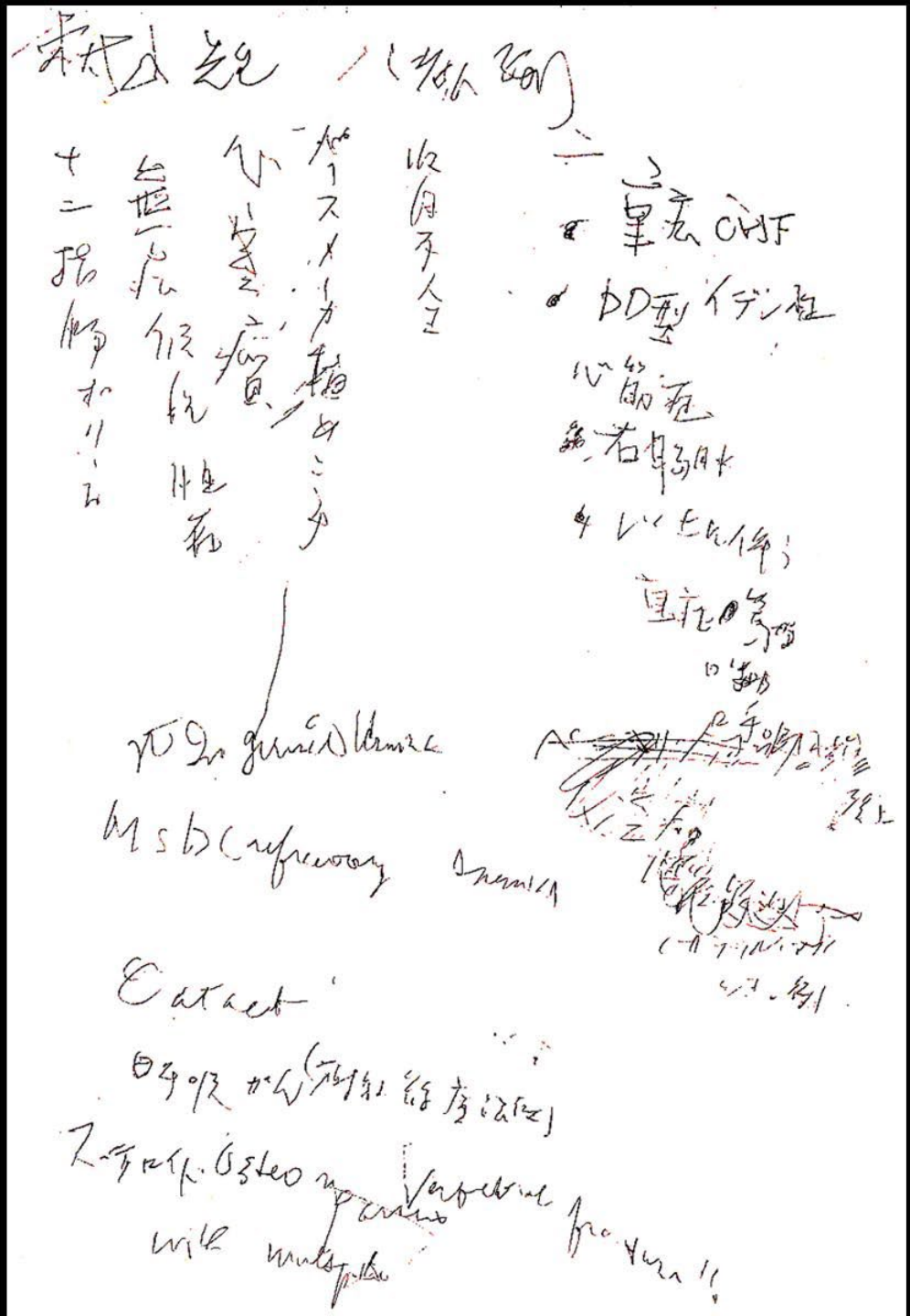
Brain Donation Program

Dr. Yasuo Toyokura

80y.o. +
Em. Pro. Univ. Tokyo
Em. Direc. TMGHIG
The first brain donor of BBAR
Death Note:
"Please use our body to conquer diseases that will kill me (and you cannot cure) ."

2003-

Donor Card



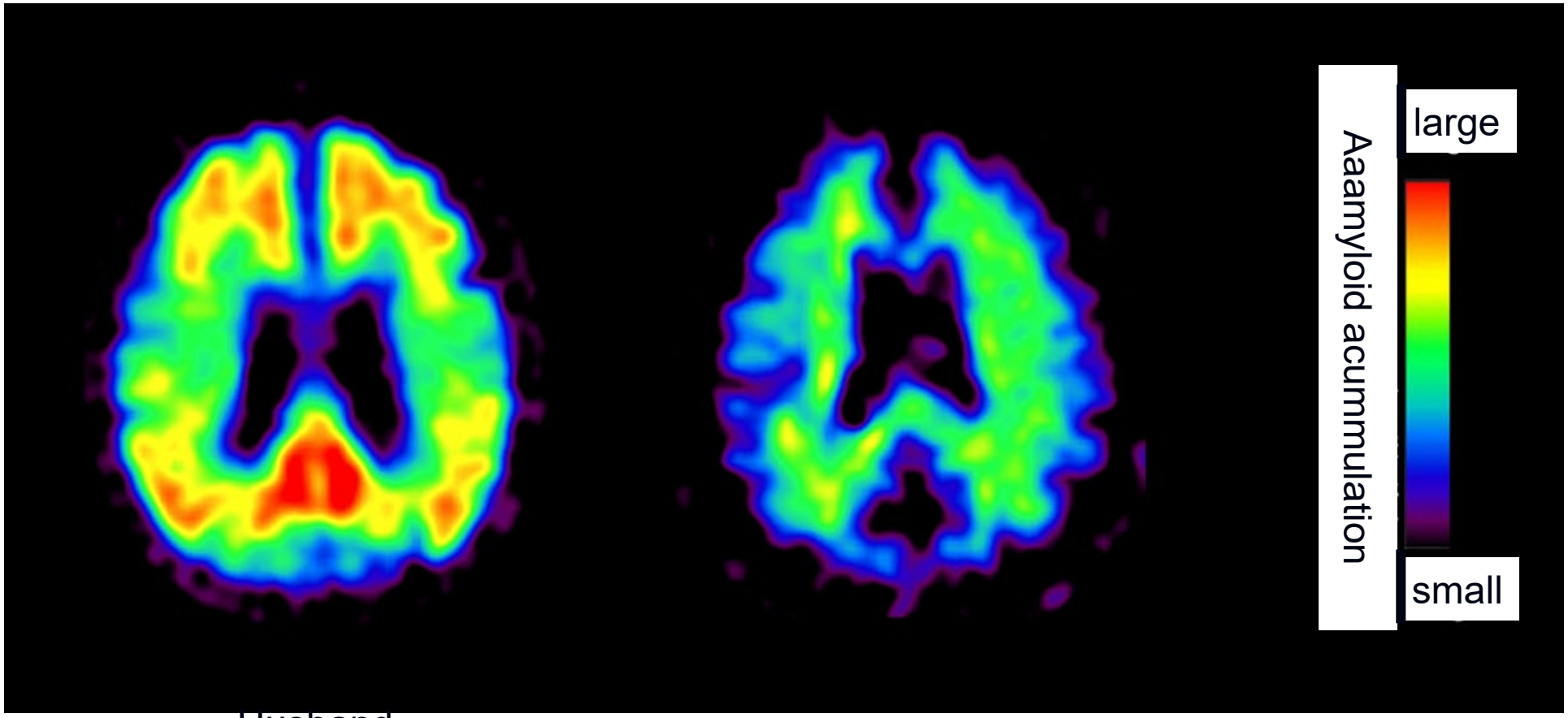
Brain Donors (2022/ 8) : (pre registrants: 231)

No.	Age	Gen	Dix	Con	Death/ Autopsy
1	80	M	(heart disease)	Self	TMIGG
2	83	M	FAD	F	Outside H/ TMIGG
3	79	W	FAD	F	Outside H
4	69	W	CBD-PNFA/ TDP-43 type A	F	Outside H/ TMIGG
5	86	M	AD	F	Outside H
6	91	M	AD/CAA/DG/ HS-TDP-43	S	Outside H/ TMIGG
7	84	W	PSP	S	Outside H/ TMIGG
8	89	W	(colon Ca)	S	TMIGG
9	84	M	CVD I	F	TMIGG
10	86	M	AD	F	TMIGG
11	88	W	DLB	F	Outside H/ TMIGG
12	93	W	PD	S	TMIGG
13	99	W	DLB	F	Outside H/ TMIGG
14	73	M	Lung Ca	F	Outside H/ TMIGG
15	111	W	NFTD	F	Care C/ TMIGG
16	90	W	AD	F	Outside H/ TMIGG
17	97	M	NFTD/ PSP/LBD/DG	F	Care C/ TMIGG
18	72	M	Cereb Inf	F	Care C/ TMIGG
19	61	M	Encephal	F	Outside H/ TMIGG
20	79	M	CJD	F	Outside H/ TMiGG
21	83	M	Mal Lymph	F	Outside H/ TMIGG
22	95	W	iNPH	F	Home/ TMIGG
23	80	W	ALS	F	当センター
24	80	W	PSP	F	Outside H/ TMIGG
25	74	M	LBD	F	Outside H/ TMIGG
26	81	M	AD	F	Outside H/ TMIGG
27	91	W	AD	F	Outside H/ TMIGG
28	83	W	PSP	F	Outside H/ TMIGG
29	90	W	AD	S	Outside H/ TMIGG
30	87	W	AD	S	Outside H/ TMIGG
31	95	M	AGD	S	Care C/ TMIGG
32	85	M	AGD	F	Outside H/ TMIGG
33	80	W	ALS	F	Outside H/ TMIGG
34	80	M	SMA	F	Outside H/ TMIGG
35	70	W	PSP	F	Outside H/ TMIGG
36	68	M	CBD	F	Care C/ TMIGG
37	84	M	ALS	S	Care C/ TMIGG
38	69	M	PSP	F	Outside H
39	86	M	PDD	F	Outside H/ TMIGG
40	93	M	PSP	F	Outside H
41	87	W	Early AD	S	Care C/ TMIGG
42	77	W	AD	F	Outside H/ TMIGG
43	86	M	DLB/AD	F	Outside H/ TMIGG
44	80	M	AD/AGD	F	Outside H/ TMIGG
45	83	W	PSP	F	Outside H/ TMIGG
46	68	M	PSP	F	Outside H/ TMIGG
47	78	M	PSP	F	Outside H/ TMIGG
48	102	W	(influenza)	F	Outside H/ TMIGG
49	69	M	CVD I	F	Outside H
50	83	W	AD/DLB	F	Outside H/ TMIGG
51	63	M	Cereb Cont	F	Outside H/ TMIGG
52	86	M	FTLD-TDP typeC	F	Care C/ TMIGG
53	89	W	CJD	F	Outside H/ TMIGG
54	94	M	eAD/AGD	F	Care C/ TMIGG
55	44	M	SPG11	F	Outside H/ TMIGG
56	75	W	MSA	F	Care C/ TMIGG
57	85	M	CJD MV1	S	Outside H/ TMIGG
58	85	M	Renal Ca	S	Outside H/ TMIGG
59	83	W	AD	F	Home/ TMIGG
60	61	M	ALS	S	Outside H/ TMIGG
61	86	M	Lung Ca	F	Outside H/ TMIGG
62	82	W	Cereb Inf	F	TMIGG
63	85	W	PSP	F	Outside H/ TMIGG
64	92	M	AD	F	Care C/ TMIGG
65	61	W	fCJD	F	Outside H/ TMIGG
66	85	W	CJD/PD	F	Outside H/ TMIGG
67	82	W	PSP	F	Care C/ TMIGG
68	49	W	NMO	F	Outside H/ TMIGG
69	82	W	PSP	F	Outside H/ TMIGG
70	72	M	AD	F	Home/ TMIGG
71	41	W	SCA1	F	Outside H/ TMIGG
72	83	M	AD	F	Outside H/ TMIGG
73	92	M	AD	F	Outside H/ TMIGG
74	76	M	NFTD	F	Outside H
75	91	W	AD	F	TMIGG
76	63	W	Tauopathy	F	Outside H/ TMIGG
77	85	M	SCA6	S	Outside H/ TMIGG
78	72	W	SCD	S	Outside H
79	79	M	AD	F	Outside H
80	82	M	AD	S	Outside H/ TMIGG
81	57	M	CJD	F	Outside H/ TMIGG
82	86	M	AGD	F	Care C/TMIGG
83	65	W	CJD	F	Outside H/ TMIGG
84	72	M	TDP43 proteinopathy	S	Outside H/ TMIGG
85	75	M	CBD	F	TMIGG
86	74	W	ALS	F	TMIGG
87	73	M	Cereb Inf	S	TMIGG
88	78	M	CJD	F	Outside H/ TMIGG
89	74	M	PSP	F	Outside H/ TMIGG
90	75	W	CBD	F	Outside H/ TMIGG
91	50	W	DRPLA	F	Outside H/ TMIGG
92	54	M	Cereb Tum	F	Outside H/ TMIGG
93	58	M	control	F	Outside H/ TMIGG
94	79	M	LBD+ALS	S	TMIGG
95	50	M	ALD	F	Outside H/ TMIGG

