

Supplementary Table 1: 3R-4R Tau and TDP-43 assay validation parameters in plasma sEV and mEV

3R and 4R Tau Assay Validation					TDP-43 Assay Validation	
Parameters	sEV 3R Tau	mEV 3R Tau	sEV 4R Tau	mEV 4R Tau	sEV TDP-43	mEV TDP-43
LLOQ (conc) pg/mL	102.85	119.08	122.54	132.89	8.56	7.78
Avg % Linearity	101.30	103.30	109.03	100.32	103.65	111.02
Mean % Recovery	101.24	95.69	99.84	96.25	97.95	104.40
Avg % Parallelism	110.18	112.71	106.55	104.08	99.38	109.64
CV (%) for intra-assay precision	6.59	6.54	3.38	3.21	4.78	5.32
CV (%) for inter-assay precision	7.95	7.63	4.54	4.39	5.21	6.60

Supplementary Table 2: Two-sided Spearman correlation between EV 3R/4R Tau ratio, age, sex and disease duration in DESCRIBE subcohort 1

Parameters	Spearman r values	p values
	sEV 3R/4R Tau ratio	sEV 3R/4R Tau ratio
Age	0.089	0.185
Sex	0.063	0.123
Disease duration	0.056	0.147

Subcohort 1	AUC	SE ^a	95% CI ^b	<i>p</i> value	Subcohort 2	AUC	SE ^a	95% CI ^b	<i>p</i> value
bvFTD vs. AD									
sEV 3R/4R Tau Ratio	0.90	0.001	0.896 to 0.995	0.000033					
bvFTD vs. svPPA									
sEV 3R/4R Tau Ratio	0.95	0.000	0.901 to 0.975	0.000023					
					ALS vs HC				
					sEV TDP-43 (pg/mL)	0.99	0.003	0.972 to 1.000	0.000022
					mEV TDP-43 (pg/mL)	0.92	0.020	0.866 to 0.952	0.00004
					Plasma Nfl (pg/mL)	0.80	0.030	0.766 to 0.880	0.0157
					sEV and Plasma Nfl AUC comparison		0.032	0.107 to 0.228	0.000035
					mEV and Plasma Nfl AUC comparison		0.041	0.126 to 0.232	0.000051
					ALS vs. PSP				
					sEV TDP-43 (pg/mL)	0.99	0.003	0.980 to 1.000	0.000055
					mEV TDP-43 (pg/mL)	0.94	0.013	0.909 to 0.967	0.00002
					Plasma Nfl (pg/mL)	0.61	0.034	0.557 to 0.673	0.368
					sEV and Plasma Nfl AUC comparison		0.034	0.312 to 0.447	0.00002
					mEV and Plasma Nfl AUC comparison		0.036	0.254 to 0.398	0.00005
					ALS vs. bvFTD				
					sEV TDP-43 (pg/mL)	0.91	0.016	0.878 to 0.943	0.000043
					mEV TDP-43 (pg/mL)	0.88	0.018	0.841 to 0.916	0.000085
					Plasma Nfl (pg/mL)	0.60	0.032	0.550 to 0.661	0.268
					sEV and Plasma Nfl AUC comparison		0.036	0.237 to 0.378	0.00009

Subcohort 2				
	AUC	SE ^a	95% CI ^b	<i>p</i> value
ALS vs. bvFTD				
mEV and Plasma Nfl AUC comparison		0.023	0.202 to 0.349	0.00004
bvFTD vs. HC				
sEV TDP-43 (pg/mL)	0.85	0.0001	0.825 to 0.901	0.00047
mEV TDP-43 (pg/mL)	0.80	0.0015	0.783 to 0.853	0.00002
Plasma Nfl (pg/mL)	0.72	0.055	0.712 to 0.751	0.235
sEV and Plasma Nfl AUC comparison		0.042	0.034 to 0.203	0.005
mEV and Plasma Nfl AUC comparison		0.049	0.026 to 0.169	0.045
bvFTD vs. PSP				
sEV TDP-43 (pg/mL)	0.93	0.000245	0.865 to 0.890	0.00007
mEV TDP-43 (pg/mL)	0.85	0.0353	0.783 to 0.848	0.00004
Plasma Nfl (pg/mL)	0.63	0.0055	0.612 to 0.713	0.235
sEV and Plasma Nfl AUC comparison		0.041	0.202 to 0.169	0.00008
mEV and Plasma Nfl AUC comparison		0.049	0.209 to 0.153	0.00004

^a Hanley & McNeil. 1982¹

^b Binomial exact

SE: Standard Error

95% CI: 95% Confidence Interval

Paired t-test

1. Hanley, J. A. & McNeil, B. J. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* **148**, 839-843 (1983). <https://doi.org/10.1148/radiology.148.3.6878708>

Supplementary Table 4: Two-sided Spearman correlation between EV 3R/4R Tau ratio with clinical and neuropsychological and clinical scales in DESCRIBE subcohort 1: PSP cases

Parameters	Spearman <i>r</i> values	<i>p</i> values
	sEV 3R/4R Tau Ratio	sEV 3R/4R Tau Ratio
MMSE	0.213	0.017
MoCA	0.468	0.0034
NPI-Q	-0.334	0.053
FAQ	-0.030	0.881
PSP-RS	-0.497	0.0007
PSP-SS	-0.512	0.0005
PSP-CDS	-0.402	0.0001
UPDRS-III	-0.551	0.0001
SAS	-0.345	0.002
SEADL	0.591	2.92067E-05
CGIs	-0.597	3.76451E-05
FAB	-0.355	0.02
PSP-QoL	-0.613	1.20461E-05
Plasma Nfl	-0.436	0.012

Bold values denote statistical significance at the $p < 0.05$ level.

