

Online Supplement for:

Tau Pathology Influences Dementia Onset and Survival in Lewy Body Spectrum Disorders

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Supplemental Methods:

Patients

Patients were recruited from clinical cores associated with the Udall Center for Excellence in Parkinson's Disease Research at the University of Pennsylvania (Penn) (Penn Parkinson's Disease & Movement Disorders Center, Philadelphia VA Medical Center, Alzheimer's Disease Core Center or Frontotemporal Degeneration Center) or the Pacific Northwest Udall Center (University of Washington, UW) and Oregon Health & Science University) or clinical cores associated with the Alzheimer's Disease Research Centers (ADRCs) at the University of Pittsburgh or Sanders-Brown Center on Aging at the University of Kentucky. All patients met either formal clinical criteria for probable DLB¹ or PDD², as described³ with autopsy confirmation of brainstem, transitional or neocortical stage LBSD synucleinopathy^{1, 4} with varying degrees of co-morbid AD neuropathologic change. The majority of patients had detailed ante mortem clinical characterizations for the onset of Parkinsonism (i.e. bradykinesia with tremor and/or rigidity) and dementia, including assessment of formal clinical diagnostic criteria by the treating physician, as previously described³ and were obtained from clinical databases at each center. The MDI was calculated by subtracting the age at dementia onset from the age at onset of motor parkinsonism. Thus, some DLB patients have negative values for this variable if dementia preceded motor symptoms. Overall survival was calculated by subtracting the age at the onset of the presenting syndrome of disease (i.e. disease onset characterized by motor parkinsonism and/or dementia) from the age at death. In a subset of cases (n=66) these data were extracted from the clinical records by an experienced clinician (DJI, KL). A subset of neuropathologic and genetic data presented here were previously reported on a subset of patients in a different analysis of PDD³ and/or the frequency of genetic variants in LBSD compared with controls (n=103)^{5, 6}. All procedures were performed in accordance with local IRB guidelines and approvals at each center. *Neuropathological Data*

As part of the neuropathologic assessment at each center, slides were immunostained with well-characterized antibodies or histochemically stained using accepted methods⁴ to detect NFTs, neuritic plaques (NPs) and SYN pathology and graded on an ordinal scale (0=none/rare, 1=mild, 2=moderate, 3=severe).⁴ NFTs and SYN pathology were detected using immunohistochemistry (IHC) for phosphorylated tau, and alpha-synuclein, respectively, at each center. NPs were detected using accepted protocols⁴ including IHC for phosphorylated tau (UW=38, UK=14) or histochemical staining using Thioflavin-S (PENN=133), Bielschowsky silver stain (PITT=15), or a combination of IHC and silverstain (OHSU=13). We examined the following regions: ventromedial temporal lobe (average of amygdala, hippocampus entorhinal cortex, hippocampal cornu ammonis), superior-mid temporal cortex, mid-frontal cortex, anterior cingulate gyrus, and angular gyrus. The cerebral score for each pathologic change was calculated as the average of these five regions, as previously described³. Braak and CERAD scores were assigned according to criteria⁴. Since occipital cortex was not routinely sampled we used the density of tau pathology in the hippocampal sub-fields and neocortex to determine Braak V-VI. We modified AA/NIA Neuropathologic Criteria for AD⁴ neuropathology to classify patients into four groups: 1) No AD neuropathology (i.e. "pure SYN"), 2) "low-level" AD, 3) "intermediate-level" AD and 4) "high-level" AD. We also dichotomized the burden of AD neuropathologic change into SYN+AD (intermediate/high AD) and SYN-AD (no/low AD) groups. Briefly, Braak NFT stage and CERAD NP scores in the following combinations defined these groups: Pure SYN= B0/C0, B1/C0; Low AD= B1/C1-C3, B2/C0-1; Intermediate AD= B2/C2-3, B3/C1; High AD= B3/C2-3.

