Supplemental Material:

APOE, *MAPT*, and *COMT* and Parkinson's disease susceptibility and cognitive symptom progression

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Supplemental Table 1. Genotype frequency in longitudinal cohort.

Characteristic	Cohort (N=246)	Lost to follow-up (N=108)
APOE		
ε2-	210 (0.90)	93 (0.89)
ε2+	23 (0.10)	12 (0.11)
ε4-	179 (0.77)	73 (0.70)
ε4+	54 (0.23)	32 (0.30)
COMT rs4680		
Met/Met (AA)	63 (0.27)	20 (0.19)
Met/Val (AG)	116 (0.50)	55 (0.52)
Val/Val (GG)	52 (0.23)	30 (0.29)
MAPT rs1052553		
H1/H1 (AA)	161 (0.66)	78 (0.72)
H1/H2 (AG)	80 (0.33)	29 (0.27)
H2/H2 (GG)	2 (0.01)	1 (0.01)
MAPT rs1724425		
CC	96 (0.40)	45 (0.42)
CT	115 (0.48)	45 (0.42)
TT	31 (0.13)	16 (0.15)

Supplemental Table 2. Full solutions for repeated measures linear mixed effects models predicting repeated measurements of MMSE.

	APOE 4		APOE 2		MAPT H1 / H2		MAPT rs1724425		COMT Val / Met	
Covariate	Estimate ± SD	p-value	Estimate ± SD	p-value	Estimate ± SD	p-value	Estimate ± SD	p-value	Estimate ± SD	p-value
Genetic Variant[a]	0.158 ± 0.31	0.61	-0.005 ± 0.44	0.99	-0.468 ± 0.27	0.09	-0.216 ± 0.26	0.41	0.116 ± 0.28	0.68
Age (continuous)	-0.067 ± 0.02	<.0001	-0.085 ± 0.01	<.0001	-0.091 ± 0.02	<.0001	-0.080 ± 0.02	0.00	-0.039 ± 0.02	0.10
Age*Gene[a]	-0.068 ± 0.03	0.03	0.017 ± 0.05	0.72	0.023 ± 0.03	0.40	-0.004 ± 0.03	0.90	-0.052 ± 0.03	0.06
Female[b]	0.636 ± 0.26	0.02	0.607 ± 0.26	0.02	0.615 ± 0.25	0.02	0.611 ± 0.26	0.02	0.543 ± 0.26	0.03
Non-European Ancestry[c]	-1.039 ± 0.34	0.003	-1.040 ± 0.35	0.003	-1.030 ± 0.34	0.003	-0.977 ± 0.34	0.004	-0.964 ± 0.34	0.005
Years of schooling (continuous)	0.111 ± 0.03	0.001	0.106 ± 0.03	0.001	0.113 ± 0.03	0.0004	0.114 ± 0.03	0.0004	0.108 ± 0.03	0.002
Ever smoker[d]	0.012 ± 0.26	0.96	-0.073 ± 0.26	0.78	-0.036 ± 0.26	0.89	-0.067 ± 0.26	0.79	-0.139 ± 0.25	0.58
PD Duration prior to baseline (0-3 yrs)	-0.290 ± 0.09	0.001	-0.286 ± 0.09	0.001	-0.242 ± 0.08	0.005	-0.249 ± 0.09	0.004	-0.182 ± 0.09	0.03
GDS (at each exam)	-0.168 ± 0.03	<.0001	-0.163 ± 0.03	<.0001	-0.176 ± 0.03	<.0001	-0.175 ± 0.03	<.0001	-0.172 ± 0.03	<.0001
Levodopa Use[e]	-0.053 ± 0.28	0.85	-0.019 ± 0.27	0.95	-0.017 ± 0.27	0.95	-0.050 ± 0.27	0.85	-0.141 ± 0.27	0.60

[a]APOE 4+ relative to all other APOE genotypes; APOE 2+ relative to all other APOE genotypes; MAPT H1/H1 relative to H1/H2 and H2/H2; rs1724425 CT/TT relative to CC; Comt Met/Met relative to all other COMT genotypes

[b]Relative to Male

[c]Relative to those of European ancestry

[d]Relative to never smokers

[e]Relative to those who did not take Levodopa

Supplemental Table 3. Full solutions for repeated measures linear mixed effects models with APOE 4 predicting repeated measurements of the Stroop Executive Index and Trails Executive Index.