Supplementary Table 5: Two-sided Spearman correlation between EV 3R/4R Tau ratio with clinical and neuropsychological scales in DESCRIBE subcohort 1: bvFTD cases

	Spearman <i>r</i> values	<i>p</i> values
Parameters	sEV 3R/4R Tau Ratio	sEV 3R/4R Tau Ratio
MMSE	-0.618	0.00001
MoCA	-0.667	0.00014
NPI-Q	0.445	0.0039
FAQ	0.512	0.00085
CDR-SB	0.523	0.00053
CDR plus NACC FTLD	0.503	0.00063
CBI-M	0.618	2.07836E-05
Plasma Nfl	0.512	0.00068

Bold values denote statistical significance at the $p < 0.05$ level.

Supplementary Table 6: Two-sided Spearman correlation between CSF and plasma EV tau results in DESCRIBE subcohort 1

	Spearman <i>r</i> values			<i>p</i> values		
	CSF sEV 3R Tau	CSF sEV 4R Tau	CSF sEV 3R/4R Tau ratio	CSF sEV 3R Tau	CSF sEV 4R Tau	CSF sEV 3R/4R Tau ratio
Plasma sEV 3R Tau	0.240	-0.396	0.389	0.02	0.02	0.02
Plasma sEV 4R Tau	-0.065	0.030	0.006	0.52	0.87	0.98
Plasma sEV 3R/4R Tau ratio	0.193	-0.339	0.278	0.06	0.05	0.12
Bold values denote statistical significance at the $p < 0.05$ level.						
Detected CSF EV samples: CSF sEV 3R Tau n=100. CSF sEV 4R Tau n=34.						

Supplementary Table 7: Two-sided Spearman correlation between EV 3R/4R Tau ratio, EV TDP-43, age, sex and disease duration in DESCRIBE subcohort 2

Parameters	Spearman r values				p values			
	sEV TDP-43	mEV TDP-43	sEV 3R/4R Tau ratio	mEV 3R/4R Tau ratio	sEV TDP-43	mEV TDP-43	sEV 3R/4R Tau ratio	mEV 3R/4R Tau ratio
Age	0.089	0.057	0.102	0.087	0.145	0.524	0.143	0.134
Sex	0.053	-0.041	0.071	0.103	0.102	0.245	0.178	0.254
Disease duration	0.074	0.033	-0.023	-0.038	0.236	0.145	0.224	0.329

Supplementary Table 8: Two-sided Spearman correlation between EV 3R/4R Tau ratio, EV TDP-43 and clinical and neuropsychological scales in DESCRIBE subcohort 2: PSP cases

Parameters	Spearman <i>r</i> values				<i>p</i> values			
	sEV TDP-43	mEV TDP-43	sEV 3R/4R Tau ratio	mEV 3R/4R Tau ratio	sEV TDP-43	mEV TDP-43	sEV 3R/4R Tau ratio	mEV 3R/4R Tau ratio
MMSE	0.062	0.0495	0.386	0.303	0.654	0.724	0.003	0.039
MoCA	0.056	-0.070	0.363	0.306	0.538	0.445	0.002	0.039
NPI-Q	0.023	0.020	-0.367	-0.362	0.176	0.235	0.024	0.029
FAQ	0.013	0.018	0.0512	0.066	0.268	0.146	0.499	0.460
PSP-RS	-0.007	0.030	-0.304	-0.377	0.930	0.730	0.002	0.003
PSP-SS	0.011	-0.037	-0.383	-0.391	0.893	0.669	0.030	0.002
PSP-CDS	0.006	-0.002	-0.365	-0.241	0.588	0.236	0.006	0.002
UPDRS	0.010	-0.052	-0.225	-0.237	0.229	0.559	0.017	0.011
SAS	-0.046	-0.065	-0.387	-0.346	0.465	0.365	0.002	0.019
SEADL	-0.022	-0.042	0.390	0.396	0.791	0.623	0.002	0.002
CGIs	-0.012	0.032	-0.226	-0.189	0.883	0.995	0.027	0.029
FAB	0.062	-0.095	-0.194	-0.134	0.515	0.320	0.031	0.041
PSP-QoL	-0.088	-0.063	-0.306	-0.320	0.403	0.546	0.030	0.002
Plasma NfI	-0.006	-0.011	-0.373	-0.352	0.941	0.178	0.013	0.025

Bold values denote statistical significance at the $p < 0.05$ level.

Supplementary Table 9: Two-sided Spearman correlation between EV 3R/4R Tau ratio, EV TDP-43 and clinical and neuropsychological scales in DESCRIBE subcohort 2: bvFTD cases

Parameters	Spearman <i>r</i> values				<i>p</i> values			
	sEV TDP-43	mEV TDP-43	sEV 3R/4R Tau ratio	mEV 3R/4R Tau ratio	sEV TDP-43	mEV TDP-43	sEV 3R/4R Tau ratio	mEV 3R/4R Tau ratio
MMSE	-0.301	-0.259	-0.220	-0.242	0.031	0.0423	0.034	0.031
MoCA	-0.332	-0.322	-0.253	-0.234	0.026	0.0318	0.029	0.022
NPI-Q	0.292	0.103	0.561	0.363	0.005	0.006	0.003	0.002
FAQ	0.281	0.257	0.371	0.254	0.001	0.004	0.003	0.003
CDR-SB	0.274	0.209	0.330	0.379	0.021	0.029	0.003	0.002
CDR plus NACC FTLD	0.461	0.371	0.391	0.469	0.001	0.0002	0.001	0.001
CBI-M	0.343	0.284	0.349	0.314	0.001	0.007	0.001	0.002
Plasma Nfl	0.234	0.22	0.347	0.316	0.002	0.0004	0.005	0.0002

Bold values denote statistical significance at the $p < 0.05$ level.