We assessed for the presence or absence of cerebrovascular disease (CVD) through examination of gross brain for infarcts or the presence of ≥ 2 microinfarcts on examination of hematoxylin and eosin stained slides in 5 standardly sampled regions according to established criteria⁴. We also examined these cases for the presence or absence of hippocampal TDP-43 pathology⁷, argyrophilic grain disease (AGD)⁸ and hippocampal sclerosis (HpScI)⁹. Finally, ordinal scores were separately obtained for SYN dystrophic LNs in CA2/3 of the hippocampus (SYNDN)¹⁰, congophilic angiopathy (CAA) in the midfrontal cortex and for basal ganglia (BG) NFT, NP and SYN pathology.

Statistical Analyses

Continuous variables were assessed for normality using graphical techniques. Normally distributed variables are represented by mean (standard deviation) and analyzed with one-way ANOVA and post-hoc independent t-tests for significant ANOVA results only. Non-normally distributed variables are represented by median (25th, 75th quartile) and analyzed with Kruskal-Wallis and post-hoc Mann-Whitney U analysis for significant results only. Frequency of categorical variables between groups was performed using a chi-square contingency analysis and a post-hoc Mantel-Haenszel test for linear group trend was performed for significant associations only. Genotype frequencies were performed in additive and dominant models with the exception of MAPT haplotype, which was analyzed in a

recessive model, based on the low population frequency of the H2 haplotype. Correlations of cerebral scores with pathological and clinical features was performed using a Spearman correlation. A partial correlation was used to examine the strength of association of individual pathologies with MDI and survival while controlling for co-variables of interest. All analyses were 2-sided ($\alpha=0.05$). We adjusted correlation analyses with $\alpha=0.003$ to correct for multiple comparisons and reduce the likelihood of false positive discovery and performed using STATA v12.1 (Statacorp College station, TX).

