

**Lewy pathology of the esophagus correlates with the progression of Lewy body disease: a Japanese cohort study of autopsy cases**

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### Supplementary materials

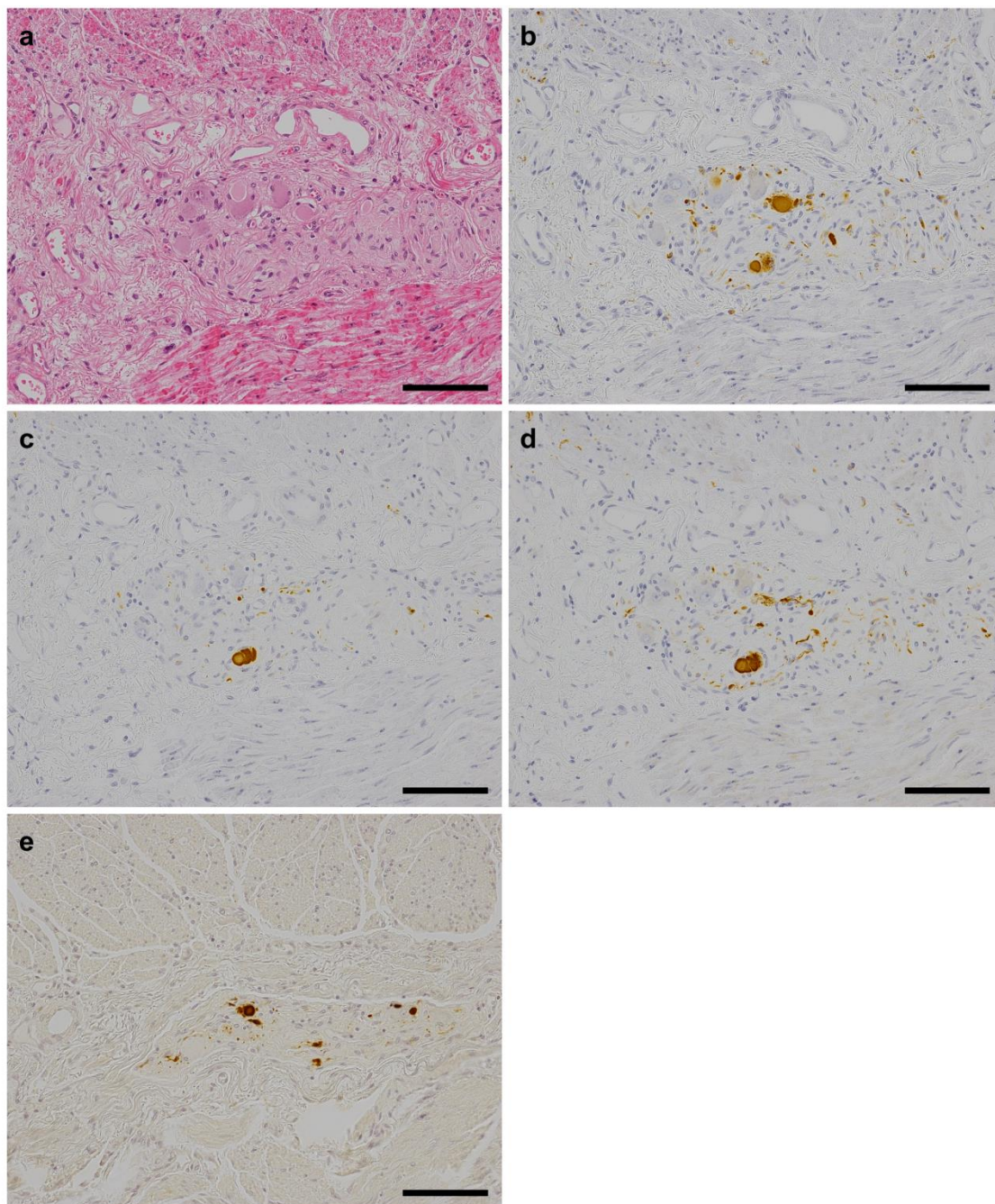
**Supplementary Figure 1** Immunohistochemistry using four different anti- $\alpha$ -synuclein antibodies. (a) LB in Auerbach's plexus of the esophagus. (b–e) Immunoreactivity of LB and neuronal processes observed in four anti- $\alpha$ -synuclein antibodies. H&E (a), pSyn#64 (b), MJF-R13 (c), LB509 (d), and Pser129 (e). Scale bar = 100  $\mu$ m.