Amyloid (^{11}C- PIB) PET

Alzheimer's disease

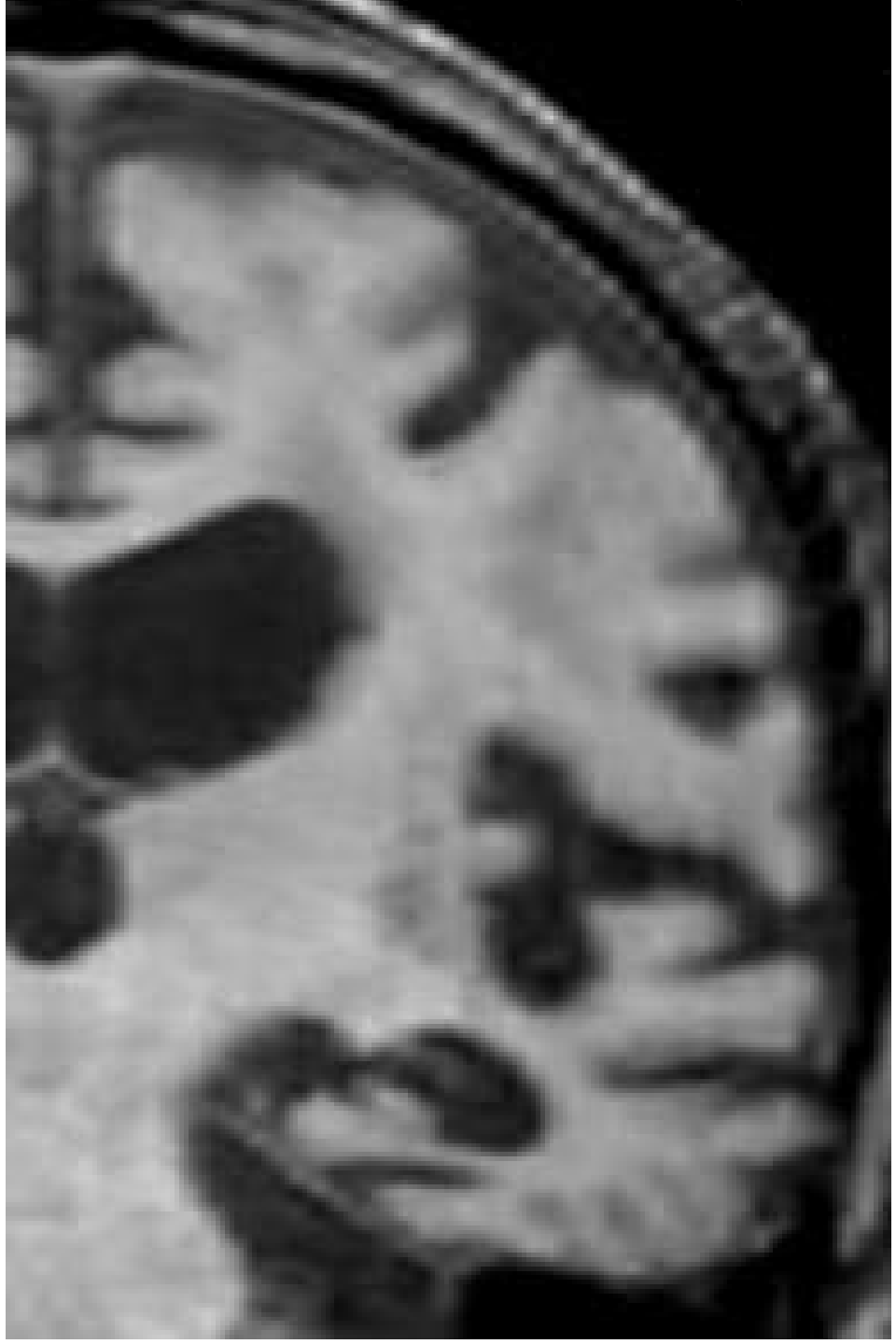
Normal Control

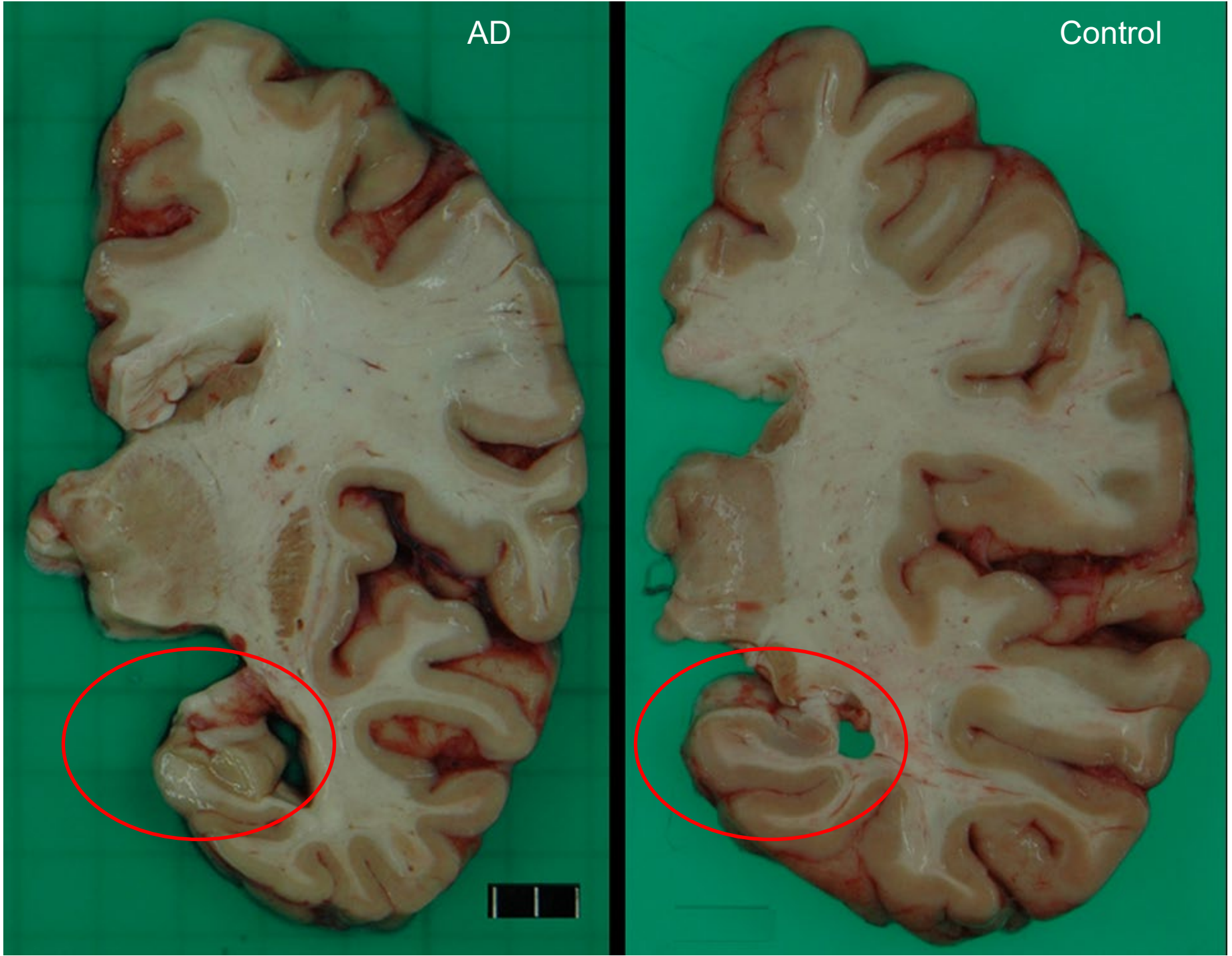


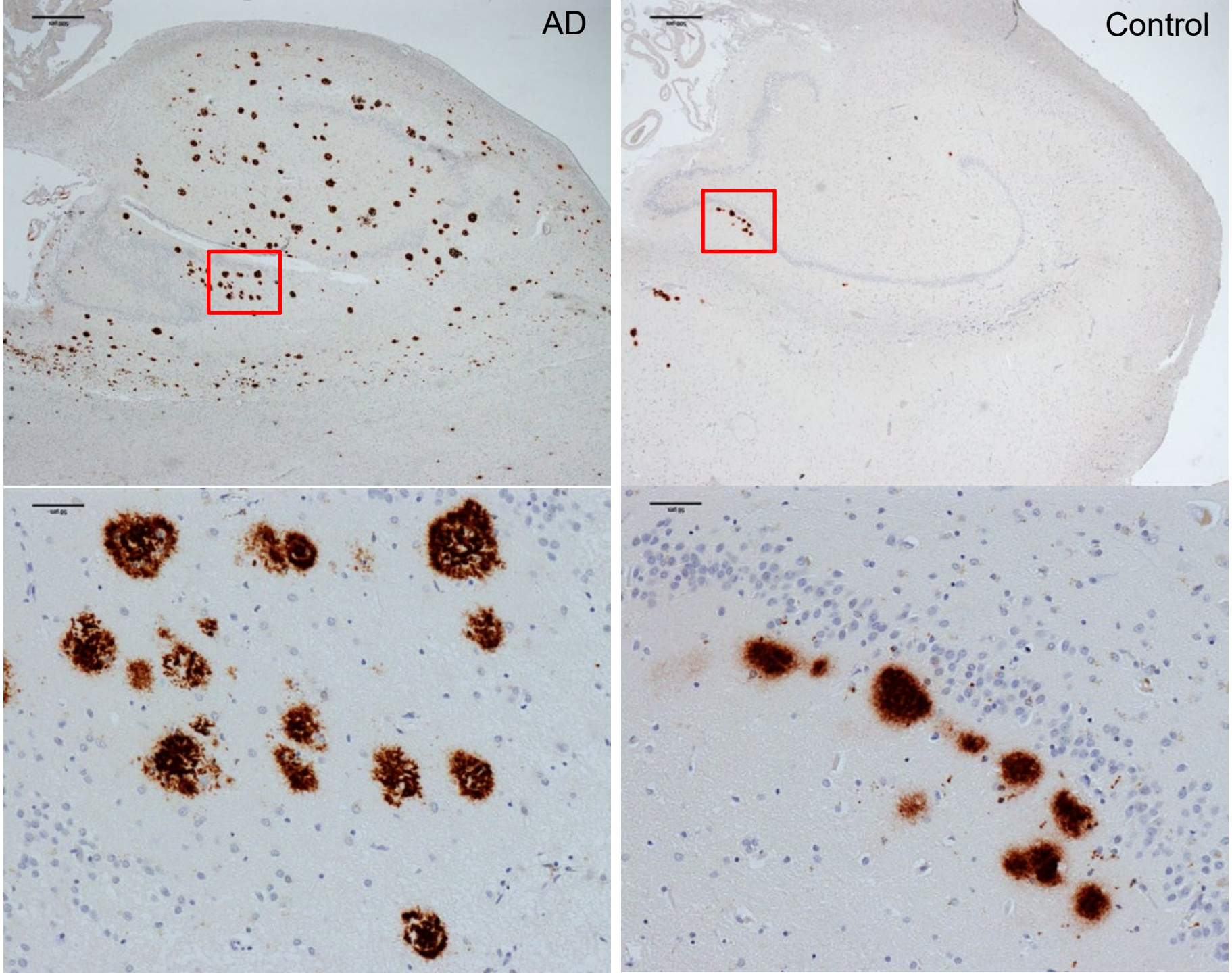
Husband

Wife

the Brain Bank for Aging Research Brain Donation Program




AD
Control


AD
Control

Registration of Outside Cases

Informed consents from three parties:

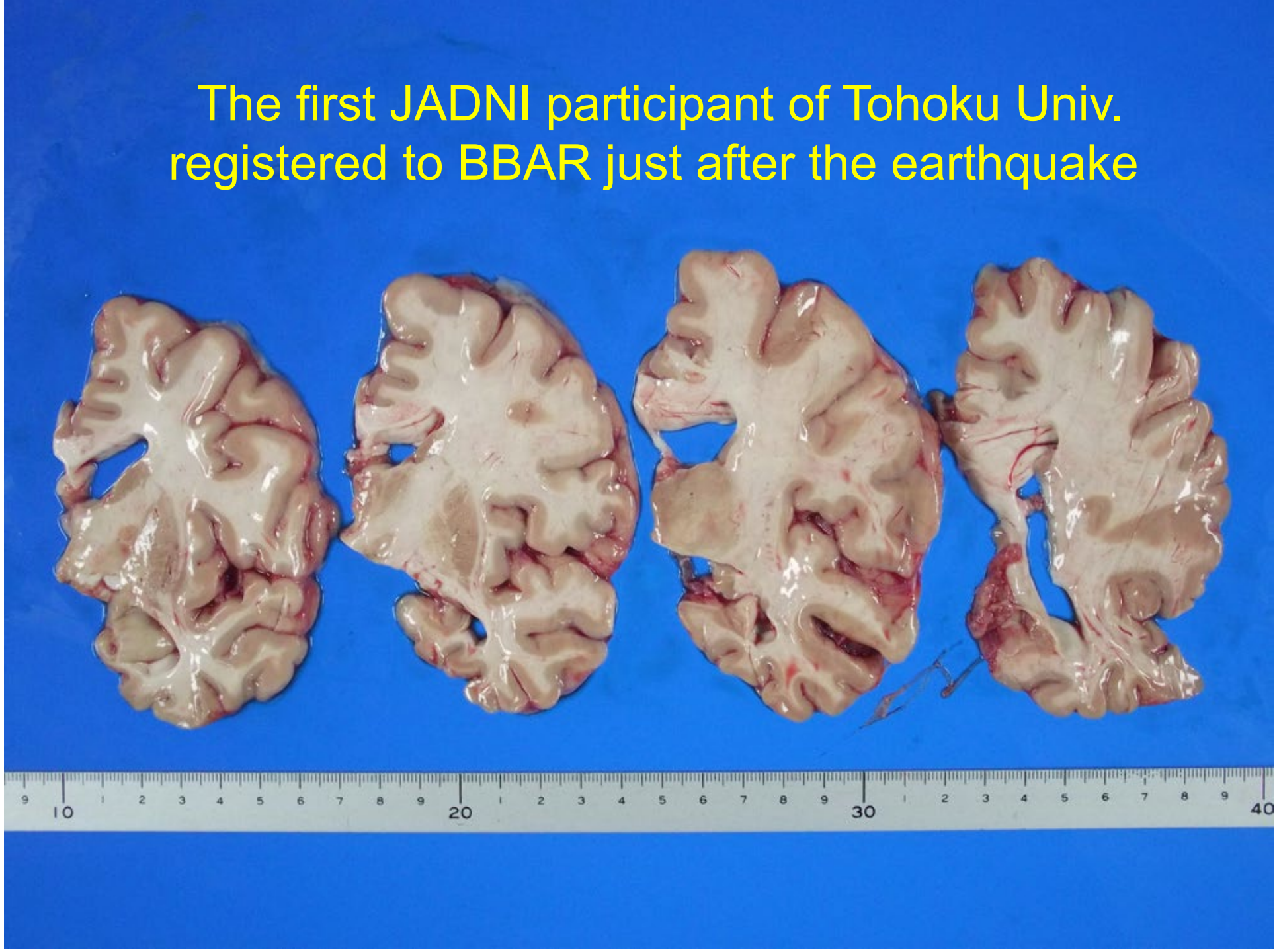
The attending physician

The first kin of relatives

The attending autopsy pathologist

2011	
Kashima Rosai Hosp.	CARASIL
Tohoku Univ.	AD (JADNI case)
2012	
National Defense Hosp.	NMO, familial
2015	
Himeji Central Hospital	AD tx Aβ mb
2016	
Tokushima University	HDLS (CSF1 mut.)