Multivariate Regression Modelling

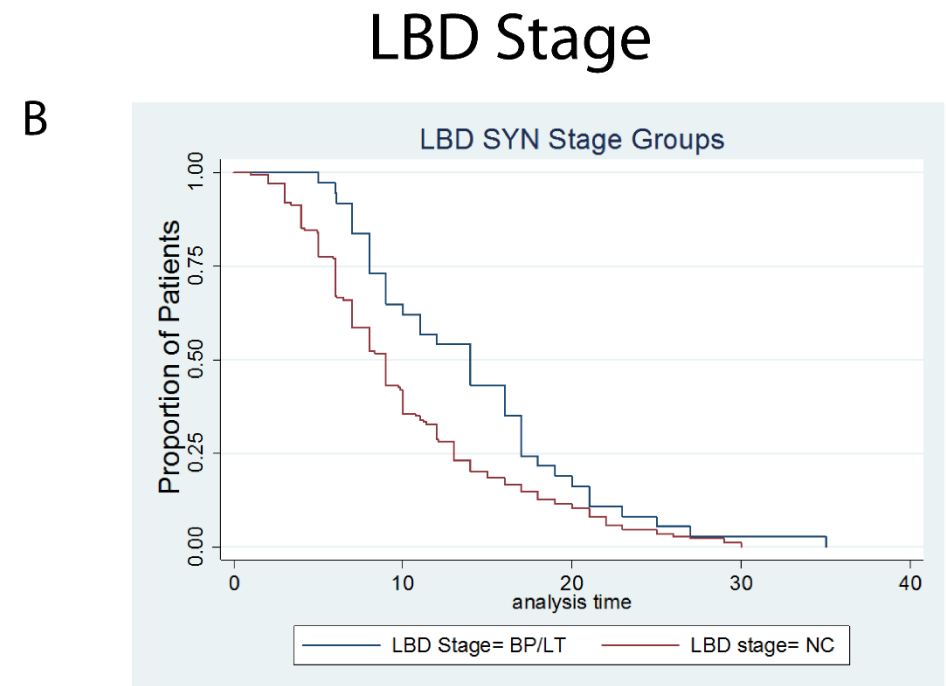
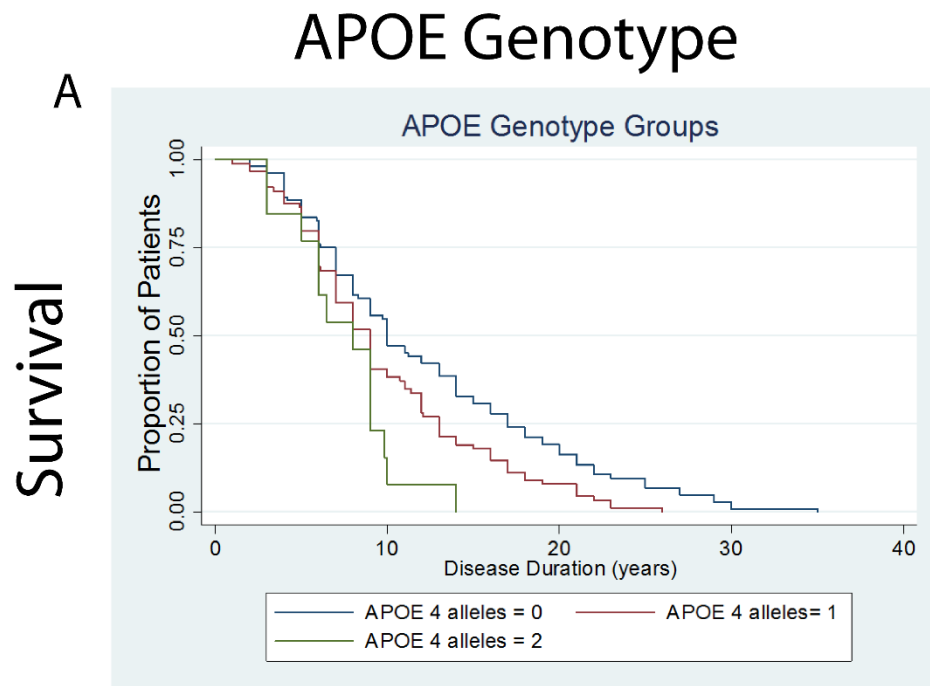
A multivariate linear regression model-building procedure was used to develop a final model to examine the association of independent continuous neuropathological variables (cerebral NFT score, cerebral NP score, cerebral SYN score) with MDI or survival as the dependent variable to test our hypothesis that AD-related pathology influences a shorter time to dementia and death in LBSD. Due to the linear association between these pathological variables and MDI/survival (Fig.3) and because continuous variables have more information than categorical variables, we chose these continuous measures of pathology and did not examine categorical stages of NFTs, NPs and SYN pathology (i.e. Braak, CERAD and Lewy body stages). We also explored the influence of the presence/absence co-morbid CVD pathology associated with LBSD¹¹(CVD). Finally, genetic risk variants associated with LBSD^{5-6,12-13} were examined in a dominant model (*APOE*, *SNCA*, *GBA*) or recessive model (*MAPT*) based on previous genetic associations. We did not include variables with missing data for >20% of the cohort (Limbic TDP-43, *GBA* genotype) or rare categorical variables present in <10% of the cohort (HPScl=17, AGD=3 cases). We did not include ordinal scores for region-specific NFT, NP and SYN pathology (i.e. BG NFT, BG NP, BG SYN, CAA, SYN DN) since these are directly-related to the underlying biological processes for the corresponding cerebral scores. Ordinal variable categories were collapsed when <20% frequency of total cases was present in a stratum (*APOE*). We did not use Cox regression to examine factors influencing survival because there is no censoring in the data. Model assumptions of linear regression models were verified. Examination of the distribution of MDI and survival finds these variables are suitable for linear regression.

We used Bayesian Information Criteria (BIC), along with biological rationale to guide model-building procedures. Variables were kept in the model when they improved BIC values $> 2^{14}$. Co-linearity between variables was tested using variance inflation factor (VIF) with a conservative cut-off of <5 to exclude unstable models due to co-linearity¹⁵. Interaction terms were explored based on known associations of *APOE* genotype and NP pathology¹⁶ and between NFT and SYN pathology³ and tested based on significance of the Wald statistic ($p<0.05$) and improvement on BIC value >2 . Final models were derived through comparison of BIC between models co-varying for age at death and gender: We performed a bootstrapped random patient selection for each final model with 1,000 bootstrap samples to reduce overfitting. This bootstrap procedure serves as an internal validation in the absence of an external validation sample. We report mean beta estimates and 95% CI for each variable from the bootstrapping procedure and adjusted R^2 values.