**Supplementary Figure 2** Cause of death for the 518 BBAR cases at autopsy. Three-fourths of the individuals died of respiratory diseases, malignant neoplasm, or cardiovascular disease. Dotted areas in the inner circle show comorbidity with neurodegenerative diseases, such as AD, PD, PDD, DLB, argyrophilic grain disease, neurofibrillary tangle predominant dementia, frontotemporal lobar degeneration, progressive supranuclear palsy, or others.

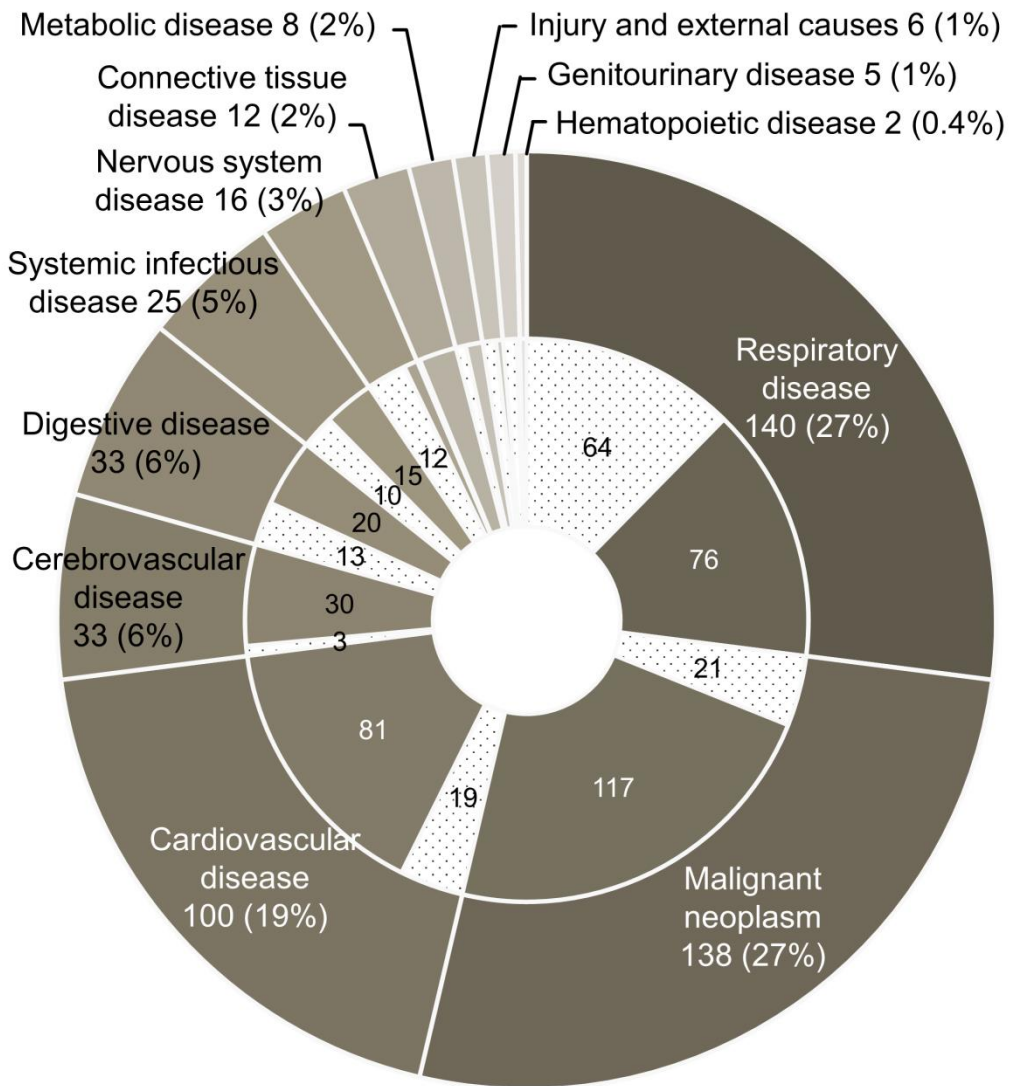
**Supplementary Figure 3** List of the 178 BBAR cases who showed Lewy pathology in their nervous systems. Semi-quantitative analyses of the  $\alpha$ -synuclein deposition are colored in blue gradation (score 0–4 according to DLB Consensus guidelines). *AA*, amyloid angiopathy; *AAD*, acute aortic dissection; *AAneu*, aortic aneurysm; *AD*, Alzheimer's disease; *Adr*, adrenal gland; *AF*, autonomic failure; *Af*, atrial fibrillation; *AGD*, argyrophilic grain disease; *ALS*, amyotrophic lateral sclerosis; *AMI*, acute myocardial infarction; *AML*, acute myeloid leukemia; *Amy*, amygdala; *AON*, anterior olfactory nucleus; *AS*, aortic valve stenosis; *BBAR LB*, Lewy body stage of the Brain Bank for Aging Research; *BT*, brain tumor; *Braak LB*, Braak Lewy body stage; *BH*, brain hemorrhage; *BI*, brain infarction; *BW*, brain weight (g); CERAD, 0 = none, A = sparse, B = moded, C = frequent; *ca*, cancer; *CBS*, corticobasal syndrome; *CHF*, congestive heart failure; *Cing*, anterior cingulate gyrus; *CML*, chronic