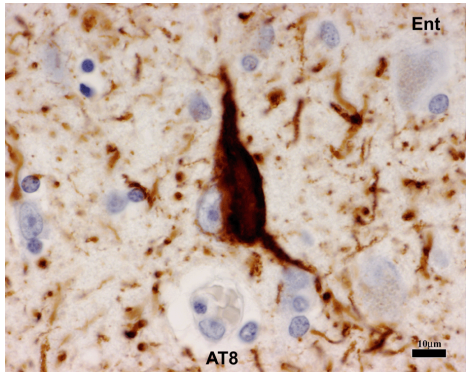
The first JADNI participant of Tohoku Univ. registered to BBAR just after the earthquake

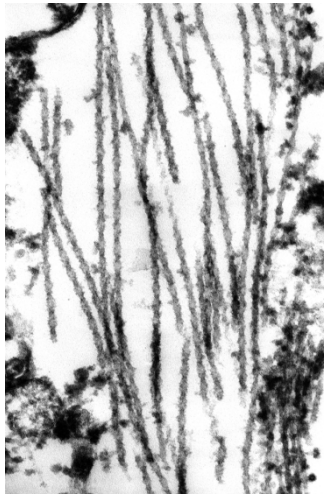


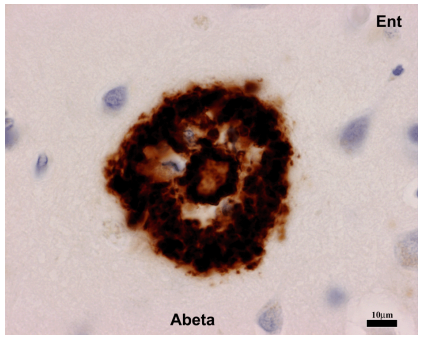
Japanese Brain Bank Network for Neuroscience Research

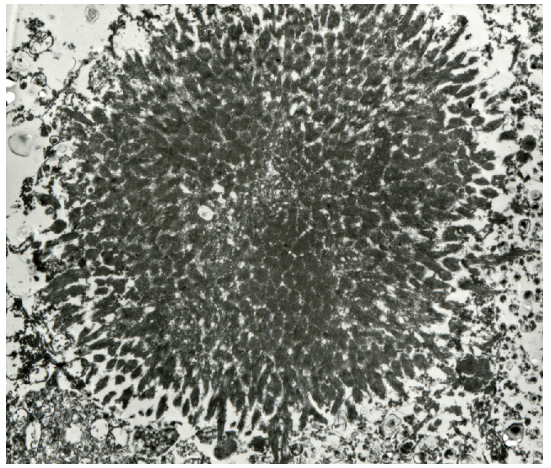
Insitute	Clinial/ Pathology	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Osaka U	Mochizuki, H. /Murayama S.				3	4	6	6	5	14	7
NHO Osaka Toneyama MC	Toyooka K / Inoue K	13	12	9	7	11	8	14	12	11(2)	14
BBAR	Iwata A/ Saito Y	39	39	45	64	52	39	36	36	34(3)	40
Fukushimura	Kaneda D/ Hashizume Y	31	27	25	25	21	25	33	40	33 (3)	32
NCNP	Takahashi Y/ Takao M	10	11	9	13	18	24	14	22	20	48
Miahara Memorial H	Mihara B/ Takao M	26	15	19	23	16	19	33	18	12	10
Univ. Tokyo	Kubota A/ Ikemura M	23	22	25	26	15	17	18	21	18	10
NCGM	Arai N/ Igari T	16	17	27	17	17	9	9	7	12	12
National Tokyo H	Komiya T/ Muayama S	5	2	4	3	0	1	1	1	0	0
Shizuoka Epi Neuro C	Obi T/ Murayama S	5	4	6	5	4	6	2	1	6	0
Yokohama Rosai H	Imafuku I/ Kakuta Y	6	6	8	8	4	4	4	2	1	0
Kameda H	Ando T/ Takeuchi R	10	6	9	12	10(2)	10(2)	10(2)	5(4)	6	3
Kitasato U	Nishiayama K/ Ichinohe M	9	5	4	2	6	6	1	1	2	2
Tokushima U	Izumi Y/ Tsuneyama K	3	5	10	4	12	4	5	3	3	1
IUHW Mita	Iwata N/ Aida S	3	2	0	2	1	1	2	0	(1)	1
Kagawa U	Kagawa M/ Ueno M	4	3	1	1	1	2	1	0	0	1
Toranomon H	Uesaka Y/ Ito S	3	1	2	2	3	1	8	2	6	3
Teikyo U	Sonoo M/ Saito Y	2	2	0	4	0	4	2	0	1	1
Tokyo Teishin H	Shiio Y/ Kishida Y	5	2	2	3	5	3	3	3(2)	7	3
Tokyo Medical U	Shimizu S/ Kuroda M			1	0	0	1	0	1	1	1
NHO Hiroshima WMC	Watanabe T/ Tachiyama Y			3	4	4	2	4	0	0	1
Osaka Metropolitan U	Ito Y/ Osawa M		1	1	1	1	0	1	0	0	0
NHO Sagamihara H	Hasegawa K/ Yagishita S				8	10	18	18	17	8	21
NHO Okinawa H	Suwazaono H/ Atami E				1	2	2	4	2	0	0
Open Resource		122	112	119	168	170	174	173	164	157	181
Institutional Collection		79	85	84	105	74	69	50	67	39	31

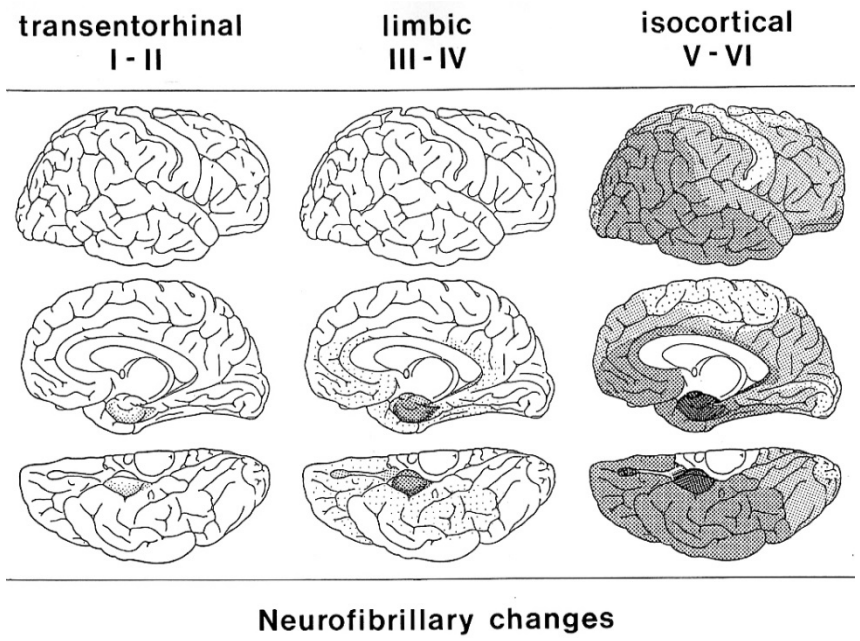
BBAR adopts Braak's Staging of Alzheimer Pathology



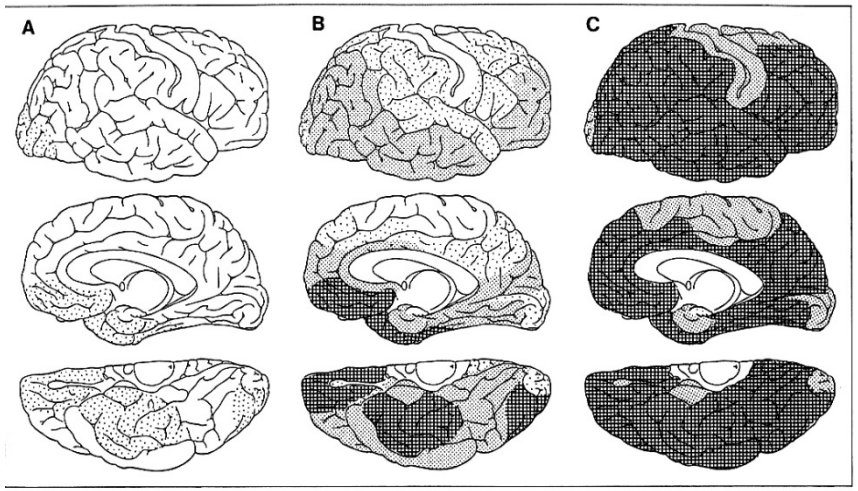






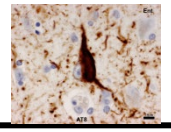


NFT stage

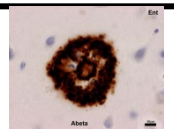


SP stage

Braak
NFT/ SP



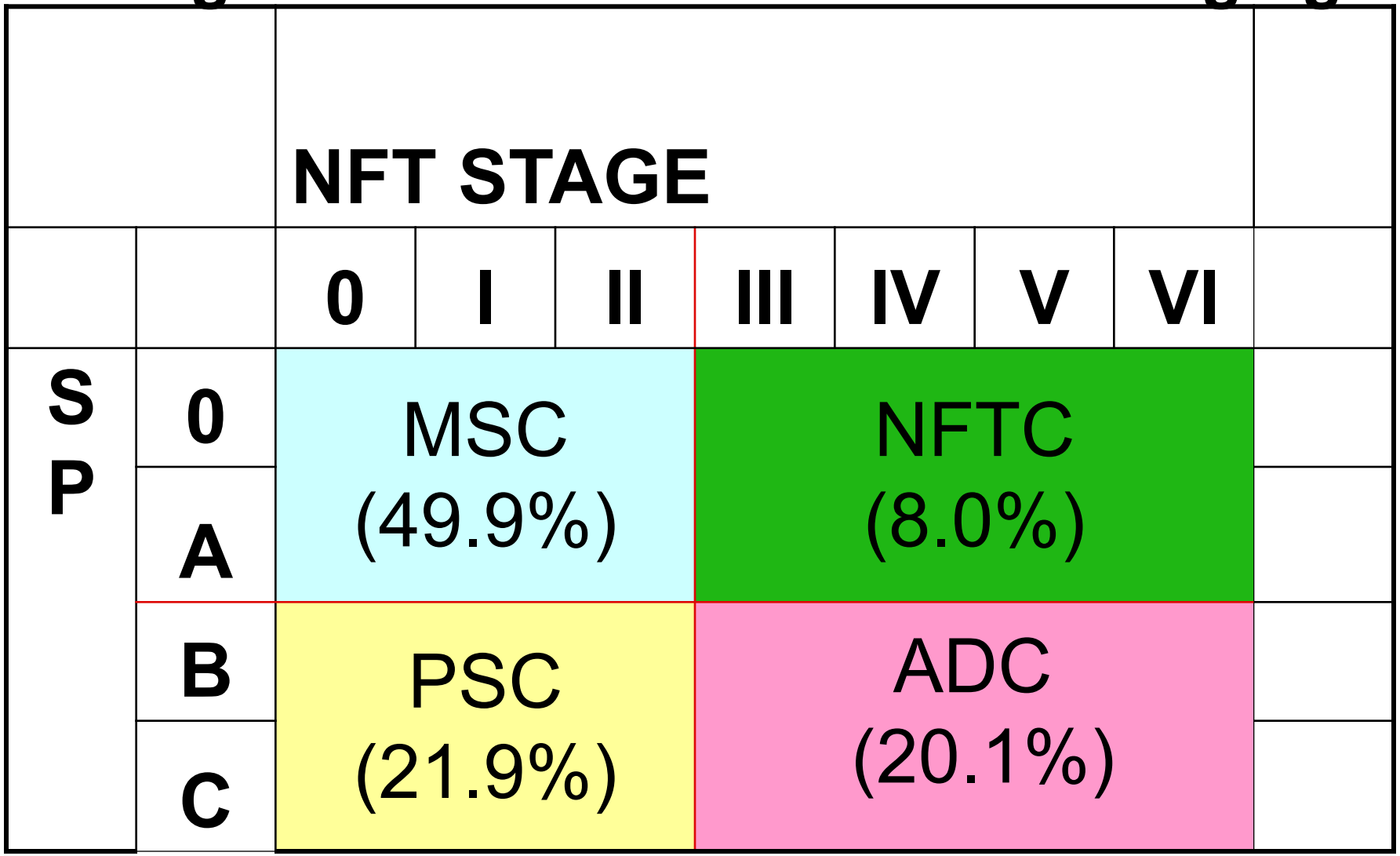
DNA Resource (1,890 cases)

	0	I	II	III	IV	V	VI	計
0	34 66.3	314 75.8	102 81.8	46 85.6	12 85.4	1 81.0	0 -	509 77.5
A	16 75.5	350 78.0	149 83.6	74 86.2	23 88.6	1 99.0	0 -	613 80.6
B	8 76.1	169 79.9	91 82.8	70 85.6	23 91.2	2 82.0	1 94.0	364 82.4
C	3 76.0	50 79.4	51 83.0	80 84.5	80 86.6	100 86.4	40 83.9	404 84.4
計	61 70.5	883 77.7	393 82.9	270 85.4	138 87.6	104 86.4	41 84.1	1890 80.9

Case #
Average Age

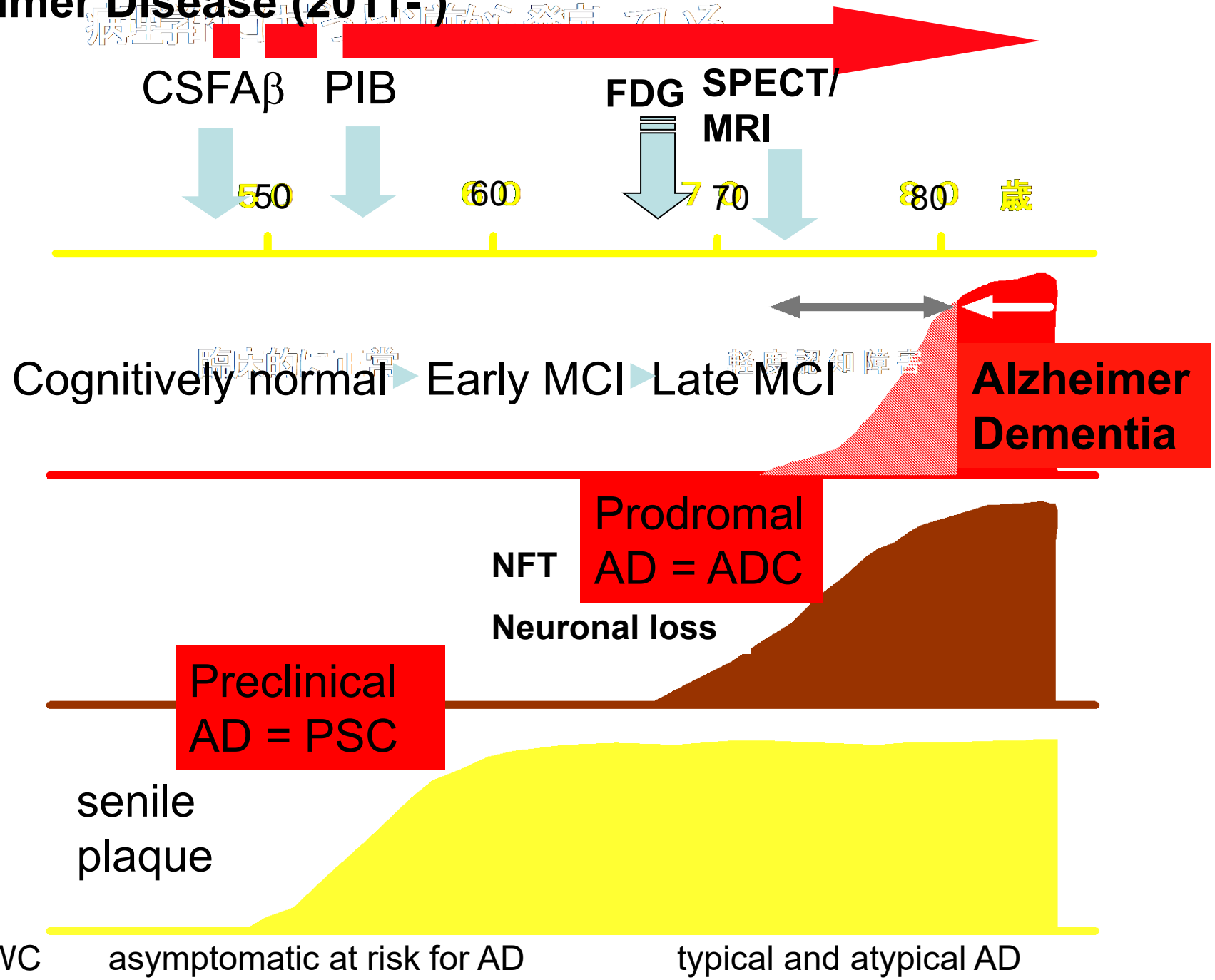
Alzheimer Disease: 220/ 1890 = 11.6%

Categorization based on Braak's Staging



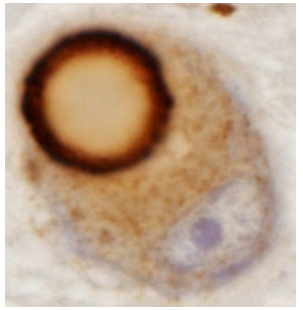
MSC : minimal senile change; NFTC : NFT dominant change
PSC : plaque- dominant change; ADC : Alzheimer disease change

