

Supplementary Online Content

Heckman MG, Brennan RR, Labbé C, et al. Association of *MAPT* subhaplotypes with risk of progressive supranuclear palsy and severity of tau pathology. *JAMA Neurol*. Published online March 18, 2019. doi:10.1001/jamaneurol.2019.0250

eTable 1. Allele and Genotype Counts and Frequencies

eTable 2. Summary of Semi-Quantitative Tau Pathology Measures for CB, NFT, TA, and NT

eTable 3. Number of PSP Patients and Controls Needed to Have 80% Power at the $P < .0025$ Significance Level to Detect Given Odds Ratios at Various Haplotype Frequencies in Controls

eTable 4. Number of PSP Patients Needed to Have 80% Power at the $P < .0031$ (Analysis of CB, NFT, and NT Overall Tau Pathology Scores) and $P < .0029$ (Analysis of TA Overall Tau Pathology Score) Significance Levels to Detect Given Mean Differences at Various Haplotype Frequencies

eTable 5. P Values for Association Between *MAPT* Haplotypes and Semi-Quantitative Tau Pathology Measures (0=none; 1=mild; 2=moderate; 3=severe) in Each Separate Neuroanatomical Region for Haplotypes That Showed a Nominally Significant ($P < 0.05$) Association With Overall Tau Pathology Scores

eTable 6. Details of Strongest Associations ($P \leq 0.001$) Between *MAPT* Haplotypes and Semi-Quantitative Tau Pathology Measures in Specific Neuroanatomical Regions

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Allele and Genotype Counts and Frequencies

Variant	Minor allele count and frequency	Major allele count and frequency	Genotype 1 count and frequency	Genotype 2 count and frequency	Genotype 3 count and frequency
rs1467967					
PSP patients	G: 558 (34.8%)	A: 1046 (65.2%)	AA: 341 (42.5%)	AG: 364 (45.4%)	GG: 97 (12.1%)
Controls	G: 869 (32.4%)	A: 1775 (67.6%)	AA: 603 (46.0%)	AG: 569 (43.4%)	GG: 140 (11.7%)
rs242557					
PSP patients	A: 904 (56.4%)	G: 700 (43.6%)	GG: 154 (19.2%)	AG: 392 (48.9%)	AA: 256 (31.9%)
Controls	A: 965 (36.8%)	G: 1659 (63.2%)	GG: 548 (20.9%)	AG: 563 (21.5%)	AA: 201 (7.7%)
rs3785883					
PSP patients	A: 338 (21.1%)	G: 1266 (78.9%)	GG: 514 (64.1%)	AG: 238 (29.7%)	AA: 50 (6.2%)
Controls	A: 472 (18.0%)	G: 2152 (82.0%)	GG: 879 (67.0%)	AG: 394 (30.0%)	AA: 39 (3.0%)
rs2471738					
PSP patients	T: 460 (28.7%)	C: 1144 (71.3%)	CC: 412 (51.4%)	CT: 320 (39.9%)	TT: 70 (8.7%)
Controls	T: 542 (20.7%)	C: 2082 (79.3%)	CC: 842 (64.2%)	CT: 398 (30.3%)	TT: 72 (5.5%)
rs8070723					
PSP patients	G: 85 (5.3%)	A: 1519 (94.7%)	AA: 720 (89.8%)	AG: 79 (9.9%)	GG: 3 (0.4%)
Controls	G: 603 (23.0%)	A: 2021 (77.0%)	AA: 784 (59.8%)	AG: 453 (34.5%)	GG: 75 (5.7%)
rs7521					
PSP patients	G: 679 (42.3%)	A: 925 (57.7%)	AA: 272 (33.9%)	AG: 381 (47.5%)	GG: 149 (18.6%)
Controls	G: 1401 (53.4%)	A: 1223 (46.6%)	AA: 296 (22.6%)	AG: 631 (48.1%)	GG: 385 (29.3%)

eTable 2. Summary of Semi-Quantitative Tau Pathology Measures for CB, NFT, TA, and NT