myeloid leukemia; *COPD*, chronic obstructive pulmonary disease; *CRF*, chronic renal failure; *CVD*, cerebrovascular disease; *DLB*, dementia with Lewy bodies; *DM*, diabetes mellitus; *DMNV*, dorsal motor nucleus of the vagus; *DLB 4th*, fourth consensus report of the DLB consortium; *DLBN*, dementia with Lewy bodies, neocortical form; *DLBT*, dementia with Lewy bodies, transitional form; *DNTC*, diffuse neurofibrillary tangles with calcification; *Eso*, esophagus; *Esophagus M*, mucosa of the esophagus; *Esophagus MM*, muscularis mucosa; *Esophagus SM*, submucosa; *Esophagus MP*, muscularis propria; *Esophagus ADV*, adventitia; *F*, frontal lobe; *FTLD*, frontotemporal lobar degeneration; *GI bleed*, gastrointestinal bleeding; *Grain*, Saito grain stage; *HCM*, hypertrophic cardiomyopathy; *He*, heart; *HY*, Hoehn and Yahr scale; *IE*, infective endocarditis; *IHC*, immunohistochemistry, ✓ = performed; *IHD*, ischemic heart disease; *Int Perf*, intestinal perforation; *IPneu*, interstitial pneumonia; *IVL*, intravascular lymphoma; *LBD*, Lewy body disease; *LC*, locus coeruleus; *M*, medullar oblongata; *MDD*, major depressive disorder; *MDS*, myelodysplastic syndrome; *ML*, malignant lymphoma; *MM*, multiple myeloma; *MPA*, microscopic polyangiitis; *NA*, not available; *nbM*, nucleus basalis of Meynert; *NFT*, Braak neurofibrillary tangle stage; *NFTD*, neurofibrillary tangle predominant dementia; *NPD*, neuropathological diagnosis; *OB*, olfactory bulb; *P*, parietal lobe; *PA*,