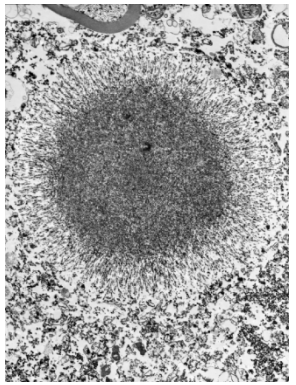
Alzheimer Disease (2011-)



2014 IWC asymptomatic at risk for AD typical and atypical AD

BBAR Lewy Body Stage





	SN	LB						
Stage	Loss of pigment	ANS (preG)	SN/ Stri	Limb./ NeoCx.	LB Score	Dement	PA	
0	-	-	-	-	0			
0.5	-	+/-	+/-	+/-	0			
I	-	+/-	+/-	+/-	0-10			**preclinical**
II	+	+/-	+	+/-	0-10	-	-	**prodromal**
III	+	+	+	+	0-2(10)	-	+	**PD w/o D**
IV	+	+	+	+	3-6	+	+/-	**PDD/DLBL**
V	+	+	+	+	7-10	+	+/-	**PDD/DLBN**

Saito Y et al: J Neuropath Exp Neurol (2004)

High quality of the resource from the Japanese Brain Banks

- Japanese brain banks are based on general autopsy and recover body organs as well as brains. Brain banks in US and Europe only recover brains.
- The Brain Bank Committee, Japanese Society of Neuropathology guides brain banks to keep quality control of neuropathological diagnosis. In US and Europe, neuropathological reports of brain banks are for research use only and usually handled by Ph.D. or its candidates.
- The recovery of brain bank resource was done by neuropathologists in Japan. In US and Europe, technicians are responsible for brain banking.
- Neuropathological examination of neurodegenerative disorders follow CJD surveillance protocols: clinical and radiological findings, CSF biomarkers, mutation analysis of *prion* gene, Western blotting and immunohistochemistry with anti– prion antibody of autopsy brains.

CJD Surveillance Committee Pathology Core (I)

- To promote autopsies of prion disease.
- To receive autopsies of outside cases.
- To report to the surveillance committee autopsy- proven prion cases (pathology route)
- To establish a national prion back- up bank.
- To study natural course of prion disease.

Grants in Aid from Ministry of Health, Labor and Welfare, Japan

CJD Surveillance Committee Pathology Core (II)

- Clinical and radiological findings, CSF biomarkers, analysis of prion gene, immunocytochemistry and Westen blots of postmortem brains form a neuropathological diagnostic base of neurodegenerative disorders in Japan.
- BBAR guides neuropathological diagnostic protocol in close collaboration with the Brain Bank Committee and the Prion Autopsy Promotion Committee, the Japanese Society of Neuropathology.

Grants in Aid from Ministry of Health, Labor and Welfare, Japan

BBAR Lewy Pathology Report

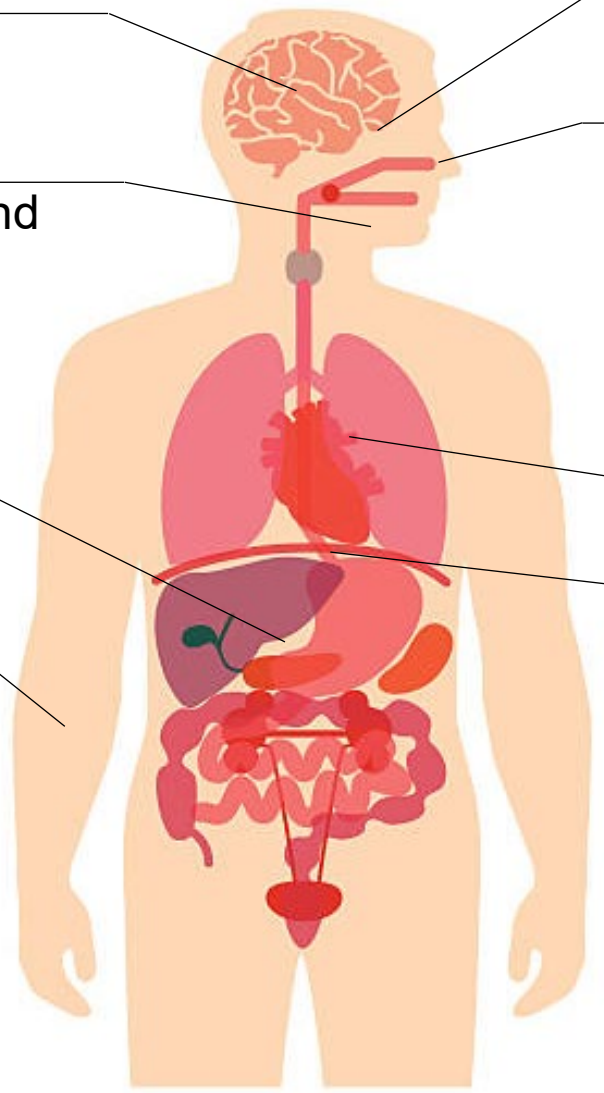
Saito, 2003, 2004
JNEN
Senile Brain

Sakashita, 2021
Neuropathology
Submandibular Grand
(JSNP Award)

Ito, 2014
Int. J. C.E.P
GI tract

Ikemura, 2008
JNEN
Shishido 2010
Neurology
Skin

Sumikura, 2015
Acta Neuropath Com
DRG, Spinal cord



Sengoku, 2008
JNEN (Cover)
(Moore Award)
Olfactory bulb

Funabe, 2013
Neuropathology
(Jsnp Award)
Saito 2016
Movement Diord (Cover)
Olfactory Epithelium

Mitsui, 2006
JNS
Matsubara 2021
Neurology
Heart

Tanei, 2021
Acta Neuropath
Esophagus

Fumimura, 2007
JNEN
Adrenal gland

Hatsuta, 2016
J Park Dis
Spinal ventral roots

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

AD Change

Peripheral autonomic nervous system

Brain stem

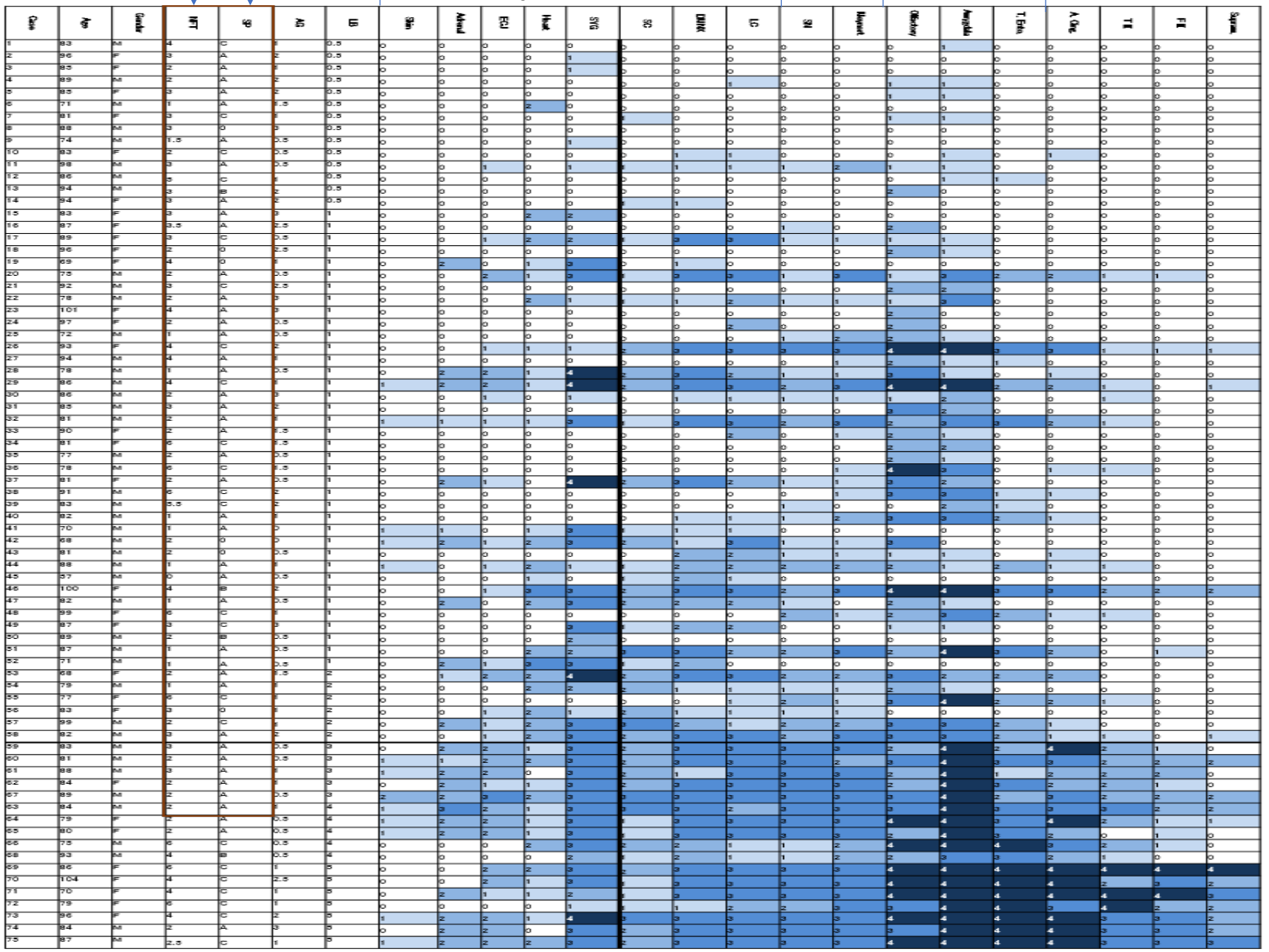
SC

Olfactory

Cerebral Cortex

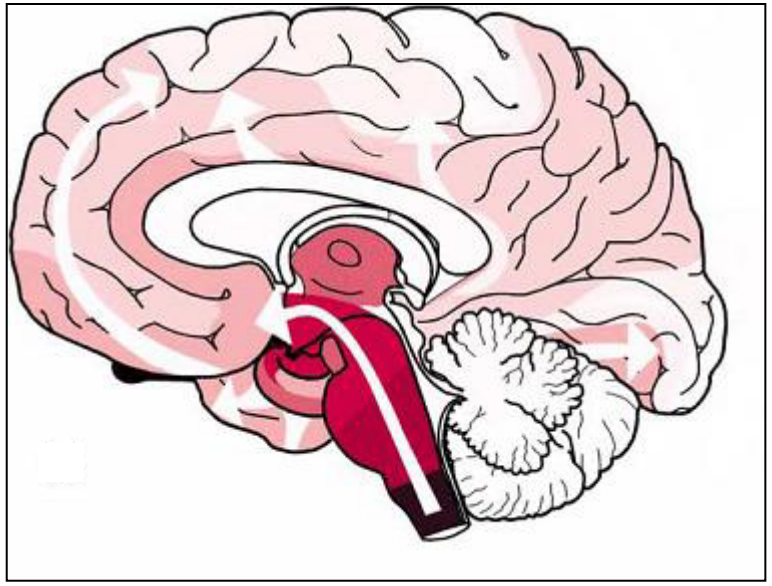
75 Lewy+/ 205 (36.6%)

PD/ DLB



Braak's Rostral Extension Pradigm of Lewy body pathology

Body First



Neocortex

↑

Limbic

↑ (rostral extension)

DMNX

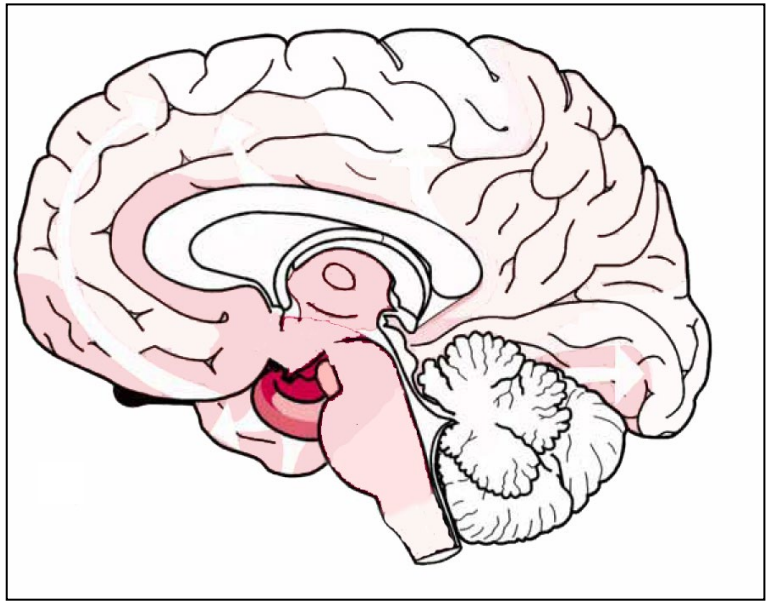
Brain Stem (B)