Neuroanatomical region	CB	NFT	TA	NT
Basal nucleus				
Missing	20	1	43	4
0=None	183 (23.4%)	1 (0.1%)	391 (51.5%)	31 (3.9%)
1=Mild	530 (67.8%)	24 (3.0%)	323 (42.6%)	156 (19.5%)
2=Moderate	65 (8.3%)	259 (32.3%)	44 (5.8%)	319 (40.0%)
3=Severe	4 (0.5%)	517 (64.5%)	1 (0.1%)	292 (36.5%)
Caudate putamen				
Missing	1	0	1	12
0=None	24 (3.0%)	1 (0.1%)	3 (0.4%)	42 (5.3%)
1=Mild	416 (51.9%)	277 (34.5%)	58 (7.2%)	470 (59.5%)
2=Moderate	250 (31.2%)	458 (57.1%)	188 (23.5%)	245 (31.0%)
3=Severe	111 (13.9%)	66 (8.2%)	552 (68.9%)	33 (4.2%)
Globus pallidus				
Missing	2	1	37	7
0=None	15 (1.9%)	2 (0.2%)	276 (36.1%)	33 (4.2%)
1=Mild	148 (18.5%)	136 (17.0%)	311 (40.7%)	170 (21.4%)
2=Moderate	292 (36.5%)	455 (56.8%)	159 (20.8%)	356 (44.8%)
3=Severe	345 (43.1%)	208 (26.0%)	19 (2.5%)	236 (29.7%)
Hypothalamus				
Missing	79	19	87	26
0=None	419 (58.0%)	0 (0%)	566 (79.2%)	67 (8.6%)
1=Mild	291 (40.2%)	40 (5.1%)	138 (19.3%)	353 (45.5%)
2=Moderate	12 (1.7%)	254 (32.4%)	7 (1.0%)	249 (32.1%)
3=Severe	1 (0.1%)	489 (62.5%)	4 (0.6%)	107 (13.8%)
Motor cortex				
Missing	4	2	5	13
0=None	22 (2.8%)	10 (1.3%)	15 (1.9%)	47 (6.0%)
1=Mild	156 (19.5%)	183 (22.9%)	123 (15.4%)	180 (22.8%)
2=Moderate	369 (46.2%)	418 (52.3%)	198 (24.8%)	302 (38.3%)
3=Severe	251 (31.5%)	189 (23.6%)	461 (57.8%)	260 (33.0%)
Subthalamic nucleus				
Missing	2	2	16	4
0=None	4 (0.5%)	1 (0.1%)	162 (20.6%)	3 (0.4%)
1=Mild	157 (19.6%)	64 (8.0%)	205 (26.1%)	36 (4.5%)
2=Moderate	334 (41.8%)	250 (31.3%)	210 (26.7%)	102 (12.8%)
3=Severe	305 (38.1%)	485 (60.6%)	209 (26.6%)	657 (82.3%)
Temporal cortex				
Missing	60	19	40	83
0=None	456 (61.5%)	155 (19.8%)	184 (24.1%)	533 (74.1%)
1=Mild	255 (34.4%)	484 (61.8%)	461 (60.5%)	96 (13.4%)
2=Moderate	28 (3.8%)	96 (12.3%)	101 (13.3%)	33 (4.6%)
3=Severe	3 (0.4%)	48 (6.1%)	16 (2.1%)	57 (7.9%)
CB=coiled bodies; NFT=neurofibrillary tangles; TA=tufted astrocytes; NT=neuropil threads.				

eTable 2 (continued). Summary of Semi-Quantitative Tau Pathology Measures for CB, NFT, TA, and NT