Supplementary Table 10: Descriptive data of mutations in bvFTD and ALS

Mutations (n=37)	Clinical Diagnosis	Mutation types
<i>C9orf72</i>	bvFTD (n=13), ALS (n=5)	hexanucleotide (G4C2) _n repeat expansion
<i>GRN</i>	bvFTD (n=4)	Pathogenic/p.Val8vs Pathogenic/p.Cys26 Pathogenic/p.Ser226fs Pathogenic/p.Met142fs
<i>VCP</i>	bvFTD (n=4)	Pathogenic/p.Gly157Arg Pathogenic/p.Arg95Cys Pathogenic/p.Gly159Arg Pathogenic/p.Gly157Arg
<i>*TBK1</i>	bvFTD (n=1) ALS (n=1)	Potentially Pathogenic/p.Leu555Ter Potentially Pathogenic/p.Glu643del
<i>*MAPT</i>	bvFTD (n=3)	Pathogenic/P301L Pathogenic/P364S Pathogenic/IVS 10+16 C>T
<i>CHCHD10</i>	bvFTD (n=1) ALS (n=1)	Pathogenic/p.Ser59Leu Pathogenic/p.Arg15Leu
<i>*SOD-1</i>	ALS (n=2)	Pathogenic/p.Gly115Ser Pathogenic/p.Leu145Phe
<i>FUS</i>	ALS (n=2)	Pathogenic/p.Pro525Leu Pathogenic/p.Ser57Del
*2 <i>TBK1</i> , 1 <i>MAPT</i> , 1 <i>CHCHD10</i> , and 1 <i>SOD-1</i> mutation carriers with autopsy confirmed diagnosis		

Supplementary Table 11: Descriptive data of neuropathological diagnoses in ALS, bvFTD, and PSP

Neuropathological diagnosis	ADNC	Lewy pathology stage	Other neuropathological findings	Gene mutation	Clinical diagnosis
ALS-TDP	A3, B2, C2		CAA		ALS
ALS-TDP	A1, B2, C0		CAA		ALS
ALS-TDP	A0, B2, C0				ALS
ALS-TDP	A0, B1, C0				ALS
ALS-TDP	A1, B1, C0		CAA		ALS
ALS-TDP	A0, B1, C0				ALS
ALS-TDP	A1, B2, C0		ARTAG		ALS
ALS-TDP	A1, B1, C0				ALS
ALS-TDP	A1, B1, C0				ALSci
ALS-TDP	A0, B2, C0		CAA		ALSci
ALS-TDP	A1, B1, C0				ALS
ALS-TDP	A1, B1, C0	brainstem predominant			ALS
ALS-TDP	A0, B0, C0				ALS
ALS-TDP	A0, B1, C0	brainstem predominant			ALSci
ALS-TDP	A1, B1, C0				ALS
ALS-TDP	A0, B1, C0	brainstem predominant	CAA		ALS
ALS-TDP	A1, B2, C0			<i>TBKI</i>	ALS
ALS/FTLD-TDP (subtype B)	A1, B1, C0		CAA		ALSci
ALS/FTLD-TDP (subtype B)	A1, B1, C0				bvFTD+ALS
ALS/FTLD-TDP (subtype B)	A1, B2, C1		B cell lymphoma, CAA		ALSci
ALS/FTLD-TDP (subtype B)	A0, B0, C0		granulomatous angiitis		ALSci/ALSbi
ALS/FTLD-TDP (subtype B)	A0, B1, C0	brainstem predominant			ALS+PPA
ALS/FTLD-TDP (subtype B)	A0, B1, C0				bvFTD
FTLD-TDP (subtype A)	A1, B1, C0			<i>TBKI</i>	bvFTD
FTLD-Tau (GGT type)	A2, B1, C1		CAA		ALSbi
FTLD-Tau (<i>MAPT</i> mutation)	A1, BX, C0		CAA	<i>MAPT P301L</i>	bvFTD
PSP	A0, B0, C0				PSP (possible)
PSP	A2, B1, C0		AGD, ATRAG		PSP (probable)
PSP	A3, B2, C1		AGD		PSP (possible)
ALS-SOD1	A1, B1, C0		CAA	<i>SOD-1</i>	ALSci
ALS-UPS	A1, B1, C0	none		<i>CHCHD10</i>	ALS

ADNC, Alzheimer disease neuropathological change; AGD, argyrophilic grain disease; ALS, amyotrophic lateral sclerosis; ALSci, amyotrophic lateral sclerosis, cognitively impaired; ALSbi, amyotrophic lateral sclerosis, behaviorally impaired; ALS-TDP, ALS with TDP-43 pathology; ALS-SOD1, ALS due to SOD1 mutation; ALS-UPS, ALS with TDP-43/tau/FUS negative inclusions positive for markers of ubiquitin-proteasome system; ARTAG, aging related tau astroglipathy; CAA, cerebral amyloid angiopathy; CBD, corticobasal degeneration; FTLD-tau, frontotemporal lobar degeneration with tau pathology; FTLD-TDP, frontotemporal lobar degeneration with TDP-43 pathology; PPA, primary progressive aphasia; svPPA, semantic variant of PPA; bvFTD, behavioral variant of FTD. PSP, progressive supranuclear palsy;

Supplementary Table 13: Two-sided Spearman correlation between EV 3R/4R Tau ratio, age, sex, and disease duration in Sant Pau cohort

Parameters	Spearman <i>r</i> values		<i>p</i> values	
	sEV 3R/4R Tau ratio	sEV TDP-43	sEV 3R/4R Tau ratio	sEV TDP-43
Age	0.005	0.087	0.256	0.274
Sex	0.075	0.096	0.345	0.330
Disease duration	0.023	0.156	0.145	0.089

Supplementary Table 14: The receiver operating characteristic area under the curve of diagnostic groups for EV 3R/4R Tau ratio and EV TDP-43 levels