Limbic (L)

Neocortical (N)

Olfactory- Amygdala Extension of Lewy body pathology

Brain First



Sengoku et al 2008

Olfactory Bulb

Periphery → AON → Amygdala (A)

Amygdala (A) → (Limbic)

(Limbic) → Neocortex

(Limbic) → DMNX

American Association of Neuropathologists

Moore Award

Presented to

R. Sengoku, Y. Saito, M. Ikemura, H. Hatsuta, Y. Sakiyama, M. Sawabe, K. Inoue, H. Mochizuki and S. Murayama

For the Best Paper on Clinico-Pathological Correlation

Incidence and Extent of Lewy Body-Related α-synucleinopathy in Human Aging Olfactory Bulb

San Diego, California
7 April 2008

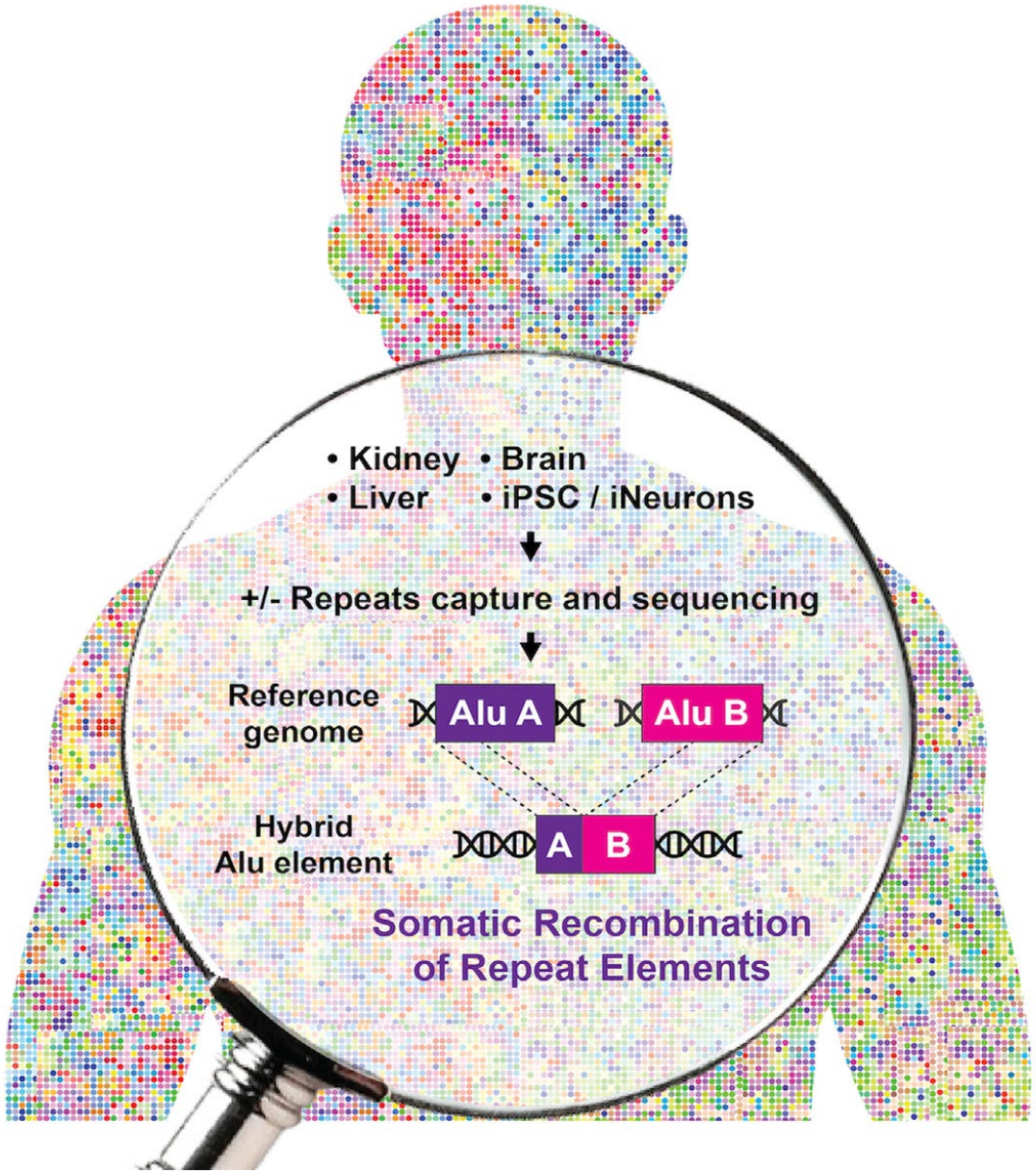
Ronald L. Hamilton
Awards Committee Chair

Jeffrey A. Golden
President

George Perry
Secretary-Treasurer

Recombination of repeat elements generates somatic complexity in human genomes

Cell 185, 3025–3040, August 4, 2022



1. Somatic recombination of Alu and L1 elements is widespread in the human genome.
2. Somatic recombination events of Alu and L1 elements exhibit tissue-specific hallmarks.
3. Neuronal differentiation of iPSCs is accompanied by changes in recombination profiles
4. Somatic recombination profiles are altered in Parkinson's and Alzheimer's diseases

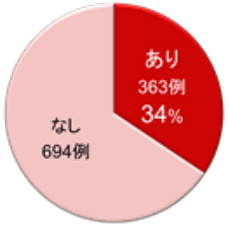
Methods:
All post-mortem human samples were obtained from the Brain Bank for Ageing Research

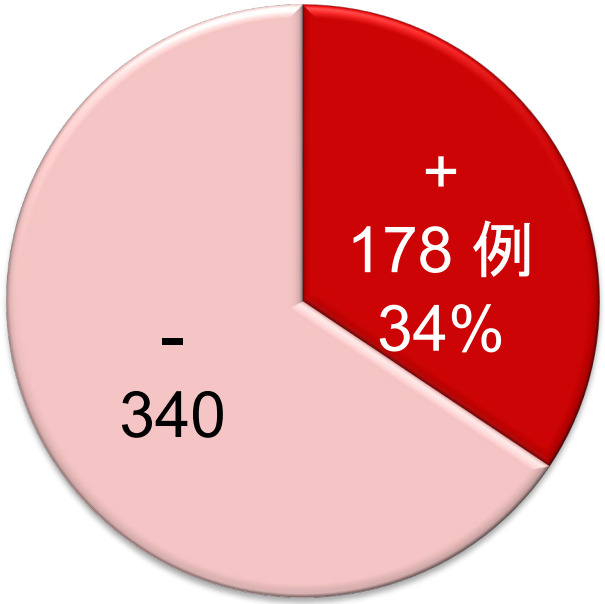
Lewy body disease body resource

One third of geriatric cohort contained Lewy pathology in the body.

Acta Neuropathologica Tanei et al 2021

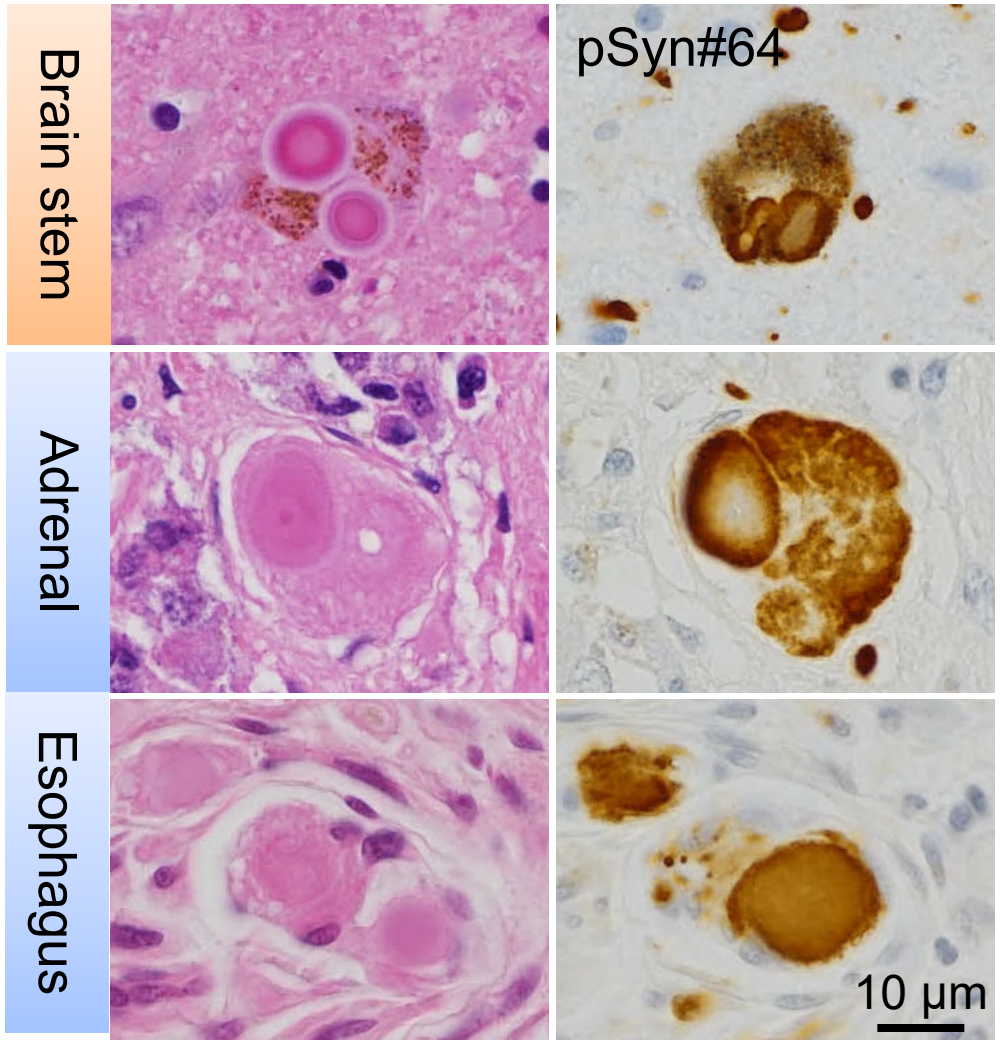
TMIGG consecutive autopsy cases 1,057（2003～2018）





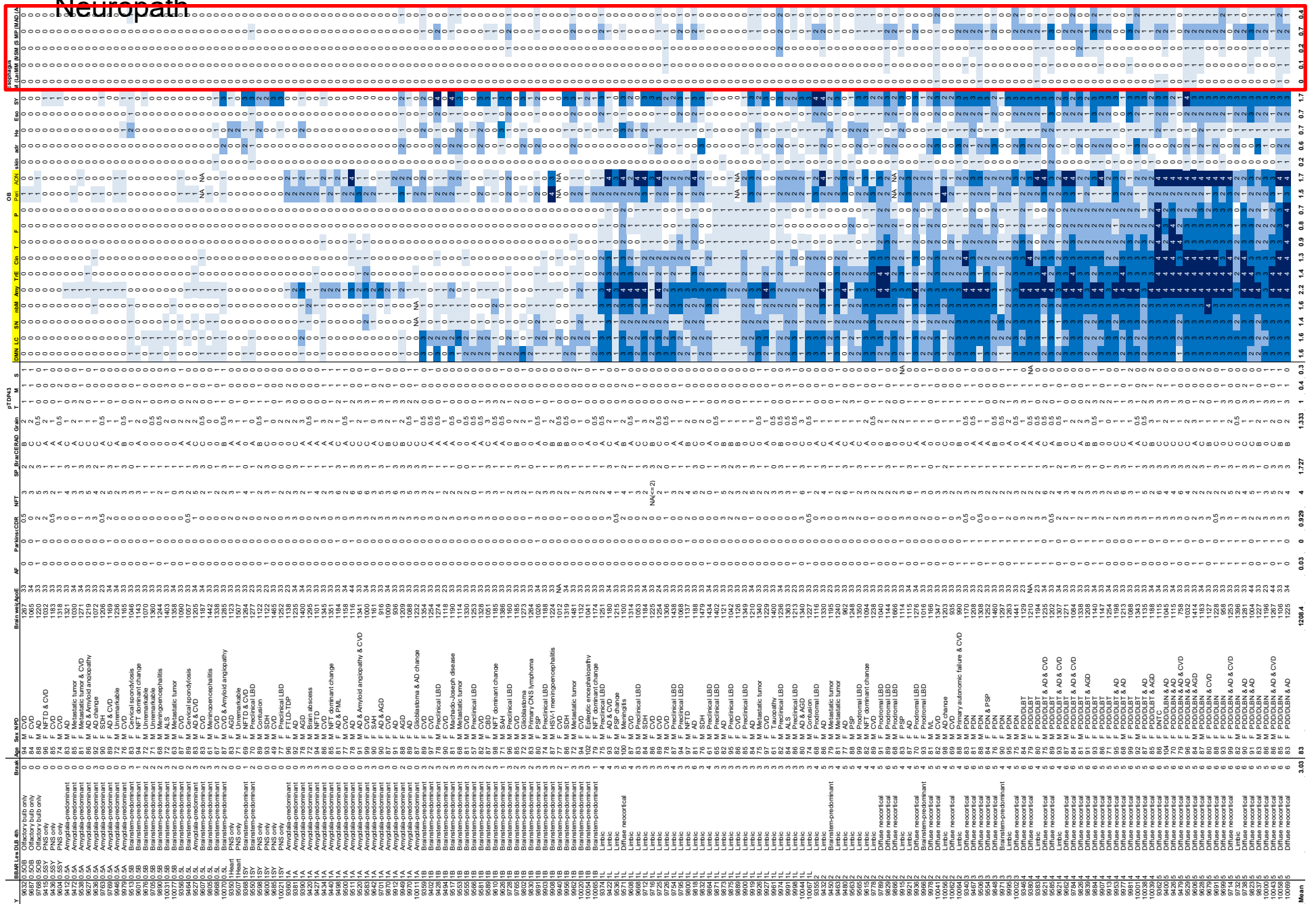
518
（2008- 2018）

To examine GI tracts carefully



Lewy pathology in esophagus correlates with severity of PD

Tanei et al 2020 Acta Neuropath



Yomiuri Newspaper

デイサービス 利用控え8割

コロナ感染警戒

パーキンソン病「原因」

高齢者1/3に蓄積

研究成果発表

これぞ産直の味

Incidence of TDP-43 proteinopathy in aging human brain

286 consecutive autopsy cases

TDP-43 positive cases

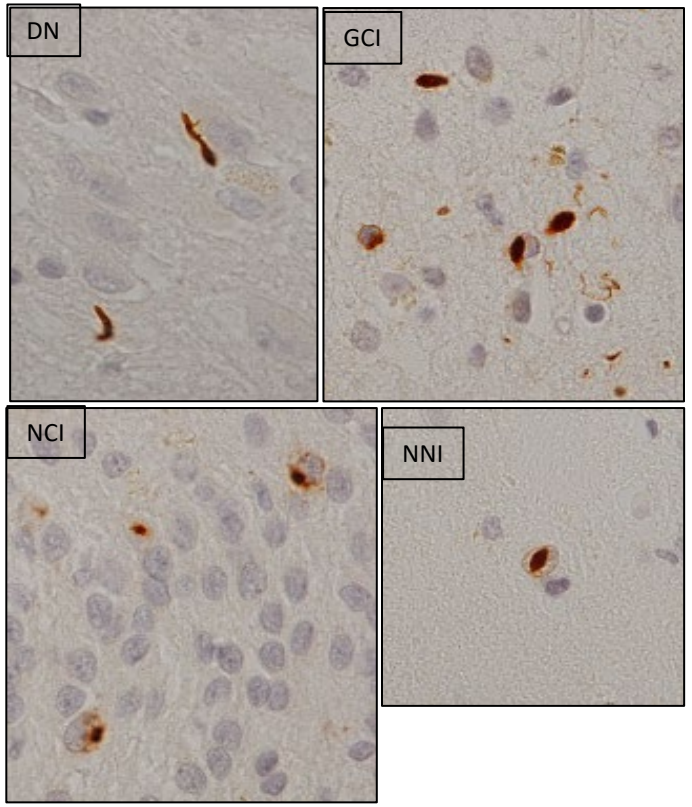
Normal Controls
Braak NFT stage <=2;
Braak SP stage <=A ;
AGD stage <=2;
& LB stage <=2
→ 55/ 136 (40%)