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Supplemental Figure 1. Comparison of disease duration across APOE genotype and LBD pathology stages. Kaplan-Meier curves depict the proportion of patients surviving at given time points across observed disease duration. There is an incremental dose-effect of burden of APOE 4 genotype (A) and increasing LBD pathological stage (B) for a shorter overall disease duration. Patients with ≥ 1 copies of APOE $\epsilon 4$ had shorter survival compared to those with 0 copies ($p < 0.01$). Patients with NC LBD SYN stage had a shorter survival compared to those with BP/LT ($p < 0.01$). BP=brainstem predominant LBD stage, LT= limbic/transitional LBD stage, NC=neocortical LBD stage.

Supplementary Table 1. Neuropathological Group Data- Dichotomous Classification of AD. Chart depicts neuropathological, genetic and clinical data of group-wise comparisons SYN+AD and SYN-AD subgroups.

	LBD with INT/HIGH AD (SYN+AD) N=108	LBD with NO/LOW AD (SYN-AD) N=105	P Value
Clinical Phenotype	PDD=39 (36.1%) DLB=69 (63.9%)	PDD=76 (72.4%) DLB=29 (27.6%)	<0.001
%Male	65.7%	77.1%	0.06
Brain weight (g)	1279.6 (156.0) N=85	1309.4 (152.7) N=94	0.2
Post-mortem Interval (hours)	10 (5,16.25)	8 (5,15)	0.6
Braak/CERAD	B2/C2=17 B2/C3=25 B3C1=3 B3C2=16 B3/C3=47	B0/C0=8 B1/C0=41 B1/C1=7 B1/C2=16 B1/C3=17 B2/C0=11 B2/C1=5	-
Lewy body Stage	Brainstem=0 Limbic=11 Neocortical=97	Brainstem=4 Limbic=23 Neocortical=78	0.006
VMTL NFT Score	2.7 (2,3) N=105	1.5 (1,2) N=103	<0.001
ACG NFT Score	1 (1,2) N=103	0 (0,0) N=95	<0.001
MFC NFT Score	1 (0,2) N=101	0 (0,0) N=103	<0.001
ANG NFT Score	1 (1,2) N=103	0 (0,0) N=104	<0.001
SMT NFT Score	2 (1,3) N=106	0 (0,0) N=98	<0.001
Global Average NFT Score	1.6 (1.1, 2.2) N=105	0.3 (0.2, 0.6) N=97	<0.001
VMTL NP Score	2 (1.7,2.5) N=104	0 (0,1.3) N=103	<0.001
ACG NP Score	2 (1,3) N=104	0 (0,1) N=100	<0.001
MFC NP Score	2 (2,3) N=105	0 (0,1) N=104	<0.001
ANG NP Score	2 (2,3) N=104	0 (0,1) N=103	<0.001
SMT NP Score	3 (2,3) N=106	0 (0,1.5) N=101	<0.001
Global Average NP Score	2.2 (1.9, 2.7) N=105	0.1 (0,1.4) N=101	<0.001
VMTL SYN Score	2.3 (2.0,2.6) N=103	2.0 (1.6,2.6) N=102	0.2
ACG SYN Score	3 (2,3) N=105	2 (1.3,2) N=96	<0.001
MFC SYN Score	2 (1,2) N=103	1 (0,2) N=103	<0.001
ANG SYN Score	1 (0,1) N=99	2 (1,2) N=98	<0.001
SMT SYN Score	2 (1,3) N=104	1 (0.5,2) N=101	<0.001
Global Average SYN Score	2.0 (1.5,2.5) N=104	1.4 (1.0,2.0) N=98	<0.001
NFT Basal Ganglia	1 (0,1) N=85	0 (0,0) N=90	<0.001
NP Basal Ganglia	0 (0,2) N=85	0 (0,0) N=95	<0.001
SYN Basal Ganglia	1 (1,2) N=88	1 (0,2) N=88	0.007
SYN DN Score	2 (1,3) N=83	2 (1,2) N=91	0.7
Limbic TDP-43 Frequency	19/63 (30.2%)	16/87 (18.4%)	0.09
AGD Frequency	2/95 (2.1%)	1/97 (1.0%)	0.5
HpScl Frequency	8/105 (7.6%)	10/99 (10.1%)	0.5
CVD Frequency	17/103 (16.5%)	18/101 (17.8%)	0.8