Neuroanatomical region	CBs	NFTs	TAs	NTs
Thalamic fasciculus				
Missing	2	---	---	3
0=None	2 (0.3%)	---	---	5 (0.6%)
1=Mild	77 (9.6%)	---	---	83 (10.4%)
2=Moderate	271 (33.9%)	---	---	293 (36.7%)
3=Severe	450 (56.3%)	---	---	418 (52.3%)
Ventral thalamus				
Missing	1	1	14	2
0=None	6 (0.7%)	4 (0.5%)	82 (10.4%)	9 (1.1%)
1=Mild	121 (15.1%)	151 (18.9%)	303 (38.5%)	35 (4.4%)
2=Moderate	280 (35.0%)	429 (53.6%)	297 (37.7%)	202 (25.3%)
3=Severe	394 (49.2%)	217 (27.1%)	106 (13.5%)	554 (69.3%)
Cerebellar white matter				
Missing	5	---	---	10
0=None	20 (2.5%)	---	---	52 (6.6%)
1=Mild	157 (19.7%)	---	---	341 (43.1%)
2=Moderate	371 (46.5%)	---	---	249 (31.4%)
3=Severe	249 (31.2%)	---	---	150 (18.9%)
Dentate nucleus				
Missing	31	9	83	8
0=None	187 (24.3%)	3 (0.4%)	612 (85.1%)	17 (2.1%)
1=Mild	515 (66.8%)	114 (14.4%)	96 (13.4%)	260 (32.7%)
2=Moderate	67 (8.7%)	312 (39.3%)	10 (1.4%)	461 (58.1%)
3=Severe	2 (0.3%)	364 (45.9%)	1 (0.1%)	56 (7.1%)
Inferior olive				
Missing	58	53	91	50
0=None	89 (12.0%)	27 (3.6%)	496 (69.8%)	11 (1.5%)
1=Mild	504 (67.7%)	312 (41.7%)	190 (26.7%)	52 (6.9%)
2=Moderate	140 (18.8%)	292 (39.0%)	24 (3.4%)	171 (22.7%)
3=Severe	11 (1.5%)	118 (15.8%)	1 (0.1%)	518 (68.9%)
Locus ceruleus				
Missing	135	38	---	39
0=None	592 (88.8%)	0 (0.0%)	---	12 (1.6%)
1=Mild	67 (10.0%)	27 (3.5%)	---	100 (13.1%)
2=Moderate	6 (0.9%)	218 (28.5%)	---	328 (43.0%)
3=Severe	2 (0.3%)	519 (67.9%)	---	323 (42.3%)
Medullary tegmentum				
Missing	43	38	126	40
0=None	75 (9.9%)	1 (0.1%)	604 (89.3%)	1 (0.1%)
1=Mild	409 (53.9%)	10 (1.3%)	67 (9.9%)	35 (4.6%)
2=Moderate	237 (31.2%)	174 (22.8%)	4 (0.6%)	99 (13.0%)
3=Severe	38 (5.0%)	579 (75.8%)	1 (0.1%)	627 (82.3%)
CB=coiled bodies; NFT=neurofibrillary tangles; TA=tufted astrocytes; NT=neuropil threads. --- is given when the given lesion was not assessed in the given anatomical structure.				

eTable 2 (continued). Summary of Semi-Quantitative Tau Pathology Measures for CB, NFT, TA, and NT