Pure AD
NFT>= 4; SP =3;
Lewy<= 2& AGD<= 2
→ 21/ 29 (72.4%)

Pure LBD
Lewy>= 3
NFT<= 3 & AGD<= 2
→ 8/ 11 (72.7%)

AGD
AG=3,
NFT<= 3 and Lewy <= 2
→ 6/ 11 (54.5%)

Mixed Pathology
AD+ LBD (5/ 6), AD+ AGD (3/ 3), AD+ PSP (1/ 1), AD+ HS (1/ 1),
LBD+ AGD (1/ 1), LBD+ PSP (0/ 1), AGD+ HS (1/ 1)
Other Degenerative and Specific Pathology
HS (2/ 2), NFTD (3/ 6), CJD (0/ 4), MSA (2/ 3), SCA6 (2/ 2), PSP (2/ 2) , DRPLA (0/ 1), CBD (1/ 1), SCA3 (0/ 1), MELAS (0/ 1), ALS- TDP (4/ 4), FTLD-TDP (1/ 1)
Intermediate Pathology not fulfilling above diagnostic criteria
ADC (8/17), NFTC (14/28), PSC (6/12),



pTDP-43- immunoreactive structures in normal control mainly consist of DNs and are preferentially present in uncinate gyrus.

AD: Alzheimer disease, LBD:Lewy body disease (Parkinson disease and dementia with Lewy bodies) , AGD: argyrophilic grain disease, CJD : Creutzfeldt-Jakob disease, MSA : multiple system atrophy, SCA : spinocerebellar ataxia, PSP : progressive supranuclear palsy, HS : hippocampal sclerosis, DRPLA : dentato- rubro-pallidoluysian atrophy, CBD : corticobasal degeneration, MELAS : Mitochondrial encephalopathy with lactic acidosis and stroke like episode, NFTD : neurofibrillary tangle (NFT)- predominant form of senile dementia, NFTC : NFT- dominant senile change, PSC : plaque- dominant senile change, ADC : AD- type change

Article

Novel tau filament fold in corticobasal degeneration

https://doi.org/10.1038/s41586-020-2043-0

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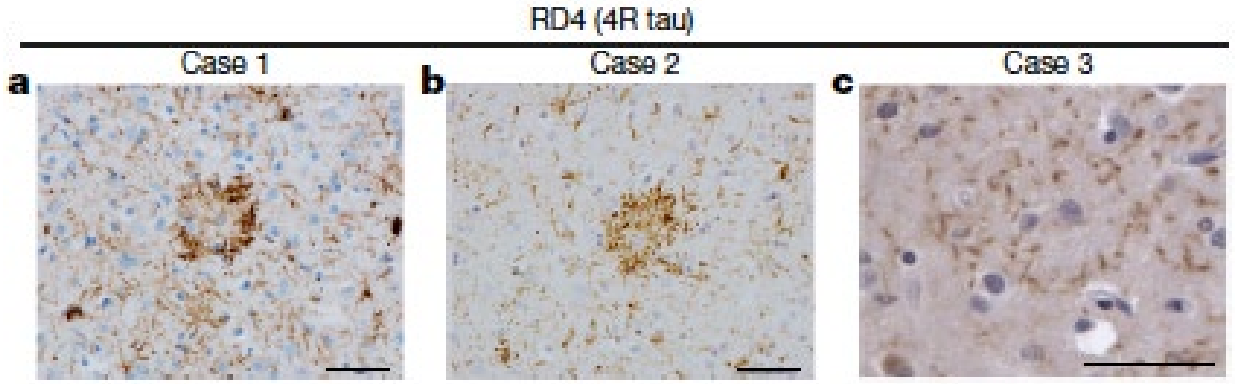
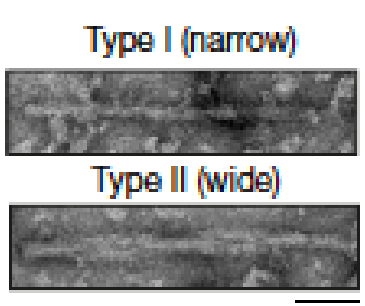
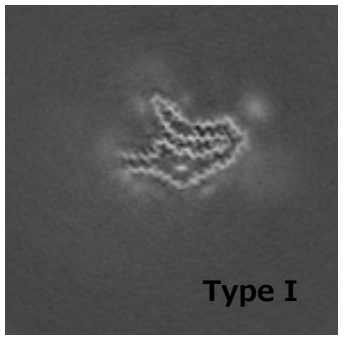
Published online: 12 February 2020

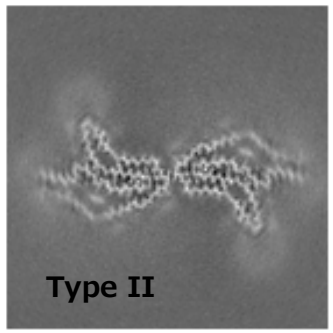
Wenjuan Zhang[1], Airi Tarutani[2], Kathy L. Newell[3], Alexey G. Murzin[1], Tomoyasu Matsubara[4], Benjamin Falcon[1], Ruben Vidal[3], Holly J. Garringer[3], Yang Shi[1], Takeshi Ikeuchi[5], Shigeo Murayama[4], Bernardino Ghetti[3], Masato Hasegawa[2], Michel Goedert[1,6]✉ & Sjors H. W. Scheres[1,6]✉

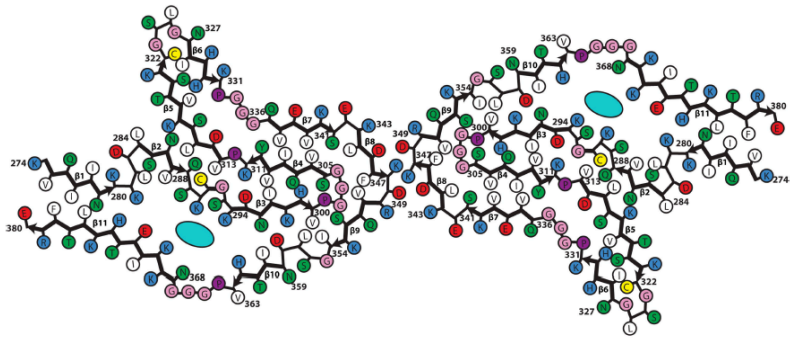
Nature 2021





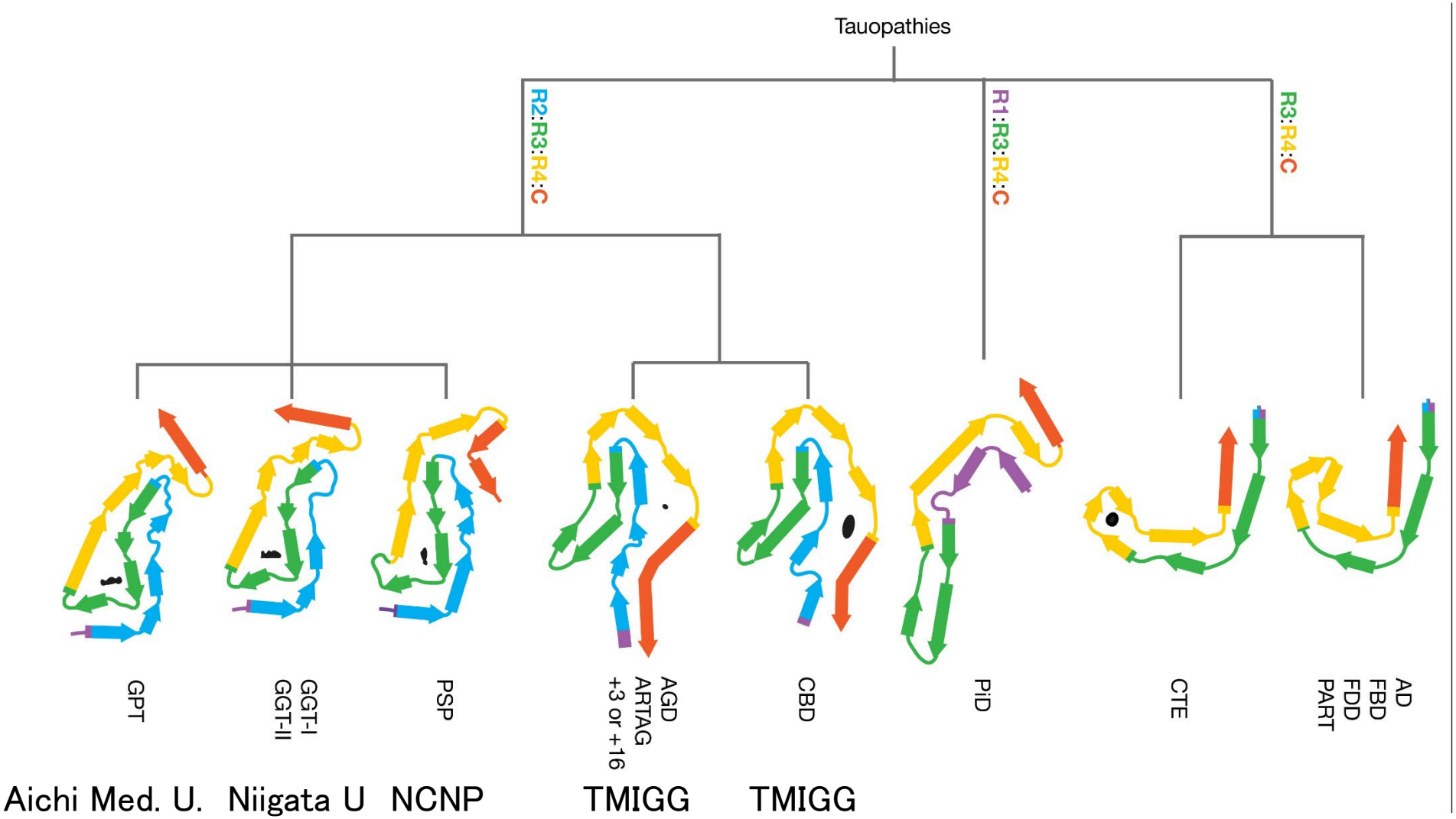






Structure- based classifications of tauopathies

Nature
2021



Article

Structures of α-synuclein filaments from multiple system atrophy

https://doi.org/10.1038/s41586-020-2317-6

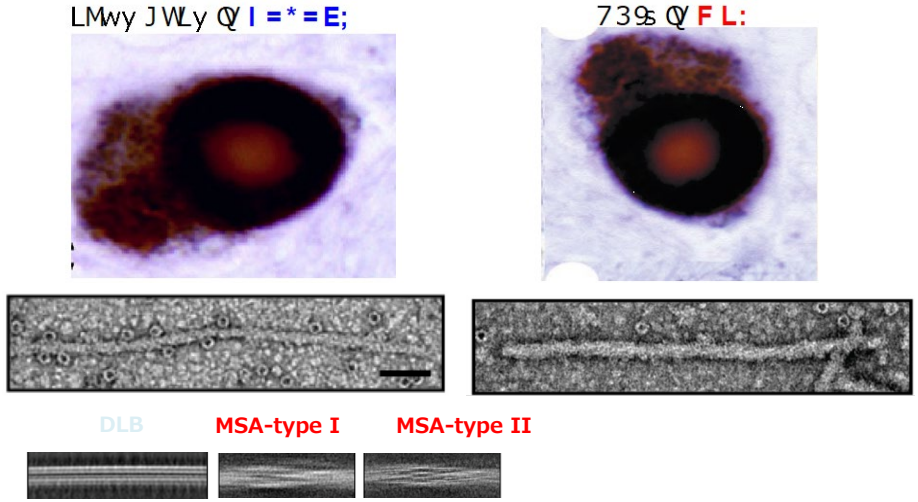
Received: 5 February 2020

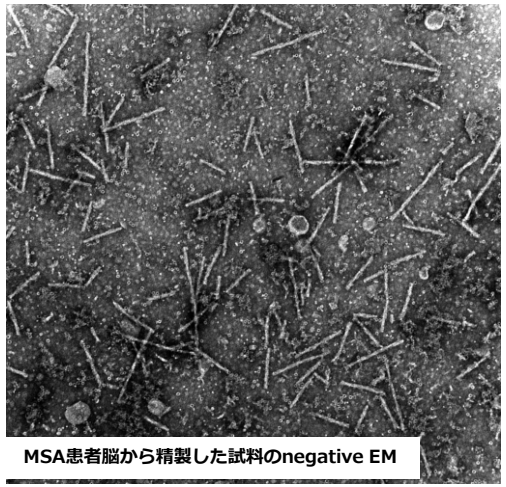
Accepted: 22 April 2020

Published online: 27 May 2020

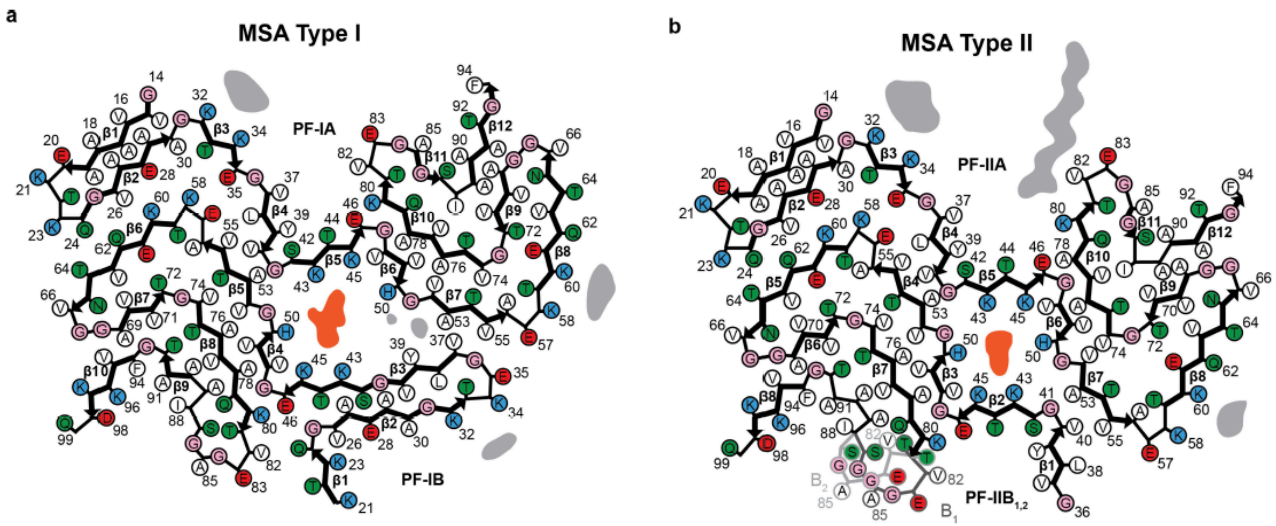
Manuel Schweighauser[1,9], Yang Shi[1,9], Airi Tarutani[2,3], Fuyuki Kametani[2], Alexey G. Murzin[1], Bernardino Ghetti[4], Tomoyasu Matsubara[5], Taisuke Tomita[3], Takashi Ando[6], Kazuko Hasegawa[7], Shigeo Murayama[5], Mari Yoshida[8], Masato Hasegawa[2], Sjors H. W. Scheres[1,10]✉ & Michel Goedert[1,10]✉