Sant Pau cohort	AUC	SE ^a	95% CI ^b	<i>p</i> value
PSP vs. HC				
sEV 3R/4R Tau Ratio	1.00	0.000	0.960 to 1.000	0.00004
mEV 3R/4R Tau Ratio	1.00	0.000	0.960 to 1.000	0.00001
sEV and mEV AUC comparison		0.035	-0.020 to 0.154	0.123
PSP vs ALS				
sEV 3R/4R Tau Ratio	0.99	0.0002	0.962 to 1.000	0.00007
mEV 3R/4R Tau Ratio	0.94	0.0023	0.881 to 0.980	0.000023
sEV and mEV AUC comparison		0.036	-0.023 to 0.036	0.254
PSP vs ALS-FTD				
sEV 3R/4R Tau Ratio	0.98	0.0149	0.937 to 0.999	0.000052
mEV 3R/4R Tau Ratio	0.93	0.0253	0.870 to 0.976	0.000044
sEV and mEV AUC comparison		0.0456	-0.0032 to 0.076	0.231
PSP vs bvFTD				
sEV 3R/4R Tau Ratio	1.00	0.000	0.969 to 1.000	0.000056
mEV 3R/4R Tau Ratio	1.00	0.000	0.969 to 1.000	0.000012
sEV and mEV AUC comparison		0.085	-0.051 to 0.110	0.114
bvFTD vs HC				
sEV 3R/4R Tau Ratio	0.95	0.0163	0.905 to 0.985	0.000032
mEV 3R/4R Tau Ratio	0.96	0.0254	0.918 to 0.990	0.000014
sEV and mEV AUC comparison		0.0751	-0.041 to 0.230	0.420
bvFTD vs ALS				
sEV 3R/4R Tau Ratio	0.90	0.0239	0.845 to 0.948	0.000047
mEV 3R/4R Tau Ratio	0.93	0.0135	0.875 to 0.966	0.00003
sEV and mEV AUC comparison		0.0441	-0.017 to 0.135	0.118
bvFTD vs ALS-FTD				
sEV 3R/4R Tau Ratio	0.96	0.0140	0.920 to 0.990	0.00001
mEV 3R/4R Tau Ratio	0.97	0.0125	0.931 to 0.994	0.00004
sEV and mEV AUC comparison		0.046	-0.017 to 0.141	0.144
Sant Pau cohort				
	AUC	SE ^a	95% CI ^b	<i>p</i> value
ALS vs HC				
sEV TDP-43 (pg/mL)	0.94	0.0184	0.892 to 0.981	0.00007
mEV TDP-43 (pg/mL)	0.93	0.241	0.867 to 0.969	0.00001
sEV and mEV AUC comparison		0.051	-0.017 to 0.135	0.532
ALS vs. ALS-FTD				
sEV TDP-43 (pg/mL)	0.58	0.0519	0.491 to 0.673	0.1051
mEV TDP-43 (pg/mL)	0.56	0.0523	0.476 to 0.658	0.186
sEV and mEV AUC comparison		0.046	-0.017 to 0.245	0.148
ALS vs. PSP				

sEV TDP-43 (pg/mL)	0.96	0.0147	0.910 to 0.991	0.00004
mEV TDP-43 (pg/mL)	0.96	0.0151	0.910 to 0.991	0.00007
sEV and mEV AUC comparison		0.055	-0.021 to 0.125	0.117
ALS vs. bvFTD				
sEV TDP-43 (pg/mL)	0.76	0.0376	0.687 to 0.832	0.000045
mEV TDP-43 (pg/mL)	0.76	0.0393	0.691 to 0.835	0.000023
sEV and mEV AUC comparison		0.052	-0.021 to 0.120	0.432
bvFTD vs HC				
sEV TDP-43 (pg/mL)	0.87	0.0311	0.803 to 0.926	0.00004
mEV TDP-43 (pg/mL)	0.82	0.0365	0.744 to 0.884	0.00007
Plasma Nfl (pg/mL)	0.78	0.0265	0.734 to 0.842	0.003
sEV and mEV TDP-43 AUC comparison		0.062	-0.045 to 0.121	0.632
sEV and Plasma Nfl AUC comparison		0.0312	0.116 to 0.21	0.00008
mEV and Plasma Nfl AUC comparison		0.016	0.112 to 0.156	0.00007
bvFTD vs. ALS-FTD				
sEV TDP-43 (pg/mL)	0.82	0.0353	0.745 to 0.881	0.00001
mEV TDP-43 (pg/mL)	0.81	0.0363	0.736 to 0.874	0.00004
sEV and mEV AUC comparison		0.0785	-0.012 to 0.187	0.119
bvFTD vs. PSP				
sEV TDP-43 (pg/mL)	0.91	0.0260	0.851 to 0.959	0.00007
mEV TDP-43 (pg/mL)	0.89	0.0273	0.830 to 0.947	0.00009
Plasma Nfl (pg/mL)	0.71	0.0365	0.689 to 0.789	0.0874
sEV and mEV AUC comparison		0.063	-0.046 to 0.176	0.896
sEV and Plasma Nfl AUC comparison		0.0152	0.102 to 0.256	0.00007
mEV and Plasma Nfl AUC comparison		0.0315	0.147 to 0.175	0.00001
ALS-FTD vs. HC				
sEV TDP-43 (pg/mL)	0.98	0.0003	0.946 to 0.999	0.000045
mEV TDP-43 (pg/mL)	0.98	0.0025	0.933 to 0.997	0.000014
sEV and mEV AUC comparison		0.075	-0.012 to 0.176	0.119
ALS-FTD vs. PSP				
sEV TDP-43 (pg/mL)	0.99	0.0004	0.955 to 1.000	0.00007
mEV TDP-43 (pg/mL)	0.99	0.0003	0.954 to 1.000	0.00008
sEV and mEV AUC comparison		0.030	-0.018 to 0.221	0.387
^a Hanley & McNeil. 1982 ^b Binomial exact SE: Standard Error 95% CI: 95% Confidence Interval Paired t-test				

Supplementary Table 15: Descriptive data of mutations in bvFTD and ALS in Sant Pau cohort