Parkinsonism. 1 = presence, 0 = absence; *PAF*, pure autonomic failure; *Peri*, the periphery of the OB; *PD*, Parkinson's disease; *PDD*, Parkinson's disease with dementia; *Pneu*, pneumonia; *PSP*, progressive supranuclear palsy; *RA*, rheumatoid arthritis; *RF*, respiratory failure; *S*, lumbar spinal cord; *SAH*, subarachnoid hemorrhage; *SCA*, spinocerebellar ataxia; *SDH*, subdural hemorrhage; *SN*, substantia nigra; *SP*, Braak senile plaque stage; *SY*, sympathetic ganglia; *T*, temporal lobe; *Thal*, Thal senile plaque phase; *TrE*, transentorhinal cortex; *UP*, unknown primary.

**Supplementary Figure 1** Immunohistochemistry using four different anti- $\alpha$ -synuclein antibodies



**Supplementary Figure 2** Cause of death for the 518 BBAR cases at autopsy





**Supplementary Table 1** Cause of death for the 518 BBAR cases at autopsy

	Number of the cases (%)		With neurodegenerative disorder		Without neurodegenerative disorder	
<b>Respiratory disease</b>	<b>140</b>	<b>(27.0)</b>	<b>64</b>	<b>(12.4)</b>	<b>76</b>	<b>(14.7)</b>
Pneumonia	96	(18.5)	46	(8.9)	50	(9.7)
Organizing pneumonia	20	(3.9)	13	(2.5)	7	(1.4)
Interstitial pneumonia	11	(2.1)	1	(0.2)	10	(1.9)
Diffuse alveolar damage	6	(1.2)	2	(0.4)	4	(0.8)
Emphysema	5	(1.0)	1	(0.2)	4	(0.8)
Pulmonary edema	1	(0.2)	1	(0.2)	0	(0)
Pneumoconiosis	1	(0.2)	0	(0)	1	(0.2)
<b>Malignant neoplasm</b>	<b>138</b>	<b>(26.6)</b>	<b>21</b>	<b>(4.1)</b>	<b>117</b>	<b>(22.6)</b>
Lung	32	(6.2)	8	(1.5)	24	(4.6)
Leukemia	15	(2.9)	0	(0)	15	(2.9)
Lymphoma	14	(2.7)	0	(0)	14	(2.7)
Stomach	14	(2.7)	3	(0.6)	11	(2.1)
Large intestine	11	(2.1)	4	(0.8)	7	(1.4)
Brain	10	(1.9)	0	(0)	10	(1.9)
Pancreas	7	(1.4)	1	(0.2)	6	(1.2)
Prostate gland	5	(1.0)	1	(0.2)	4	(0.8)
Gallbladder	4	(0.8)	1	(0.2)	3	(0.6)
Urinary bladder	4	(0.8)	1	(0.2)	3	(0.6)
Others	18	(3.5)	2	(0.4)	16	(3.1)
<b>Cardiovascular disease</b>	<b>100</b>	<b>(19.3)</b>	<b>18</b>	<b>(3.5)</b>	<b>82</b>	<b>(15.8)</b>
Acute myocardial infarction	31	(6.0)	7	(1.4)	24	(4.6)
Acute aortic dissection	14	(2.7)	2	(0.4)	12	(2.3)
Aortic aneurysm	10	(1.9)	2	(0.4)	8	(1.5)
Aortic valve stenosis	8	(1.5)	1	(0.2)	7	(1.4)
Chronic myocardial infarction	8	(1.5)	1	(0.2)	7	(1.4)
Pulmonary embolism	5	(1.0)	1	(0.2)	4	(0.8)
Dilated cardiomyopathy	4	(0.8)	1	(0.2)	3	(0.6)
Infective endocarditis	4	(0.8)	0	(0)	4	(0.8)
Others	16	(3.1)	3	(0.6)	13	(2.5)
<b>Cerebrovascular disease</b>	<b>33</b>	<b>(6.4)</b>	<b>3</b>	<b>(0.6)</b>	<b>30</b>	<b>(5.8)</b>
Infarction	19	(3.7)	1	(0.2)	18	(3.5)