Nature
2020





MSA患者脳から精製した試料のnegative EM



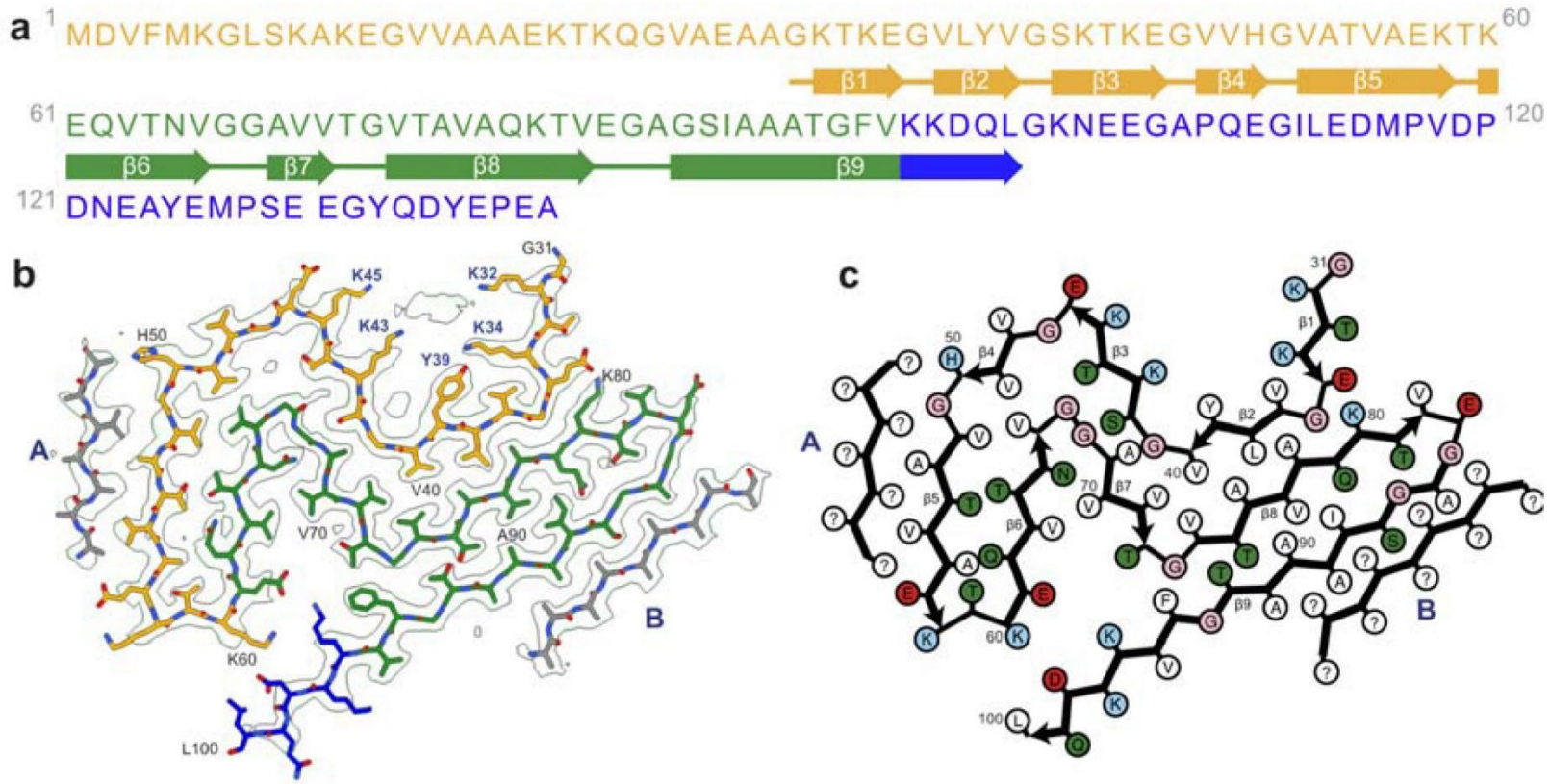


Figure 2. Cryo-EM structure of α-synuclein filaments from Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies (Lewy fold). (a). Amino acid sequence of human α-synuclein. N-terminal region (residues 1-60) in orange, NAC region (residues 61-95) in green and C-terminal region (residues 96-140) in blue. Thick connecting lines with arrowheads indicate β-strands. (**b).** Cryo-EM density map and atomic model of the Lewy fold. The filament core extends from G31-L100. Islands A and B are indicated in grey. **(c).** Schematic of the Lewy filament fold of α-synuclein. Negatively charged residues are in red, positively charged residues in blue, polar residues in green, apolar residues in white, sulfur-containing residues in yellow and glycines in pink. Thick connecting lines with arrowheads indicate β-strands. Unknown residues are indicated by question marks.

Nature on line
2022.9.26

npj | parkinson's disease

www.nature.com/npjparkd

ARTICLE OPEN

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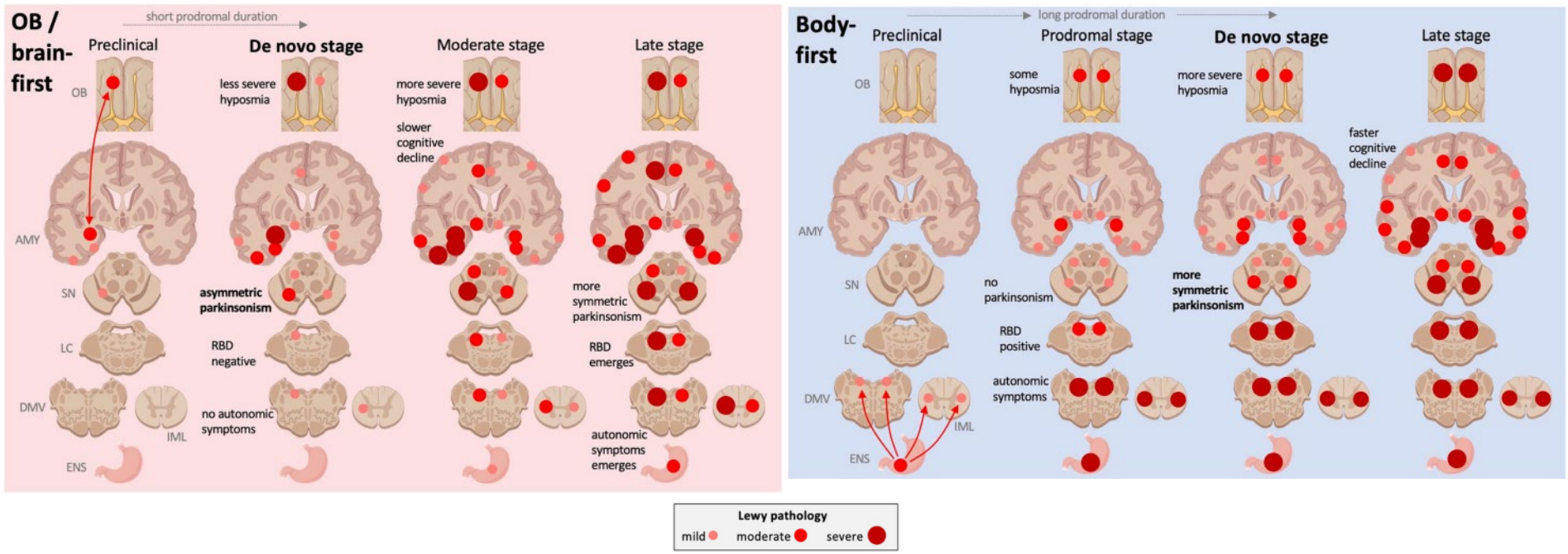
A postmortem study suggests a revision of the dual-hit hypothesis of Parkinson's disease

Per Borghammer[1,2]✉, Mie Kristine Just[1,2], Jacob Horsager[1], Casper Skjærbæk[1,2], Anna Raunio[3], Eloise H. Kok[3], Sara Savola[3], Shigeo Murayama[4,5], Yuko Saito[5], Liisa Myllykangas[3] and Nathalie Van Den Berge[1,2]



Incidence of TDP-43 proteinopathy in aging human brain

286 consecutive autopsy cases

TDP-43 positive cases

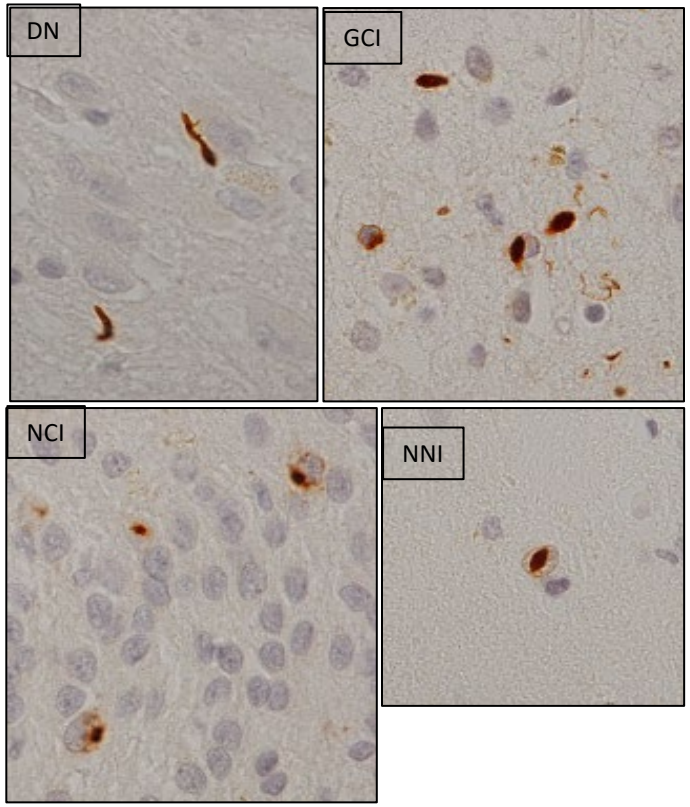
Normal Controls
Braak NFT stage <=2;
Braak SP stage <=A ;
AGD stage <=2;
& LB stage <=2
→ 55/ 136 (40%)

Pure AD
NFT>= 4; SP =3;
Lewy<= 2& AGD<= 2
→ 21/ 29 (72.4%)

Pure LBD
Lewy>= 3
NFT<= 3 & AGD<= 2
→ 8/ 11 (72.7%)

AGD
AG=3,
NFT<= 3 and Lewy <= 2
→ 6/ 11 (54.5%)

Mixed Pathology
AD+ LBD (5/ 6), AD+ AGD (3/ 3), AD+ PSP (1/ 1), AD+ HS (1/ 1),
LBD+ AGD (1/ 1), LBD+ PSP (0/ 1), AGD+ HS (1/ 1)
Other Degenerative and Specific Pathology
HS (2/ 2), NFTD (3/ 6), CJD (0/ 4), MSA (2/ 3), SCA6 (2/ 2), PSP (2/ 2) , DRPLA (0/ 1), CBD (1/ 1), SCA3 (0/ 1), MELAS (0/ 1), ALS- TDP (4/ 4), FTLD-TDP (1/ 1)
Intermediate Pathology not fulfilling above diagnostic criteria
ADC (8/17), NFTC (14/28), PSC (6/12),



pTDP-43- immunoreactive structures in normal control mainly consist of DNs and are preferentially present in uncinate gyrus.