CAA Score	1 (0,2) N=83	0 (0,0) N=93	<0.001
<i>APOE</i> 4 Frequency	0= 44/103 (42.7%) 1= 49/103 (47.5%) 2= 10/103 (9.7%)	0= 60/105 (57.1%) 1= 41/105 (39.1%) 2= 4/105 (3.8%)	Add=0.05 Dom=0.04
<i>MAPT</i> H1 Haplotype	H2/H2=3/101 (3.0%) H1/H2=33/101 (32.7%) H1/H1=65/101 (64.3%)	H2/H2=2/101 (2.0%) H1/H2=28/101 (27.7%) H1/H1=71/101 (70.3%)	Dom=0.6 Rec=0.4
<i>SNCA</i> rs356219 Genotype	GG=25/101 (24.8%) GA=62/101 (61.4%) AA=14/101 (13.9%)	GG=28/101 (27.7%) GA=57/101 (56.4%) AA=16/101 (15.8%)	Add=0.7 Rec=0.9
<i>GBA</i> E326K Genotype	GG=73/73 (100%) GA=0 (0%) AA=0	GG=59/67 (88.1%) GA=8/67 (11.9%) AA=0	Add=NA Dom=0.002
<i>GBA</i> Mutation	<u>Positive= 3/79 (3.8%)</u> N370S=2 Rec1=1	<u>Positive=14/78 (17.9%)</u> N370S=6 N370S, R463C=1 Rec1=1 A456P=1 L444P=1 R163X=1 R359X=1 S196P=1 V394L=1	0.004
Age at Onset (years)	70.7 (8.1) N=106	63.3 (11.2) N=105	<0.001
Age at Dementia (years)	76.0 (69.0, 80.0) N=104	73.0 (64.0, 78.0) N=102	0.06
Motor-Dementia Interval (years)	1.88 (6.4) N=88	7.9 (7.9) N=98	<0.001
Age at Death (years)	81.0 (74.3, 85.0) N=108	77.0 (72.0, 81.0) N=105	0.002
Dementia Death Interval (years)	5.0 (3.7) N=104	5.0 (2.7) N=101	0.3
Disease Duration (years)	8.9 (5.4) N=106	13.1 (7.0) N=105	<0.001

Supplemental Table 2. MDI and disease duration for LBSD Neuropathological Groups based on Braak and CERAD stages.

Chart displays MDI and Disease Duration for LBSD patients (PDD/DLB) with increasing A) CERAD and B) Braak Pathology. Bold text denotes significant results.

A	LBSD with CERAD C (C3) N=87	LBSD with CERAD B (C2) N=49	LBSD with CERAD A (C1) N=15	LBSD with CERAD 0 (C0) N=60	P-Value ANOVA
Motor-Dementia Interval (years)	2.2 (6.5) ††, ** N=76	4.0 (5.9) ††	8.4 (8.9) N=14	8.5 (8.7) N=59	<0.001
Disease Duration (years)	9.3 (5.8) †† N=87	9.3 (5.2) ††	11.8 (7.5) N=15	14.5 (7.3) N=60	<0.001
B	LBSD with Braak V-VI (B3) N=64	LBSD with Braak III-IV (B2) N=58	LBSD with Braak I-II (B1) N=81	LBSD with Braak 0 (B0) N=8	P-Value ANOVA
Motor-Dementia Interval (years)	1.3 (6.2) ††, **, # N=51	4.1 (8.4) †† * N=52	7.7 (7.2) N=75	10.6 (8.6) N=8	<0.001
Disease Duration (years)	8.1 (5.1) ††, **, ## N=64	10.5 (6.8) †* N=58	13.0 (6.7) N=81	16.8 (4.8) N=8	<0.001