Hemorrhage	9	(1.7)	1	(0.2)	8	(1.5)
Subarachnoid hemorrhage	4	(0.8)	1	(0.2)	3	(0.6)
Subdural hemorrhage	1	(0.2)	0	(0)	1	(0.2)
<b>Digestive disease</b>	<b>33</b>	<b>(6.4)</b>	<b>13</b>	<b>(2.5)</b>	<b>20</b>	<b>(3.9)</b>
Ischemic enteritis	8	(1.5)	4	(0.8)	4	(0.8)
Intestinal perforation	5	(1.0)	5	(1.0)	0	(0)
Duodenal ulcer	4	(0.8)	0	(0)	4	(0.8)
Liver cirrhosis	3	(0.6)	0	(0)	3	(0.6)
Others	13	(2.5)	4	(0.8)	9	(1.7)
<b>Systemic infectious disease</b>	<b>25</b>	<b>(4.8)</b>	<b>10</b>	<b>(1.9)</b>	<b>15</b>	<b>(2.9)</b>
Sepsis	13	(2.5)	3	(0.6)	10	(1.9)
Tuberculosis	6	(1.2)	5	(1.0)	1	(0.2)
Nontuberculous mycobacteria infection	2	(0.4)	0	(0)	2	(0.4)
Others	4	(0.8)	2	(0.4)	2	(0.4)
<b>Nervous system disease</b>	<b>16</b>	<b>(3.1)</b>	<b>12</b>	<b>(2.3)</b>	<b>4</b>	<b>(0.8)</b>
Amyotrophic lateral sclerosis	7	(1.4)	7	(1.4)	0	(0)
Frontotemporal lobar degeneration	2	(0.4)	2	(0.4)	0	(0)
Others	7	(1.4)	3	(0.6)	4	(0.8)
<b>Connective tissue disease</b>	<b>12</b>	<b>(2.3)</b>	<b>1</b>	<b>(0.2)</b>	<b>11</b>	<b>(2.1)</b>
Rheumatoid arthritis	4	(0.8)	1	(0.2)	3	(0.6)
Spondylodiscitis	3	(0.6)	0	(0)	3	(0.6)
Others	5	(1.0)	0	(0)	5	(1.0)
<b>Metabolic disease</b>	<b>8</b>	<b>(1.5)</b>	<b>3</b>	<b>(0.6)</b>	<b>5</b>	<b>(1.0)</b>
Senile systemic amyloidosis	4	(0.8)	3	(0.6)	1	(0.2)
Amyloid light-chain amyloidosis	3	(0.6)	0	(0)	3	(0.6)
Pellagra	1	(0.2)	0	(0)	1	(0.2)
<b>Injury and external causes</b>	<b>6</b>	<b>(1.2)</b>	<b>4</b>	<b>(0.8)</b>	<b>2</b>	<b>(0.4)</b>
Tracheobronchial foreign body	5	(1.0)	4	(0.8)	1	(0.2)
Ruptured spleen	1	(0.2)	0	(0)	1	(0.2)
<b>Genitourinary disease</b>	<b>5</b>	<b>(1.0)</b>	<b>4</b>	<b>(0.8)</b>	<b>1</b>	<b>(0.2)</b>
Chronic kidney disease	3	(0.6)	2	(0.4)	1	(0.2)
Pyelonephritis	2	(0.4)	0	(0)	2	(0.4)
<b>Hematopoietic disease</b>	<b>2</b>	<b>(0.4)</b>	<b>0</b>	<b>(0)</b>	<b>2</b>	<b>(0.4)</b>
<b>Total</b>	<b>518</b>	<b>(100)</b>	<b>153 (29.5)</b>		<b>365 (70.5)</b>	

*BBAR*, the Brain Bank for Aging Research.

**Supplementary Table 2** Incidence of Lewy pathology in the PNS

BBAR LB stage	Number of cases (Mean Age at death)	Esophagus <i>n</i> (%)	Sympathetic ganglia <i>n</i> (%)	Heart <i>n</i> (%)	Adrenal gland <i>n</i> (%)	Skin <i>n</i> (%)
0.5	29 (81.2, SD 9.6)	1 (3.4)	9 (31.0)	3 (10.3)	1 (3.4)	1 (3.4)
1	83 (82.9, SD 10.1)	23 (27.7)	51 (61.4)	38 (45.8)	19 (22.9)	8 (9.6)
2	20 (83.8, SD 9.5)	13 (65.0)	19 (95.0)	15 (75.0)	10 (50.0)	7 (35.0)
3	8 (84.0, SD 6.8)	6 (75.0)	8 (100)	6 (75.0)	6 (75.0)	2 (25.0)
4	19 (85.2, SD 8.2)	17 (89.5)	19 (100)	18 (94.7)	12 (63.2)	9 (47.4)
5	19 (86.9, SD 7.6)	18 (94.7)	19 (100)	16 (84.2)	11 (57.9)	5 (26.3)
Total	178	78 (43.8)	125 (70.2)	98 (55.1)	60 (33.7)	32 (18.0)

*BBAR*, the Brain Bank for Aging Research; *LB*, Lewy body; *SD*, standard deviation.

**Supplementary Table 3** Summary of 9 cases with PNS-only Lewy pathology

Age	Gen der	AF	PA	NPD	BW	NFT	SP	BB		Lewy pathology*															
								AR LB	DM NV	LC	SN	nbM	Amy	TrE	Ci ng	T	F	P	OB	Sk in	Adr	He	Eso	SY	
74	M	0	0	CVD	1318	1	1	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
85	F	0	0	CVD	1183	2	1	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
96	F	0	0	NFTD CVD	1032	3	1	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
49	M	0	0	CVD	1466	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
71	M	0	0	Pr LBD	1507	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0
77	F	0	0	Pr LBD	1252	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	3
83	F	0	0	AGD	1123	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	1
89	M	0	0	Cont	1122	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	2
93	M	1†	0	SDH	1122	3	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2