Neuroanatomical region	CBs	NFTs	TAs	NTs
Midbrain tectum				
Missing	6	19	23	6
0=None	12 (1.5%)	1 (0.1%)	37 (4.7%)	5 (0.6%)
1=Mild	84 (10.6%)	168 (21.5%)	135 (17.3%)	38 (4.8%)
2=Moderate	257 (32.3%)	401 (51.2%)	317 (40.7%)	109 (13.7%)
3=Severe	443 (55.7%)	213 (27.2%)	290 (37.2%)	644 (80.7%)
Oculomotor complex				
Missing	151	110	183	111
0=None	296 (45.5%)	4 (0.6%)	498 (80.5%)	23 (3.3%)
1=Mild	295 (45.3%)	133 (19.2%)	104 (16.8%)	158 (22.9%)
2=Moderate	51 (7.8%)	280 (40.5%)	16 (2.6%)	268 (38.8%)
3=Severe	9 (1.4%)	275 (39.7%)	1 (0.2%)	242 (35.0%)
Pontine base				
Missing	14	5	101	13
0=None	84 (10.7%)	11 (1.4%)	632 (90.2%)	47 (6.0%)
1=Mild	494 (62.7%)	93 (11.7%)	63 (9.0%)	208 (26.4%)
2=Moderate	199 (25.3%)	170 (21.3%)	6 (0.9%)	375 (47.5%)
3=Severe	11 (1.4%)	523 (65.6%)	0 (0%)	159 (20.2%)
Pontine tegmentum				
Missing	27	10	92	23
0=None	23 (3.0%)	0 (0.0%)	580 (81.7%)	4 (0.5%)
1=Mild	253 (32.6%)	80 (10.1%)	115 (16.2%)	44 (5.6%)
2=Moderate	354 (45.7%)	311 (39.3%)	13 (1.8%)	165 (21.2%)
3=Severe	145 (18.7%)	401 (50.6%)	2 (0.3%)	566 (72.7%)
Red nucleus				
Missing	6	3	20	3
0=None	21 (2.6%)	7 (0.9%)	132 (16.9%)	13 (1.6%)
1=Mild	118 (14.8%)	188 (23.5%)	260 (33.2%)	74 (9.3%)
2=Moderate	215 (27.0%)	369 (46.2%)	261 (33.4%)	182 (22.8%)
3=Severe	442 (55.5%)	235 (29.4%)	129 (16.5%)	530 (66.3%)
Substantia nigra				
Missing	5	3	29	3
0=None	44 (5.5%)	0 (0%)	317 (41.0%)	1 (0.1%)
1=Mild	386 (48.6%)	88 (11.0%)	300 (38.8%)	167 (20.9%)
2=Moderate	297 (37.3%)	379 (47.4%)	139 (18.0%)	435 (54.4%)
3=Severe	69 (8.7%)	332 (41.6%)	17 (2.2%)	196 (24.5%)
CB=coiled bodies; NFT=neurofibrillary tangles; TA=tufted astrocytes; NT=neuropil threads.				

eTable 3. Number of PSP Patients and Controls Needed to Have 80% Power at the $P < .0025$ Significance Level to Detect Given Odds Ratios at Various Haplotype Frequencies in Controls

Haplotype frequency in controls	Odds ratio	Number of PSP patients and controls needed have 80% power to detect the given odds ratio at the $P < .0025$ significance level.	
		Number of PSP patients needed	Number of controls needed
1.0%	1.25	44,972	73,754
1.0%	1.50	20,944	12,771
1.0%	1.75	6,355	16,777
1.0%	2.00	3,957	6,489
1.0%	2.25	2,777	4,554
1.0%	2.50	2,098	3,441
1.0%	2.75	1,666	2,732
1.0%	3.00	1,371	2,248
2.0%	1.25	22,753	37,315
2.0%	1.50	6,469	10,609
2.0%	1.75	3,223	5,286
2.0%	2.00	2,008	3,293
2.0%	2.25	1,410	2,312
2.0%	2.50	1,066	1,748
2.0%	2.75	847	1,389
2.0%	3.00	698	1,145
3.0%	1.25	15,351	25,176
3.0%	1.50	4,370	7,167
3.0%	1.75	2,179	3,574
3.0%	2.00	1,359	2,229
3.0%	2.25	955	1,566
3.0%	2.50	723	1,186
3.0%	2.75	575	943
3.0%	3.00	473	776
4.0%	1.25	11,652	19,109
4.0%	1.50	3,322	5,448
4.0%	1.75	1,658	2,719
4.0%	2.00	1,035	1,697
4.0%	2.25	728	1,194
4.0%	2.50	551	904
4.0%	2.75	438	718
4.0%	3.00	361	592
5.0%	1.25	9,435	15,473
5.0%	1.50	2,693	4,417
5.0%	1.75	1,346	2,207
5.0%	2.00	841	1,379
5.0%	2.25	592	971
5.0%	2.50	448	735
5.0%	2.75	357	585
5.0%	3.00	294	482
10.0%	1.25	5,021	8,234
10.0%	1.50	1,443	2,367
10.0%	1.75	725	1,189
10.0%	2.00	455	746
10.0%	2.25	321	526
10.0%	2.50	244	400
10.0%	2.75	195	320
10.0%	3.00	161	264
20.0%	1.25	2,872	4,710
20.0%	1.50	836	1,371
20.0%	1.75	425	697
20.0%	2.00	269	441
20.0%	2.25	192	315
20.0%	2.50	147	241
20.0%	2.75	118	194
20.0%	3.00	98	161