†† p≤0.01, † p<0.05 compared to C0/B0

** p<0.01, *p<0.04 compared to C1/B1

p<0.03, # p≤0.05 compared to B2

Supplementary Table 3. Neuropathological Group Data PDD/DLB clinical groups. Chart depicts neuropathological, genetic and clinical data of group-wise comparisons of PDD and DLB clinical subgroups.

	DLB N=98	PDD N=115	P Value
Proportion Male	64/98	88/115	0.07
Brain weight (g)	1279.6 (156.0) N=85	1309.4 (152.7) N=94	
Post-mortem Interval (hours)	8 (4,14) N=72	11 (6,17) N=109	
Braak/CERAD	B0/C0=1 B1/C0=9 B1/C1=0 B1/C2=5 B1/C3=6 B2/C0=5 B2/C1=3 B2/C2=6 B2/C3=15 B3C1=2 B3C2=14 B3/C3=32	B0/C0=7 B1/C0=32 B1/C1=7 B1/C2=11 B1/C3=11 B2/C0=6 B2/C1=2 B2/C2=11 B2/C3=10 B3/C1=1 B3/C2=2 B3/C3=15	<0.001
Lewy body Stage	Brainstem=2 Limbic=9 Neocortical=87	Brainstem=2 Limbic=25 Neocortical=88	0.05
VMTL NFT Score	2.7 (1.7,3) N=94	2 (1.2,3) N=114	<0.001
ACG NFT Score	1 (0,2) N=94	0 (0,1) N=104	<0.001
MFC NFT Score	1 (0,2) N=93	0 (0,0) N=111	<0.001
ANG NFT Score	1 (0,2) N=94	0 (0,0.5) N=113	<0.001
SMT NFT Score	2 (1,3) N=94	0 (0,1) N=110	<0.001
Global Average NFT Score	1.4 (0.7, 2.2) N=95	0.5 (0.3, 1) N=107	<0.001
VMTL NP Score	2 (1.2,3) N=95	2 (1.2,3) N=112	<0.001
ACG NP Score	2 (0,2) N=94	1 (0,2) N=110	0.3
MFC NP Score	2 (1,3) N=96	1 (0,2) N=113	<0.001
ANG NP Score	2 (1,3) N=94	1 (0,2) N=113	<0.001
SMT NP Score	2 (2,3) N=95	1 (0,3) N=112	<0.001
Global Average NP Score	2 (1.3, 2.7) N=96	1.1 (0.2,2) N=110	<0.001
VMTL SYN Score	2.3 (2.0,2.7) N=92	2.0 (1.7,2.4) N=113	0.02
ACG SYN Score	3 (2,3) N=94	2 (2,2) N=107	0.2
MFC SYN Score	1 (1,2) N=92	1 (1,2) N=114	0.1
ANG SYN Score	1.5 (1,2) N=90	1 (0,2) N=107	<0.001
SMT SYN Score	2 (1,3) N=93	1 (1,2) N=113	<0.001
Global Average SYN Score	1.9 (1.5,2.5) N=93	1.4 (1.0,2.0) N=98	<0.001
NFT Basal Ganglia	1 (0,1) N=72	0 (0,1) N=103	0.028
NP Basal Ganglia	0 (0,1) N=72	0 (0,0.7) N=108	0.09
SYN Basal Ganglia	1 (1,2) N=73	1 (0,2) N=103	0.026
SYN DN Score	2 (1,3) N=66	1 (1,2) N=108	0.001
Limbic TDP-43 Frequency	15/51	20/99	0.2
AGD Frequency	1/88	2/104	0.6
HpScI Frequency	8/93	10/111	0.4
CVD Frequency	14/94	21/110	0.4