*Adr*, adrenal gland; *AF*, autonomic failure. 1 = presence, 0 = absence; *AGD*, argyrophilic grain disease; *Amy*, amygdala; *BBAR LB*, Lewy body stage of the Brain Bank for Aging Research; *BW*, brain weight (g); *Cont*, contusion; *CVD*, cerebrovascular disease; *DLB*, dementia with Lewy bodies; *DMNV*, dorsal motor nucleus of the vagus; *Eso*, esophagus; *F*, frontal lobe; *He*, heart; *LBD*, Lewy body disease; *LC*, locus coeruleus; *M*, medullar oblongata; *nbM*, nucleus basalis of Meynert; *NFT*, Braak neurofibrillary tangle stage; *NFTD*, neurofibrillary tangle predominant dementia; *NPD*, neuropathological diagnosis; *OB*, olfactory bulb; *P*, parietal lobe; *PA*, Parkinsonism. 1 = presence, 0 = absence; *Pr LBD*, preclinical LBD; *SDH*, subdural hemorrhage; *SN*, substantia nigra; *SP*, Braak senile plaque stage; *SY*, sympathetic ganglia; *T*, temporal lobe; *TrE*, transentorhinal cortex.

\*Semi-quantitative analyses of the  $\alpha$ -synuclein deposition (score 0–4 according to DLB Consensus guidelines).

†Constipation.

**Supplementary Table 4** Summary of the literature on Lewy pathology in the ENS\*

Author	Year	Region	Number of subjects	Positivity of Lewy pathology				
				PD	DLB	PAF	Preclinical/ Prodromal LBD	Control
<b>Autopsy</b>								
Tanei Z	2020	L-Eso	518	6/8 (75%)	35/38 (92%)	1/1	Earliest LBD: 1/29 (3%) Prec/Prod LBD: 35/102 (34%)	0/340 (0%)
Beach TG	2016	S-Col	10	5/5 (100%)				0/5 (0%)
Gelpi E	2014	L-Eso, Sto Ile, T/D-Col Rec	28	8/10 (80%)	5/5 (100%)			1/13 (8%)
Mu L	2013	Pharynx	14	10/10 (100%)				0/4 (0%)
Gold A	2013	Col	95	10/10 (100%)				Gen 40/77 (52%) AD 3/8 (38%)
Annerino DM	2012	Sto, Duo, Ile, T-Col, Rec	29	13/13 (100%)			2/4 (50%)	0/12 (0%)
Del Tredici K	2011	L-Eso, Sto	4	3/3 (100%)			1/1 (100%)	
Beach TG	2010	U/L-Eso, Sto Duo, Jej, Ile Rec, T/S-Col Liv, Pan, Gal	92	11/17 (65%)	5/9 (56%)		1/7 (14%)	

Braak H	2006	L-Eso, Sto	10	3/3 (100%)	2/2 (100%)	0/5 (0%)
Bloch A	2006	L-Eso	98	1/2 (50%)	14/17 (82%)	
Wakabayashi K†	1988	U/M/L-Eso	31	Eso 8/8 (100%)	Eso 8/24 (33%)	
		Sto, Duo		Sto 2/8 (25%)	Sto 0/24 (0%)	
		Jej, Ile		Duo 1/7 (14%)	Duo 3/24 (13%)	
		A/T/D-Col		Jej 2/8 (25%)	Jej 1/24 (4%)	
		Rec		Ile 0/8 (0%)	Ile 1/24 (4%)	
				Col 3/8 (38%)	Col 0/24 (0%)	
				Rec 2/7 (29%)	Rec 0/24 (0%)	
Qualman SJ†	1984	L-Eso, Sto	80	2/22 (9%)		0/50 (0%)
		Jej, Ile, Col				
		Rec				
<b>Surgery</b>						
Yan, F.	2018	Sto, Col	63	Sto 6/10 (60%)		Sto 1/11 (9%)
		Rec, App		Col 5/9 (56%)		Col 2/9 (22%)
				Rec 5/9 (56%)		Rec 2/8 (25%)
				App 1/3 (33%)		App 2/8 (25%)
Shin C‡	2017	Sto	66	Sto 7/12 (58%)		
		A/T/D-Col		A/T-Col 3/9 (33%)		
		Rec		D-Col/Rec 2/12 (17%)		
Kim JS	2017	Col	12			10/12 (83%)
Stokholm MG‡	2016	Eso, Sto	147	Eso 4/7 (57%)	Eso 2/16 (13%)	Eso 2/23 (9%)
		SmI, App		Sto 4/10 (40%)	Sto 9/21 (43%)	Sto 5/31 (16%)