For the purposes of these sample size calculations, we assumed the same 0.61 to 1 ratio of PSP patients and controls that we had in our study.

eTable 4. Number of PSP Patients Needed to Have 80% Power at the $P<.0031$ (Analysis of CB, NFT, and NT Overall Tau Pathology Scores) and $P<.0029$ (Analysis of TA Overall Tau Pathology Score) Significance Levels to Detect Given Mean Differences at Various Haplotype Frequencies

		Number of PSP patients needed to have 80% power to detect the given mean difference at the $P<0.0031$ (analysis of CB, NFT and NT overall tau pathology scores) and $P<0.0029$ (analysis of TA overall tau pathology score) significance levels			
Haplotype frequency	Mean difference	Analysis of CB	Analysis of NFT	Analysis of NT	Analysis of TA
1.0%	0.05	79,900	59,800	84,300	72,300
1.0%	0.10	20,000	15,000	21,100	18,100
1.0%	0.20	5,000	3,800	5,300	4,600
1.0%	0.30	2,300	1,700	2,400	2,100
1.0%	0.40	1,300	1,000	1,400	1,200
1.0%	0.50	800	700	900	800
2.0%	0.05	40,350	30,200	42,550	36,500
2.0%	0.10	10,100	7,550	10,650	9,150
2.0%	0.20	2,550	1,900	2,700	2,300
2.0%	0.30	1,150	850	1,200	1,050
2.0%	0.40	650	500	700	600
2.0%	0.50	450	350	450	400
3.0%	0.05	27,267	20,333	28,667	24,600
3.0%	0.10	6,800	5,100	7,167	6,167
3.0%	0.20	1,700	1,300	1,800	1,567
3.0%	0.30	767	600	800	700
3.0%	0.40	433	333	467	400
3.0%	0.50	300	233	300	267
4.0%	0.05	20,600	15,400	21,725	18,625
4.0%	0.10	5,150	3,850	5,450	4,675
4.0%	0.20	1,300	975	1,375	1,175
4.0%	0.30	600	450	625	525
4.0%	0.40	350	250	350	300
4.0%	0.50	225	175	225	200
5.0%	0.05	16,660	12,460	17,560	15,060
5.0%	0.10	4,180	3,120	4,400	3,780
5.0%	0.20	1,060	780	1,100	960
5.0%	0.30	480	360	500	440
5.0%	0.40	280	200	280	240
5.0%	0.50	180	140	180	160
10.0%	0.05	8,790	6,570	9,270	7,950
10.0%	0.10	2,200	1,650	2,320	1,990
10.0%	0.20	560	420	590	510
10.0%	0.30	250	190	270	230
10.0%	0.40	150	110	150	130
10.0%	0.50	100	80	100	90
20.0%	0.05	4,945	3,700	5,215	4,470
20.0%	0.10	1,240	925	1,305	1,120
20.0%	0.20	315	240	335	285
20.0%	0.30	145	110	150	130
20.0%	0.40	85	65	90	75
20.0%	0.50	55	45	60	50

CB=coiled bodies; NFT=neurofibrillary tangles; NT=neuropil threads; TA=tufted astrocytes.

These calculations assumed standard deviations in overall tau pathology scores of 0.37 for CB, 0.32 for NFT, 0.35 for TA, and 0.38 for NT, which was the case for our data.

eTable 5. *P* Values for Association Between *MAPT* Haplotypes and Semi-Quantitative Tau Pathology Measures (0=none; 1=mild; 2=moderate; 3=severe) in Each Separate Neuroanatomical Region for Haplotypes That Showed a Nominally Significant (*P*<0.05) Association With Overall Tau Pathology Scores