CAA Score	1 (0,1) N=67	0 (0,1) N=109	<0.001
APOE 4 Frequency	0= 42/95 1= 41/95 2= 12/95	0= 62/113 1= 49/113 2= 2/113	0.006
MAPT H1 Haplotype	H2/H2=2/92 H1/H2=30/92 H1/H1=60/92	H2/H2=3/110 H1/H2=31/110 H1/H1=76/110	0.8
SNCA rs356219 Genotype	GG=30/92 GA=67/92 AA=20/92	GG=23/110 GA=67/110 AA=20/110	0.1
GBA E326K Genotype	GG=65/68 GA=3/68 AA=0	GG=67/72 GA=5/72 AA=0	0.5
GBA Mutation	7/65 positive	10/92 positive	0.9
Age at Onset (years)	71.9 (9.0) N=96	63.0 (9.8) N=115	<0.001
Age at Dementia (years)	71.0 (66.5, 79.5) N=97	74.0 (69.5, 80.0) N=109	0.4
Motor-Dementia Interval (years)	-2.2 (2.6) N=77	10.1 (6.1) N=109	<0.001
Age at Death (years)	80 (72, 85.0) N=98	79.0 (74.0, 82.0) N=115	0.4
Dementia Death Interval (years)	6.0 (4,8) N=96	3.0 (2,6) N=115	<0.001
Disease Duration (years)	6.6 (2.7) N=96	14.6 (6.7) N=115	<0.001

Supplemental Table 4• Characteristics of Clinical DLB cases with Pure SYN Pathology. Chart depicts data from subset of rare cases with DLB clinical phenotype and pure SYN neuropathology. Shaded/bolded cells indicate presence of pathological/genetic co-morbidities

Case	Age at Onset	Age at Death	MDI	Disease Duration	Gender	Braak Stage	CERAD stage	LBD Stage	APOE Genotype	GBA Mutation Status	GBA E326K Genotype	CVD	AGD	HpScl	TDP
1	50	57	-3	7	M	0	0	NC	3/3	R163X	GG	No	No	No	No
2	63	73	-3	10	M	1	0	NC	3/3	Negative	GG	No	No	No	No
3	52	61	1	9	M	1	0	NC	4/4	Rec1	GG	No	No	No	No
4	49	60	-6	11	M	1	0	NC	3/4	Negative	GA	No	No	No	No
5	62	68	-4	6	M	1	0	NC	3/3	N370S	GG	No	No	No	No
6	68	76	0	8	M	1	0	BP	3/3	NA	NA	YES	No	No	No
7	68	76	-8	8	M	1	0	NC	3/3	Negative	GA	No	No	No	No
8	76	83	0	7	M	1	0	NC	3/4	NA	NA	No	NA	No	NA
9	77	80	0	3	M	1	0	NC	3/4	Negative	GG	No	No	No	NA
10	68	75	0	7	M	1	0	NC	3/4	Negative	GG	No	NA	No	NA

NC= neocortical LBD stage, BP= brainstem predominant stage, NA=not available.

Supplemental Table 5. Linear regression models to predict the motor-dementia interval in Lewy body spectrum disorders. Chart displays univariate associations between neuropathological and genetic variables with the timing of dementia (MDI) in LBSD (PDD/DLB) in the upper panel. The lower panel displays the variables surviving the final multivariate model with beta estimates generated from bootstrapping sampling procedure with 1,000 bootstrap samples. Based on 158 observations.