		Col		SmI 1/1 (100%) App 2/3 (67%) Col 3/5 (60%)		SmI 6/7 (86%) App 5/5 (100%) Col 4/8 (50%)	SmI 3/8 (38%) App 6/8 (75%) Col 5/13 (38%)
Aldecoa I	2015	Sto, SmI, Col	18	4/6 (67%)			1/12 (8%)
Kurashiki-Osaka T	2014	Sto	1		1/1		
Masuda H	2014	T-Col	1		1/1		
Ito S	2014	Sto, SmI Col, Gal	8	4/6 (67%)		2/2 (100%)	
Sunwoo MK	2013	Sto	32	8/32 (25%)			
Bottner M	2012	Col, Rec	13				11/13 (85%)
Minguez-Castellanos A	2007	Sto, SmI LaI	77				3/77 (4%)
<b>Biopsy</b>							
Chahine LM	2020	S-Col	80	8/59 (14%)			21/21 (100%)
Leclair-Visonneau L	2019 2017	S-Col	43	20/43 (47%)			
Fenyi A	2019	S-Col, Rec	29	S-Col 5/10 (50%) Rec 0/4 (0%)			S-Col 0/1 (0%) Rec 0/2 (0%)
Lee HJ	2018	Sto, A/T/S-Col	77	12/35 (34%)			20/52 (38%)
Barrenschee M	2017	Rec	23	3/12 (25%)			4/11 (36%)
Chung SJ	2016	Sto A/T/S-Col	104	Sto 4/11 (36%) A-Col 2/25 (8%) T-Col 5/24 (21%)			Sto 10/19 (53%) A-Col 5/25 (20%) T-Col 8/36 (22%)

				S-Col 0/18 (0%)		S-Col 2/20 (10%)
Visanji NP	2015	S-Col, Rec	33	22/22 (100%)		9/11 (91%)
Sprenger FS	2015	A/T/D/S-Col	50	1/19 (5%)	4/17 (24%)	0/14 (0%)
Sanchez-Ferro A	2015	Sto	57	17/28 (61%)	1/6 (17%)	1/23 (4%)
Hilton D	2014	Eso, Sto, Gal	223	7/62 (11%)		0/161 (0%)
		SmI, LaI				
Devos D	2013	A-Col	18	12/18 (67%)		
Shannon KM	2012	S-Col	55	9/9 (100%)		Gen 0/23 (0%)
						IBD 0/23 (0%)
Shannon KM	2012	Col	3		3/3 (100%)	
Pouclet H	2012	A/D-Col	35	A-Col 17/26 (65%)		0/9 (0%)
		Rec		D-Col 11/26 (42%)		
				Rec 6/26 (23%)		
Pouclet H	2012	D/S-Col	19	5/9 (56%)		0/10 (0%)
Lebouvier T	2010	A/D-Col	39	21/29 (72%)		0/10 (0%)
Lebouvier T	2008	A-Col	10	4/5 (80%)		0/5 (0%)

*AD*, Alzheimer's disease; *App*, Appendix; *Col*, colon; *D-col*, Descending colon; *Duo*, Duodenum; *Gal*, Gallbladder; *Gen*, General Population; *IBD*, Inflammatory bowel disease; *Ile*, Ileum; *Jej*, Jejunum; *LaI*, Large intestine; *L-Eso*, Lower esophagus; *Liv*, Liver; *M-Eso*, Middle esophagus; *Pan*, Pancreas; *Prec/Prod*, Preclinical/Prodromal; *Rec*, Rectum; *SmI*, Small intestine; *Sto*, Stomach; *S-Col*, Sigmoid colon; *T-Col*, Transverse colon; *U-Eso*, Upper esophagus.

\*Ref. Wakabayashi K, Wakabayashi K, Miki Y (2018) [Multi-Organ Distribution of Alpha-Synuclein Pathology in Dementia with Lewy Bodies]. *Brain Nerve* 70: 489-500 Doi 10.11477/mf.1416201031

†These studies examined the occurrence of LB before the development of phosphorylated  $\alpha$ -synuclein immunohistochemistry.

‡Surgical and biopsy specimens.