Mutations (n=34)	Clinical Diagnosis	Mutation types
<i>C9orf72</i>	bvFTD (n=12), ALS (n=1), ALS-FTD (n=3)	hexanucleotide (G4C2) _n repeat expansion
<i>GRN</i>	bvFTD (n=6)	Pathogenic/c.933+1G>A Pathogenic/c.933+1G>A Pathogenic/c.933+1G>A Pathogenic/c.933+1G>A Pathogenic/ c.1095-1096del Pathogenic/ c.1095-1096del
<i>VCP</i>	bvFTD (n=1)	Pathogenic/ K618X
<i>TBK1</i>	bvFTD (n=3)	Pathogenic/ W445X Pathogenic/ H528Y Pathogenic/ Asp135Asn
<i>SOD-1</i>	ALS (n=3), ALS-FTD (n=1)	Pathogenic/ c.112G>A Pathogenic/ c.339C>G Pathogenic/ c.112G>A Pathogenic/ c.339C>G
<i>FUS</i>	ALS (n=3)	Pathogenic/ c.1562G>A Pathogenic/ c.169_171delTCT Pathogenic/c.1561C>T
<i>TARDBP</i> n=1	bvFTD (n=1)	Pathogenic/A90V

Supplementary Table 16: Two-sided Spearman correlation between sEV 3R/4R Tau ratio, sEV TDP-43, and clinical and neuropsychological scales in Sant Pau cohort: PSP cases

Parameters	Spearman r values				p values			
	sEV TDP-43	sEV 3R/4R Tau ratio	mEV TDP-43	mEV 3R/4R Tau ratio	sEV TDP-43	sEV 3R/4R Tau ratio	mEV TDP-43	mEV 3R/4R Tau ratio
MMSE	-0.097	0.183	-0.085	0.164	0.590	0.018	0.658	0.039
PSP-RS	0.008	-0.202	0.052	-0.167	0.961	0.009	0.452	0.002
UPDRS-III	-0.098	-0.708	-0.074	-0.304	0.392	0.006	0.365	0.001
FAB	-0.165	-0.630	-0.023	-0.307	0.431	0.003	0.152	0.032
Plasma Nfl	0.102	-0.425	0.053	-0.402	0.563	0.0001	0.223	0.001

Bold values denote statistical significance at the $p < 0.05$ level.

Supplementary Table 17: Two-sided Spearman correlation between sEV 3R/4R Tau ratio, sEV TDP-43, and clinical and neuropsychological scales in Sant Pau cohort: bvFTD cases

Parameters	Spearman <i>r</i> values				<i>p</i> values			
	sEV TDP-43	sEV 3R/4R Tau ratio	mEV TDP-43	mEV 3R/4R Tau ratio	sEV TDP-43	sEV 3R/4R Tau ratio	mEV TDP-43	mEV 3R/4R Tau ratio
MMSE	-0.200	-0.209	-0.184	-0.171	0.018	0.016	0.022	0.026
NPI-Q	0.209	0.239	0.209	0.205	0.009	0.008	0.019	0.008
CDR-SB	0.280	0.269	0.284	0.235	0.006	0.007	0.036	0.046
CDR plus NACC FTLD	0.267	0.277	0.259	0.254	0.003	0.011	0.037	0.039
Plasma Nfl	0.460	0.457	0.303	0.386	0.002	0.0001	0.008	0.001

Bold values denote statistical significance at the $p < 0.05$ level.

Supplementary Table 18: Two-sided Spearman correlation between sEV 3R/4R Tau ratio, sEV TDP-43, and clinical and neuropsychological scales in Sant Pau cohort: ALS cases

Parameters	Spearman <i>r</i> values				<i>p</i> values			
	sEV TDP-43	mEV 3R/4R Tau ratio	mEV TDP-43	mEV 3R/4R Tau ratio	sEV TDP-43	sEV 3R/4R Tau ratio	mEV TDP-43	mEV 3R/4R Tau ratio
ALS FRS-R	-0.212	-0.032	-0.200	0.056	0.015	0.776	0.011	0.236
Time since diagnosis	0.514	0.065	0.233	0.035	0.0004	0.967	0.029	0.102

Bold values denote statistical significance at the $p < 0.05$ level.

Supplementary Table 19: Two-sided Spearman correlation between sEV 3R/4R Tau ratio, sEV TDP-43, and clinical and neuropsychological scales in Sant Pau cohort: ALS-FTD cases

Parameters	Spearman <i>r</i> values				<i>p</i> values			
	sEV TDP-43	sEV 3R/4R Tau ratio	mEV TDP-43	mEV 3R/4R Tau ratio	sEV TDP-43	sEV 3R/4R Tau ratio	mEV TDP-43	mEV 3R/4R Tau ratio
MMSE	-0.535	0.0319	-0.533	0.036	0.0182	0.971	0.018	0.452
ECAS Total	-0.799	0.0492	-0.778	0.052	0.0001	0.790	0.002	0.103
ALS FRS-R	-0.702	0.124	-0.699	0.123	0.0002	0.375	0.003	0.189
Time since diagnosis	0.445	-0.090	0.404	0.009	0.0005	0.491	0.001	0.320

Bold values denote statistical significance at the $p < 0.05$ level.