Uchino et al: Acta Neuropth Com 2015

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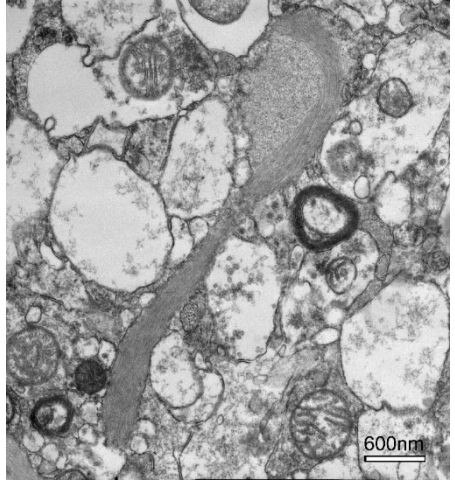
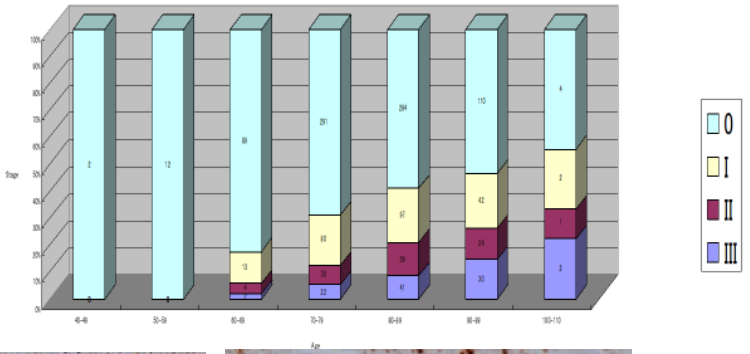
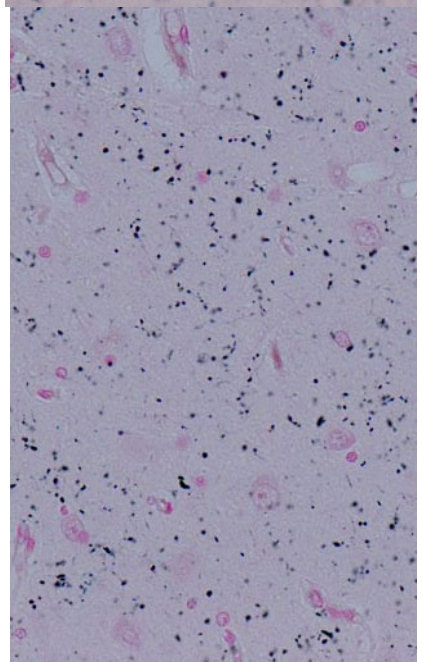
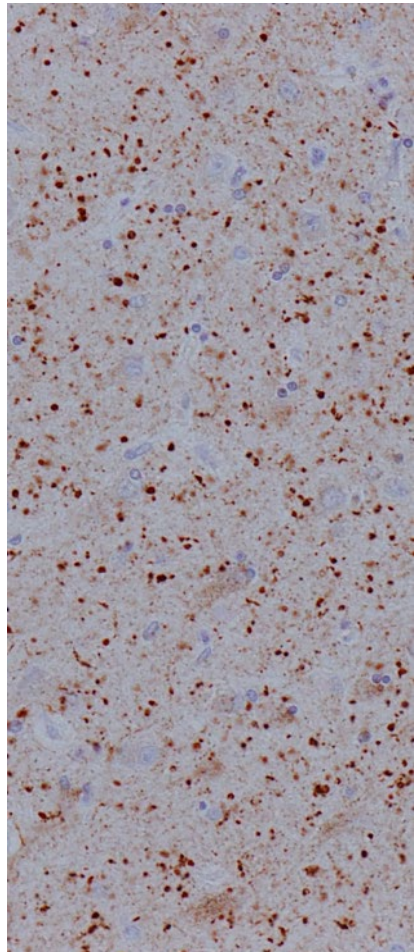
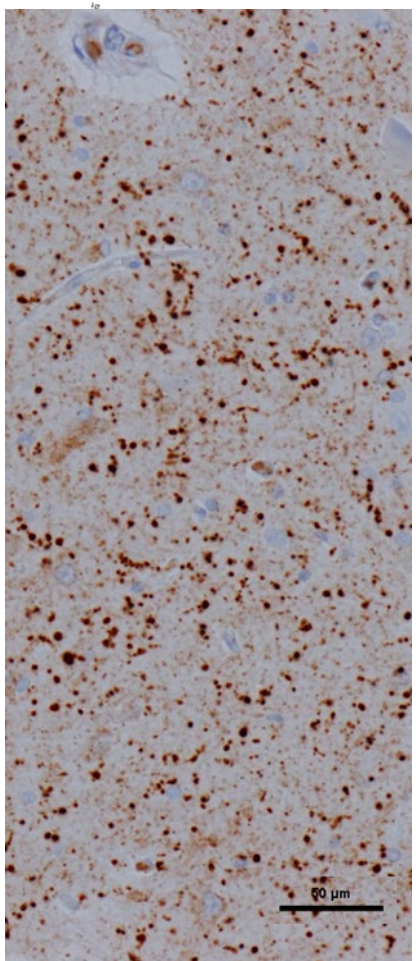
Argyrophilic Grains

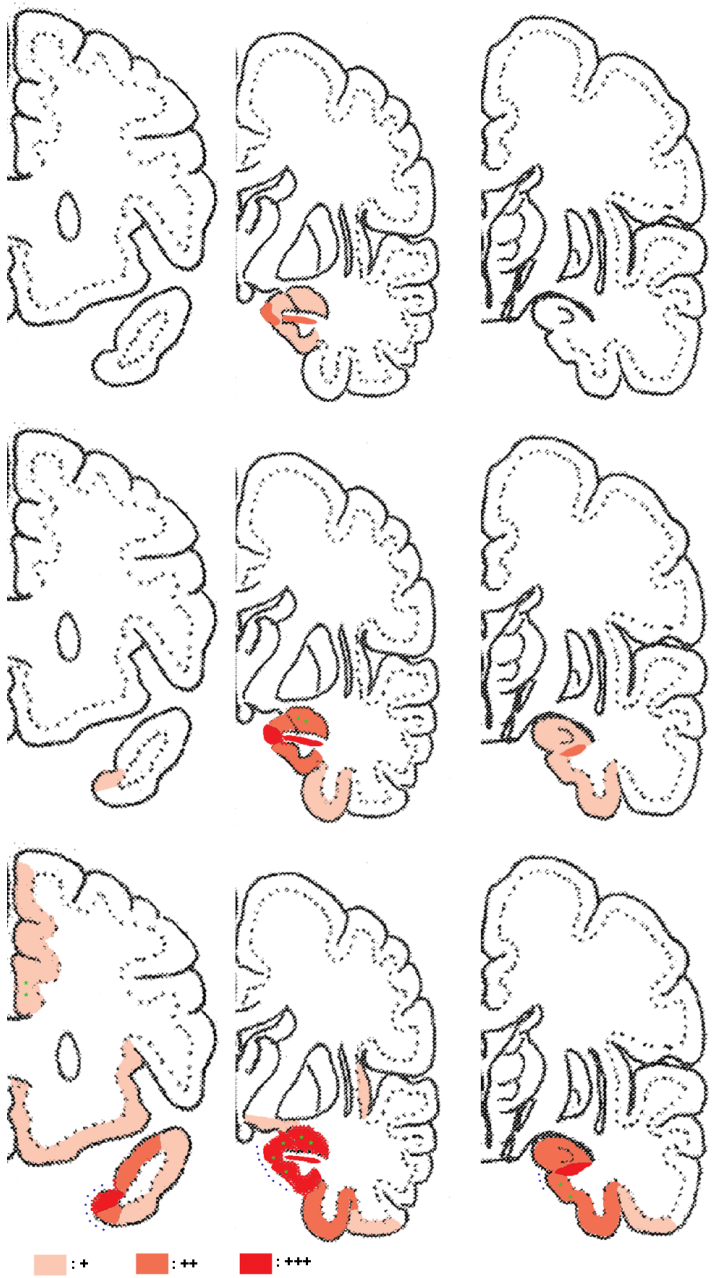












I: Ambient Stage

II: Temporal Stage

III: Frontal Stage

Saito Stage (Saito et al JNEN 2004)

Article

Structure-based classification of tauopathies

https://doi.org/10.1038/s41586-021-03911-7

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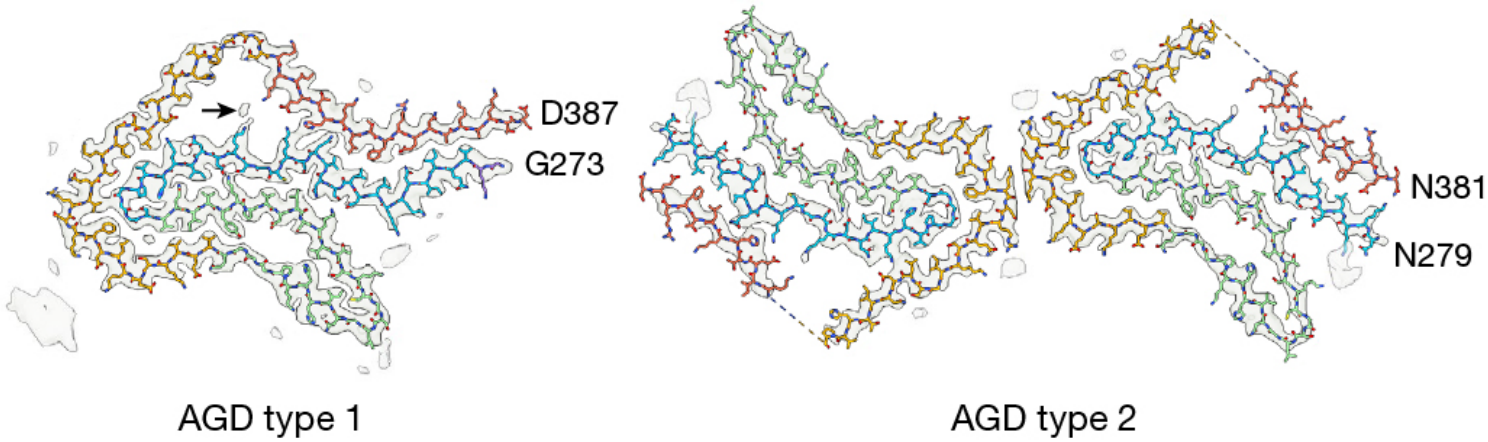
Nature | www.nature.com |

Yang Shi[1,14], Wenjuan Zhang[1,14], Yang Yang[1], Alexey G. Murzin[1], Benjamin Falcon[1], Abhay Kotecha[2], Mike van Beers[2], Airi Tarutani[3], Fuyuki Kametani[3], Holly J. Garringer[4], Ruben Vidal[4], Grace I. Hallinan[4], Tammaryn Lashley[5], Yuko Saito[6], Shigeo Murayama[7], Mari Yoshida[8], Hidetomo Tanaka[9], Akiyoshi Kakita[9], Takeshi Ikeuchi[10], Andrew C. Robinson[11], David M. A. Mann[11], Gabor G. Kovacs[12,13], Tamas Revesz[5], Bernardino Ghetti[4], Masato Hasegawa[3], Michel Goedert[1,15] ✉ & Sjors H. W. Scheres[1,15] ✉

Nature 2022

Argyrophilic Grain Fold



BBAR succeeded in confirming argyrophilic grains as an independent tauopahy.

Availability of Resource

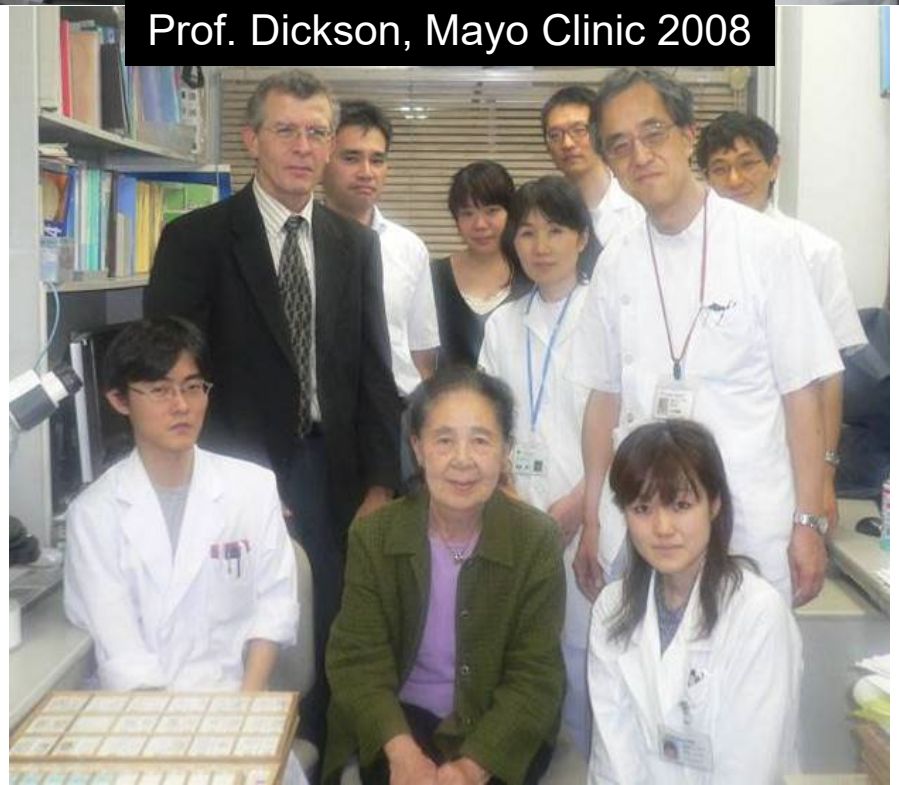
- An application form is downloadable from BBAR Home Page (www.mci.gr.jp/BrainBank/)
- Each application is peer- reviewed by BBAR members of the academic committee.
- The applicant's IRB as well as our IRB should approve the research scheme.
- The applicants should present the research scheme to our team via Skype, so that we may appoint them as a visiting scholar of TMGHIG.
- The resource is sent to the researchers as coworkers, who should file annual reports until they send back the resource.

International Standardization

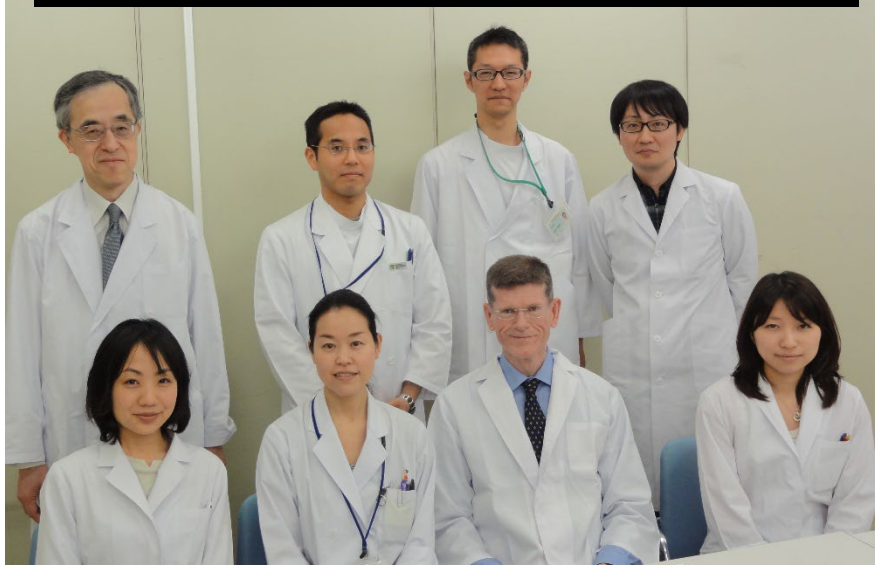
Prof. Graeber, Imperial College of London, 2007

Prof. Hedley- Whyte, MGH 2010

Prof. Dickson, Mayo Clinic 2008



Prof. Cairns, Washington University 2013



September 28, 2018
@
The Brain Bank for Aging Research
Tokyo Metropolitan Geriatric Hospital &
Institute of Gerontology

Brain Bank for Aging Research (2022) TMIGG

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