Neuroanatomical region	P-value for association between:								
	H1c and CB	H1c and TA	H1d and TA	H1e and NFT	H1q and NFT	H1q and NT	H2 and CB	H2 and NFT	H2 and NT
Basal nucleus	0.68	0.001	0.56	0.95	0.30	0.99	0.38	0.34	0.26
Caudate putamen	0.42	0.019	0.090	0.66	0.006	0.001	0.17	0.57	0.48
Globus pallidus	0.17	0.050	0.97	0.86	0.51	0.46	0.12	0.012	0.14
Hypothalamus	0.36	0.12	0.031	0.18	0.18	0.38	0.67	0.83	0.55
Motor cortex	0.40	0.51	0.78	0.21	0.005	0.002	0.064	0.27	0.093
Subthalamic nucleus	0.036	0.32	0.28	0.034	0.84	0.064	0.035	0.80	0.002
Temporal cortex	0.22	0.37	0.50	0.21	0.080	0.16	0.37	0.21	0.071
Thalamic fasciculus	0.58	---	---	---	---	0.010	0.45	---	0.78
Ventral thalamus	0.061	0.004	0.082	0.014	0.24	0.075	0.006	0.10	0.067
Cerebellar white matter	0.46	---	---	---	---	0.12	0.034	---	0.54
Dentate nucleus	0.13	0.64	0.58	0.26	0.70	0.25	0.62	0.23	0.33
Inferior olive	0.001	0.087	0.31	0.080	0.83	0.30	0.058	0.027	0.089
Locus ceruleus	0.22	---	---	0.18	0.005	0.50	0.95	0.20	0.040
Medullary tegmentum	<0.001	0.34	0.44	0.031	0.99	0.52	0.054	0.013	0.001
Midbrain tectum	0.24	0.73	0.051	<0.001	0.36	0.012	0.031	0.17	0.57
Oculomotor complex	0.037	0.28	0.032	0.32	0.031	0.16	0.15	0.001	0.71
Pontine base	0.35	0.62	0.81	0.51	0.56	0.46	0.43	0.22	0.95
Pontine tegmentum	0.002	0.89	0.062	0.65	0.46	0.24	0.12	0.11	0.029
Red nucleus	0.012	0.007	0.21	0.38	0.54	0.024	0.13	0.029	0.072
Substantia nigra	0.10	0.58	0.008	0.24	0.49	>0.99	0.14	0.33	0.10

CB=coiled bodies; NFT=neurofibrillary tangles; TA=tufted astrocytes; NT=neuropil threads. P-values result from score tests of association (under a proportional odds logistic regression framework) that were adjusted for age at death, sex, Braak stage, and Thal phase. --- is given when the given tau pathology measure was not measured in the given neuroanatomical region.

eTable 6. Details of Strongest Associations ($P \leq 0.001$) Between *MAPT* Haplotypes and Semi-Quantitative Tau Pathology Measures in Specific Neuroanatomical Regions

Association	Neuroanatomical region	Dichotomized semi-quantitative tau pathology outcome ¹	Haplotype frequency (%)		P-value
			Dichotomized tau pathology outcome present	Dichotomized tau pathology outcome not present	
H1c and CB	Inferior olive	Moderate or Severe	25.0	18.0	0.001
H1c and CB	Medullary tegmentum	Moderate or Severe	26.5	16.1	<0.001
H1c and TA	Basal nucleus	Mild, Moderate, or Severe	23.6	16.8	0.001
H1e and NFT	Midbrain tectum	Severe	15.1	6.5	<0.001
H1q and NT	Caudate putamen	Moderate or Severe	0.2	1.7	0.001
H2 and NFT	Oculomotor complex	Severe	2.1	6.5	0.001
H2 and NT	Medullary tegmentum	Severe	3.7	9.3	0.001

CB=coiled bodies; NFT=neurofibrillary tangles; TA=tufted astrocytes; NT=neuropil threads. ¹Semi-quantitative tau pathology measures in each neuroanatomical region were considered as ordinal variables (0=none; 1=mild; 2=moderate; 3=severe) in all statistical association analysis, however for the purposes of presentation in this table only these measures were also dichotomized (dichotomization was performed so that the two categories were as balanced as possible in terms of sample sizes).