Supplementary Table 20: Comparisons of AUCs and CIs for the different cohorts

	AUC	SE ^a	95% CI ^b	<i>p</i> value
3R/4R Tau ratio				
PSP vs. HC				
Subcohort 1 sEV 3R/4R Tau Ratio	0.96	0.035	0.834 to 0.984	0.00004
Subcohort 2 sEV 3R/4R Tau Ratio	0.98	0.007	0.960 to 0.997	0.000078
Sant Pau sEV 3R/4R Tau Ratio	1.00	0.000	0.960 to 1.000	0.00002
PSP vs. bvFTD				
Subcohort 1 sEV 3R/4R Tau Ratio	0.99	0.007	0.937 to 1.000	0.00001
Subcohort 2 sEV 3R/4R Tau Ratio	0.98	0.006	0.973 to 0.997	0.00003
Sant Pau sEV 3R/4R Tau Ratio	1.00	0.000	0.969 to 1.000	0.000045
bvFTD vs HC				
Subcohort 1 sEV 3R/4R Tau Ratio	0.93	0.023	0.884 to 0.996	0.000041
Subcohort 2 sEV 3R/4R Tau Ratio	0.91	0.016	0.873 to 0.944	0.000052
Sant Pau sEV 3R/4R Tau Ratio	0.95	0.0163	0.905 to 0.985	0.00004
bvFTD&ALS				
Subcohort 1 n/a				
Subcohort 2 sEV 3R/4R Tau Ratio	0.89	0.004	0.874 to 0.913	0.00007
Sant Pau sEV 3R/4R Tau Ratio	0.90	0.0239	0.845 to 0.948	0.00006
	AUC	SE ^a	95% CI ^b	<i>p</i> value
TDP-43				
bvFTD vs. PSP				
Subcohort 1 n/a				
Subcohort 2 sEV TDP-43 (pg/mL)	0.93	0.0002	0.865 to 0.890	0.00008
Sant Pau sEV TDP-43 (pg/mL)	0.91	0.0260	0.851 to 0.959	0.000047
bvFTD vs HC				
Subcohort 1 n/a				
Subcohort 2 sEV TDP-43 (pg/mL)	0.85	0.0001	0.825 to 0.901	0.000045
Sant Pau sEV TDP-43 (pg/mL)	0.87	0.0311	0.803 to 0.926	0.00002
bvFTD vs. ALS				
Subcohort 1 n/a				
Subcohort 2 sEV TDP-43 (pg/mL)	0.91	0.016	0.878 to 0.943	0.00005
Sant Pau sEV TDP-43 (pg/mL)	0.76	0.0376	0.687 to 0.832	0.00007
ALS vs. HC				
Subcohort 1 n/a				
Subcohort 2 sEV TDP-43 (pg/mL)	0.99	0.003	0.972 to 1.000	0.00008

Sant Pau (pg/mL)	sEV TDP-43	0.94	0.0184	0.892 to 0.981	0.00008
ALS vs. PSP					
Subcohort 1 n/a					
Subcohort 2 (pg/mL)	sEV TDP-43	0.99	0.003	0.980 to 1.000	0.00004
Sant Pau (pg/mL)	sEV TDP-43	0.96	0.0147	0.910 to 0.991	0.00006
Paired t-test					

Supplementary Table 21: The receiver operating characteristic area under the curve(ROCAUC)/Precision recall curve (PRAUC) of diagnostic groups for sEV and mEV 3R/4R Tau ratio, sEV and mEV TDP-43 levels and plasma Nfl levels

DESCRIBE subcohort 1	ROCAUC/ PRAUC	95% CI	Disease Prevalence	DESCRIBE subcohort 2	ROCAUC/ PRAUC	95% CI	Disease Prevalence
PSP vs. HC				PSP vs. HC			
sEV 3R/4R Tau Ratio	0.96			sEV 3R/4R Tau Ratio	0.98		
sEV 3R/4R Tau Ratio PRAUC	0.91	0.84 to 0.95	0.00005 for PSP	sEV 3R/4R Tau Ratio PRAUC	0.90	0.83 to 0.96	0.00005 for PSP
				mEV 3R/4R Tau Ratio	0.90		
				mEV 3R/4R Tau Ratio PRAUC	0.85	0.81 to 0.92	0.00005 for PSP
PSP vs. AD				PSP vs ALS			
sEV 3R/4R Tau Ratio	0.99			sEV 3R/4R Tau Ratio	0.96		
sEV 3R/4R Tau Ratio PRAUC	0.92	0.83 to 0.94	0.00005 for PSP	sEV 3R/4R Tau Ratio PRAUC	0.89-0.90	0.86 to 0.93/0.85 to 0.91	0.00005 for PSP/0.000006 for ALS
				mEV 3R/4R Tau Ratio	0.91		
				mEV 3R/4R Tau Ratio PRAUC	0.86-0.87	0.83 to 0.91/0.84 to 0.92	0.00005 for PSP/0.000006 for ALS
PSP vs. svPPA				PSP vs. bvFTD			
sEV 3R/4R Tau Ratio	0.96			sEV 3R/4R Tau Ratio	0.98		
sEV 3R/4R Tau Ratio PRAUC	0.90	0.86 to 0.92	0.00005 for PSP	sEV 3R/4R Tau Ratio PRAUC	0.92-0.93	0.86 to 0.94/0.85 to 0.96	0.00005 for PSP/0.00015 for bvFTD
				mEV 3R/4R Tau Ratio	0.97		
				mEV 3R/4R Tau Ratio PRAUC	0.90-0.91	0.83 to 0.94/0.84 to 0.95	0.00005 for PSP/0.00015 for bvFTD
PSP vs bvFTD				bvFTD vs HC			
sEV 3R/4R Tau Ratio	0.99			sEV 3R/4R Tau Ratio	0.91		

sEV 3R/4R Tau Ratio PRAUC	0.93- 0.94	0.85 to 0.96/ 0.84 to 0.97	0.00005 for PSP / 0.00015 bvFTD	sEV 3R/4R Tau Ratio PRAUC	0.86	0.81 to 0.90	0.00015 for bvFTD
				mEV 3R/4R Tau Ratio	0.90		
				mEV 3R/4R Tau Ratio PRAUC	0.84	0.79 to 0.89	0.00015 for bvFTD
bvFTD vs. HC				bvFTD vs. ALS			
sEV 3R/4R Tau Ratio	0.93			sEV 3R/4R Tau Ratio	0.89		
sEV 3R/4R Tau Ratio PRAUC	0.86	0.81 to 0.91	0.00015 for bvFTD	sEV 3R/4R Tau Ratio PR	0.83-0.85	0.78 to 0.92/0.80 to 0.93	0.00015 for bvFTD/0.000006 for ALS
				mEV 3R/4R Tau Ratio	0.86		
				mEV 3R/4R Tau Ratio PRAUC	0.80-0.82	0.76 to 0.89/0.78 to 0.92	0.00015 for bvFTD/0.000006 for ALS
bvFTD vs. AD							
sEV 3R/4R Tau Ratio	0.90						
sEV 3R/4R Tau Ratio PRAUC	0.88	0.86 to 0.93	0.00015 for bvFTD				
bvFTD vs. svPPA							
sEV 3R/4R Tau Ratio	0.95						
sEV 3R/4R Tau Ratio PRAUC	0.91	0.86 to 0.93	0.00015 for bvFTD				
				ALS vs HC			
				sEV TDP-43 (pg/mL)	0.99		