	Outcome: Stroop Executive Index		Outcome: Trails Executive Index	
Covariate	Estimate ± SD	p-value	Estimate ± SD	p-value
APOE 4+[a]	30.536 ± 10.46	0.004	33.107 ± 11.16	0.004
Age (continuous)	1.819 ± 0.49	0.0003	2.766 ± 0.51	<.0001
Age*APOE 4+[a]	1.575 ± 1.01	0.12	2.357 ± 1.05	0.03
Female[b]	-2.779 ± 9.05	0.76	-8.451 ± 9.66	0.38
Non-European Ancestry[c]	-21.013 ± 12.44	0.09	-21.586 ± 13.49	0.11
Years of schooling (continuous)	-2.156 ± 1.35	0.11	-4.797 ± 1.45	0.001
Ever smoker[d]	-10.461 ± 9.00	0.25	2.569 ± 9.54	0.79
PD Duration prior to baseline (0-3 years)	-2.832 ± 2.92	0.33	4.023 ± 3.16	0.13
GDS (at each exam)	0.968 ± 1.24	0.44	1.468 ± 1.26	0.25
Levodopa Use[e]	12.830 ± 9.37	0.17	15.206 ± 10.10	0.13

[a]APOE 4+ relative to all other APOE genotypes

[b]Relative to Male

[c]Relative to those of European ancestry

[d]Relative to never smokers

[e]Relative to those who did not take Levodopa

Supplemental Text

Case-control Study Subject Selection

At the time of this analysis, a total of 634 PD cases were recruited. In the first round (2001-2007) of case recruitment, we identified 1,167 potential PD patients through large medical groups, neurologists, and public service announcements; 604 were not eligible (397 not diagnosed with PD within 3 years of recruitment, 134 did not live in the tri-county study area, and 73 did not have PD). Of 563 potential cases, study movement disorder specialists were able to examine 473; however, since 94 did not meet published criteria for idiopathic PD [21], 13 were reclassified as not having idiopathic PD during follow-up, and 6 subjects withdrew, 360 incident (diagnosed within 3 years) PD cases were enrolled using this strategy. For a second round of case recruitment (2010-2014) we identified potential PD cases through the pilot California Parkinson's Disease Registry (CAPDR). Of 4,672 registry recorded potential PD patients with an address in the tri-county study area we were able to contact and assess reporting accuracy for 2,363. Overall 247 potential patients refused to participate, and 1,648 were found not eligible for our study (158 were diagnosed with PD more than 3 years before recruitment, 327 did not have PD, 935 were deceased, 156 were too ill, institutionalized, or unable to communicate/contact, and 92 lived outside the tri-county area). 581 potential cases were enrolled, with 472 able to be seen by our movement disorder specialists at the time of analysis, but, 69 participants did not have idiopathic PD, 10 an uncertain diagnosis and will be re-examined, 13 were too ill, and 1 withdrew. While 376 PD patients were enrolled; genotyping (2014) preceded the enrollment of 102 cases, which were excluded from genetic analyses.

A total of 879 controls were enrolled from 2001-2011 from the same tri-county area and included in genotyping for this analysis. Initially, we identified potential eligible controls through Medicare enrollee lists (2001) but switched to publicly available residential tax-collector records after the Health Insurance Portability and Accountability Act (HIPPA) was implemented. To facilitate enrolment success and increase representativeness of the source population, we employed two sampling strategies: 1) random selection of residential parcels and mail or phone enrollment and 2) clustered random selection of five households we visited in person (for more detail see [37, 38]). Using the first sampling strategy, we contacted 1,212 potential participants; 457 were ineligible (407 were younger than 35 years old, 44 too ill, and 4 did not live primarily in the study area) and 755 were eligible, but 409 declined participation; 346 population control were enrolled using this strategy. Additionally, an early mailing (with an unknown number of eligible subjects who declined) produced 62 controls we included in the analyses and considered 'restricted' controls. We screened 4,756 individuals identified during the second sampling strategy; 3,515 of these individuals were ineligible (88% were not over the age of 35), 634 were eligible but declined participation, and 607 individuals were enrolled (though 183 only completed an abbreviated interview). Of the combined 1015 enrolled controls, 879 were selected for inclusion in genotyping based on completeness of data and amount of DNA available.