Univariate Models				
Variable	Beta (95% CI)	t-value (df)	p-value	R ²
Cerebral Tau score (cont.)	-4.1 (-5.4, -2.9)	-6.6 (1)	<0.0001	0.20
Cerebral NP score (cont.)	-2.5 (-3.5, -1.6)	-5.1 (1)	<0.0001	0.12
Cerebral SYN score (cont.)	-3.1 (-4.7, -1.6)	-4.0 (1)	<0.0001	0.08
CVD (categorical)	1.9 (-1.2, 5.0)	1.2 (1)	0.217	0.003
APOE 4 (≥ 1 allele)	-2.4 (-4.6, -0.1)	-2.0 (1)	0.044	0.02
SNCA rs356219 (≥ 1 risk allele "A")	1.1 (-1.6, 3.9)	0.8 (1)	0.421	0.004
MAPT (H1/H1 haplotype)	-0.3 (-2.9, 2.2)	-0.3 (1)	0.792	0.0004
Age at Death	0.04 (-0.1, 0.2)	0.6 (1)	0.535	0.002
Gender	0.5 (-2.1, 3.2)	0.4 (1)	0.702	0.0008
Final Multivariate Model				
Variable	Beta (95% CI)	t-value (df)	p-value	R ²
Cerebral Tau score (cont.)	-4.0 (-5.5, -2.6)	-4.6 (8)	<0.0001	
Cerebral NP score (cont.)	-0.6 (-2.0, 0.8)	-0.9 (8)	0.400	
Cerebral SYN score (cont.)	-0.2 (-2.1, 1.4)	-0.2 (8)	0.830	
CVD (categorical)	1.7 (-1.4, 4.7)	1.1 (8)	0.290	
APOE 4 (≥ 1 allele)	-0.3 (-2.5, 2.0)	-0.3 (8)	0.807	
MAPT (H1/H1 haplotype)	0.3 (-2.2, 3.0)	0.3 (8)	0.829	
Age at Death	0.2 (0.002, 0.3)	2.0 (8)	0.05	
Gender	0.9 (-1.7, 3.3)	0.6 (8)	0.508	
Intercept	-3.5 (-18.3, 9.4)	-0.5 (8)	0.608	0.22

Supplemental Table 6. Linear regression models to predict survival in Lewy body spectrum disorders.

Chart displays univariate associations between neuropathological and genetic variables with overall survival in LBSD (PDD/DLB) in the upper panel. The lower panel displays the variables surviving the final multivariate model with beta estimates generated from bootstrapping sampling procedure with 1,000 bootstrap samples. Based on 175 observations.

Univariate Models				
Variable	Beta (95% CI)	t-value (df)	p-value	R ²
Cerebral Tau score (cont.)	-2.8 (-3.8, -1.8)	-5.4 (1)	<0.0001	0.13
Cerebral NP score (cont.)	-1.9 (-2.8, -1.1)	-4.7 (1)	<0.0001	0.09
Cerebral SYN score (cont.)	-2.6 (-3.9, -1.3)	-4.1 (1)	<0.0001	0.07
CVD (categorical)	2.0 (-0.5, 4.4)	1.6 (1)	0.114	0.01
APOE 4 (≥ 1 allele)	-2.7 (-4.5, -0.9)	-3.0 (1)	0.003	0.04
SNCA rs356219 (≥ 1 risk allele "A")	0.6 (-1.6, 2.7)	0.5 (1)	0.604	0.001
MAPT (H1/H1 haplotype)	-0.1 (-2.1, 1.9)	-0.1 (1)	0.912	0.0001
Age at Death	-0.02 (-0.1, 0.1)	-0.3 (1)	0.731	0.0006
Gender	0.2 (-1.8, 2.2)	0.2 (1)	0.877	0.0001
Final Multivariate Model				
Variable	Beta (95% CI)	t-value (df)	p-value	R ²
Cerebral Tau score (cont.)	-2.0 (-3.1, -0.8)	-2.7 (8)	0.003	
Cerebral NP score (cont.)	-1.0 (-2.2, 0.3)	-1.7 (8)	0.134	
Cerebral SYN score (cont.)	-0.4 (-2.2, 1.1)	-0.5 (8)	0.614	
CVD (categorical)	1.8 (-1.5, 4.6)	1.3 (8)	0.268	
APOE 4 (≥ 1 allele)	-1.7 (-3.6, 0.1)	-1.8 (8)	0.075	
MAPT (H1/H1 haplotype)	0.5 (-1.5, 2.6)	0.5 (8)	0.634	
Age at Death	0.01 (-0.1, 0.1)	0.2 (8)	0.865	
Gender	1.1 (-1.1, 3.5)	1.0 (8)	0.351	
Intercept	13.3 (2.9, 24.4)	2.5 (8)	0.023	0.15