sEV TDP-43 (pg/mL) PRAUC	0.91	0.86 to 0.93	0.000006 for ALS
mEV TDP-43 (pg/mL)	0.92		
mEV TDP-43 (pg/mL) PRAUC	0.84	0.79 to 0.91	0.000006 for ALS
Plasma Nfl (pg/mL)	0.80		
Plasma Nfl (pg/mL) PRAUC	0,74	0.68 to 0.81	0.000006 for ALS
ALS vs. PSP			
sEV TDP-43 (pg/mL)	0.99		
sEV TDP-43 (pg/mL) PRAUC	0.93-0.92	0.90 to 0.98/0.86 to 0.96	0.000006 for ALS/0.00005 for PSP
mEV TDP-43 (pg/mL)	0.94		
mEV TDP-43 (pg/mL) PRAUC	0.89-0.90	0.86 to 0.91/0.84 to 0.93	0.000006 for ALS/0.00005 for PSP
Plasma Nfl (pg/mL)	0.61		
Plasma Nfl (pg/mL) PRAUC	0.57-0.52	0.52 to 0.71/0.48 to 0.60	0.000006 for ALS/0.00005 for PSP
ALS vs. bvFTD			
sEV TDP-43 (pg/mL)	0.91		
sEV TDP-43 (pg/mL) PRAUC	0.86-0.88	0.81 to 0.92/0.82 to 0.95	0.000006 for ALS/0.00015 for bvFTD
mEV TDP-43 (pg/mL)	0.88		
mEV TDP-43 (pg/mL) PRAUC	0.82-0.85	0.78 to 0.89/0.83 to 0.96	0.000006 for ALS/0.00015 for bvFTD
Plasma Nfl (pg/mL)	0.60		
Plasma Nfl (pg/mL) PRAUC	0.55-0.52	0.80 to 0.68/0.50 to 0.63	0.000006 for ALS/0.00015 for bvFTD

bvFTD vs. HC				
sEV TDP-43 (pg/mL)	0.85			
sEV TDP-43 (pg/mL) PRAUC	0.81	0.78 to 0.86		0.00015 for bvFTD
mEV TDP-43 (pg/mL)	0.80			
mEV TDP-43 (pg/mL) PRAUC	0.76	0.72 to 0.82		0.00015 for bvFTD
Plasma Nfl (pg/mL)	0.72			
Plasma Nfl (pg/mL) PRAUC	0.63	0.55 to 0.71		0.00015 for bvFTD
bvFTD vs. PSP				
sEV TDP-43 (pg/mL)	0.93			
sEV TDP-43 (pg/mL) PRAUC	0.89-0.91	0.86 to 0.92/0.89 to 0.96		0.00015 for bvFTD/0.00005 for PSP
mEV TDP-43 (pg/mL)	0.85			
mEV TDP-43 (pg/mL) PRAUC	0.80-0.82	0.76 to 0.89/0.77 to 0.89		0.00015 for bvFTD/0.00005 for PSP
Plasma Nfl (pg/mL)	0.63			
Plasma Nfl (pg/mL) PRAUC	0.52-0.50	0.48 to 0.60/0.45 to 0.63		0.00015 for bvFTD/0.00005 for PSP

ALS prevalence 0.6 - 3.8 per 100 000 persons¹

PSP prevalence 5–7 per 100,000 persons²

bvFTD prevalence 15-22 per 100 000 person³

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Supplementary Table 22: The receiver operating characteristic area under the curve (ROCAUC)/Precision recall curve (PRAUC)of diagnostic groups for EV 3R/4R Tau ratio and EV TDP-43 levels, Sant Pau cohort

Sant Pau cohort	ROCAUC/ PRAUC	95% CI	Disease Prevalence
PSP vs. HC			
sEV 3R/4R Tau Ratio	1.00		
sEV 3R/4R Tau Ratio PRAUC	0.92	0.86 to 0.93	0.00005 for PSP
mEV 3R/4R Tau Ratio	1.00		
mEV 3R/4R Tau Ratio PRAUC	0.89	0.83 to 0.91	0.00005 for PSP
PSP vs ALS			
sEV 3R/4R Tau Ratio	0.99		
sEV 3R/4R Tau Ratio PRAUC	0.92-0.91	0.89 to 0.96 0.88 to 0.93	0.00005 for PSP /0.000006 for ALS
mEV 3R/4R Tau Ratio	0.94		
mEV 3R/4R Tau Ratio PRAUC	0.83-0.86	0.79 to 0.86 0.78 to 0.89	0.00005 for PSP /0.000006 for ALS
PSP vs ALS-FTD			
sEV 3R/4R Tau Ratio	0.98		
sEV 3R/4R Tau Ratio PRAUC	0.90	0.83 to 0.96	0.00005 for PSP
mEV 3R/4R Tau Ratio	0.93		
mEV 3R/4R Tau Ratio PRAUC	0.82	0.76 to 0.89	0.00005 for PSP
PSP vs bvFTD			
sEV 3R/4R Tau Ratio	1.00		
sEV 3R/4R Tau Ratio PRAUC	0.93-0.92	0.89 to 0.98 0.88 to 0.96	0.00005for PSP /0.00015 for bvFTD
mEV 3R/4R Tau Ratio	1.00		
mEV 3R/4R Tau Ratio PRAUC	0.90-0.91	0.86 to 0.94 0.88 to 0.96	0.00005for PSP /0.00015 for bvFTD
bvFTD vs HC			
sEV 3R/4R Tau Ratio	0.95		
sEV 3R/4R Tau Ratio PRAUC	0.90	0.87 to 0.96	0.00015 for bvFTD
mEV 3R/4R Tau Ratio	0.96		
mEV 3R/4R Tau Ratio PRAUC	0.88	0.81 to 0.90	0.00015 for bvFTD
bvFTD vs ALS			
sEV 3R/4R Tau Ratio	0.90		
sEV 3R/4R Tau Ratio PRAUC	0.86-0.87	0.81 to 0.90 0.83 to 0.92	0.00015 for bvFTD /0.000006 for ALS
mEV 3R/4R Tau Ratio	0.93		
mEV 3R/4R Tau Ratio PRAUC	0.83-0.84	0.78 to 0.91 0.80 to 0.93	0.00015 for bvFTD /0.000006 for ALS
bvFTD vs ALS-FTD			
sEV 3R/4R Tau Ratio	0.96		

sEV 3R/4R Tau Ratio PRAUC	0.91	0.90 to 0.98	0.00015 for bvFTD
mEV 3R/4R Tau Ratio	0.97		
mEV 3R/4R Tau Ratio PRAUC	0.90	0.86 to 0.95	0.00015 for bvFTD
Sant Pau cohort	ROCAUC/ PRAUC	95% CI	Disease Prevalence
ALS vs HC			
sEV TDP-43 (pg/mL)	0.94		
sEV TDP-43 (pg/mL) PRAUC	0.89	0.86 to 0.91	0.000006 for ALS
mEV TDP-43 (pg/mL)	0.93		
mEV 3R/4R TDP-43 (pg/mL) PRAUC	0.86	0.83 to 0.92	0.000006 for ALS
ALS vs. ALS-FTD			
sEV TDP-43 (pg/mL)	0.58		
sEV TDP-43 (pg/mL) PRAUC	0.45	0.38 to 0.52	0.000006 for ALS
mEV TDP-43 (pg/mL)	0.56		
mEV TDP-43 (pg/mL) PRAUC	0.49	0.41 to 0.53	0.000006 for ALS
ALS vs. PSP			
sEV TDP-43 (pg/mL)	0.96		
sEV TDP-43 (pg/mL) PRAUC	0.91-0.92	0.85 to 0.96 0.86 to 0.95	0.000006 for ALS/0.00005 for PSP
mEV TDP-43 (pg/mL)	0.96		
mEV TDP-43 (pg/mL) PRAUC	0.90-0.92	0.86 to 0.93 0.89 to 0.95	0.000006 for ALS/0.00005 for PSP
sEV and mEV AUC comparison			
ALS vs. bvFTD			
sEV TDP-43 (pg/mL)	0.76		
sEV TDP-43 (pg/mL) PRAUC	0.74-0.75	0.71 to 0.82 0.70 to 0.83	0.000006 for ALS/0.00015 for bvFTD
mEV TDP-43 (pg/mL)	0.76		
mEV TDP-43 (pg/mL) PRAUC	0.73-0.74	0.68 to 0.80 0.70 to 0.82	0.000006 for ALS/0.00015 for bvFTD
bvFTD vs HC			
sEV TDP-43 (pg/mL)	0.87		
sEV (pg/mL) PRAUC	0.83	0.78 to 0.89	0.00015 for bvFTD
mEV TDP-43 (pg/mL)	0.82		
mEV TDP-43 (pg/mL) PRAUC	0.78	0.76 to 0.85	0.00015 for bvFTD
Plasma Nfl (pg/mL)	0.78		
Plasma Nfl (pg/mL) PRAUC	0.65	0.60 to 0.75	
bvFTD vs. ALS-FTD			
sEV TDP-43 (pg/mL)	0.82		

sEV TDP-43 (pg/mL) PRAUC	0.78	0.75 to 0.85	0.00015 for bvFTD
mEV TDP-43 (pg/mL)	0.81		
mEV TDP-43 (pg/mL) PRAUC	0.76	0.72 to 0.84	0.00015 for bvFTD
bvFTD vs. PSP			
sEV TDP-43 (pg/mL)	0.91		
sEV TDP-43 (pg/mL) PRAUC	0.88-0.90	0.84 to 0.92 0.88 to 0.96	0.00015 for bvFTD/0.00005 for PSP
mEV TDP-43 (pg/mL)	0.89		
mEV 3R/4R TDP-43 (pg/mL) PRAUC	0.87 -0.88	0.85 to 0.93 0.84 to 0.95	0.00015 for bvFTD/0.00005 for PSP
Plasma Nfl (pg/mL)	0.71		
Plasma Nfl (pg/mL) PRAUC	0.60-0.61	0.58 to 0.70 0.55 to 0.72	0.00015 for bvFTD/0.00005 for PSP
ALS-FTD vs. HC			
sEV TDP-43 (pg/mL)	0.98		
sEV TDP-43 (pg/mL) PRAUC	0.94	0.90 to 0.98	0.000006 for ALS
mEV TDP-43 (pg/mL)	0.98		
mEV 3R/4R TDP-43 (pg/mL) PRAUC	0.93	0.90 to 0.97	0.000006 for ALS
ALS-FTD vs. PSP			
sEV TDP-43 (pg/mL)	0.99		
sEV TDP-43 (pg/mL) PRAUC	0.95-0.94	0.91 to 0.99 0.89 to 0.96	0.000006 for ALS/0.00005 for PSP
mEV TDP-43 (pg/mL)	0.99		
mEV 3R/4R TDP-43 (pg/mL) PRAUC	0.94-0.93	0.89 to 0.98 0.88 to 0.96	0.000006 for ALS/0.00005 for PSP
ALS prevalence 0.6 - 3.8 per 100 000 persons ¹ PSP prevalence 5–7 per 100,000 persons ² bvFTD prevalence 15-22 per 100 000 person ³			

1. Longinetti, E. & Fang, F. Epidemiology of amyotrophic lateral sclerosis: an update of recent literature. *Curr Opin Neurol* **32**, 771-776 (2019). <https://doi.org:10.1097/WCO.0000000000000730>
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