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Authors

Paul, Kimberly C
Rausch, Rebecca
Creek, Michelle M
et al.

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

Kimberly C Paul[1], **Rebecca Rausch**[2], **Michelle M Creek**[3], **Janet S Sinsheimer**[3,4], **Jeff M Bronstein**[2], **Yvette Bordelon**[2], and **Beate Ritz**[1,2]

[1]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, California, USA

[2]Department of Neurology, David Geffen School of Medicine, Los Angeles, California, USA

[3]Department of Biostatistics, UCLA Fielding School of Public Health, Los Angeles, California, USA

[4]Department of Human Genetics, David Geffen School of Medicine, Los Angeles, California, USA

Abstract

BACKGROUND—Cognitive decline is well recognized in Parkinson's disease (PD) and a major concern for patients and caregivers. Apolipoprotein E (APOE), catechol-O-methyl transferase (COMT), and microtubule-associated protein tau (MAPT) are of interest related to their contributions to cognitive decline or dementia in PD.

OBJECTIVE—Here, we investigate whether APOE, COMT, or MAPT influence the rate of cognitive decline in PD patients.

METHODS—We relied on 634 PD patients and 879 controls to examine gene-PD susceptibility associations, and nested longitudinal cohort of 246 patients from the case-control study, which followed patients on average 5 years and 7.5 years into disease. We repeatedly assessed cognitive symptom progression with the MMSE and conducted a full neuropsychological battery on a subset of 183 cognitively normal patients. We used repeated-measures regression analyses to assess longitudinal associations between genotypes and cognitive progression scores.

RESULTS—The MAPT H1 haplotype was associated with PD susceptibility. APOE 4 carriers (ε4+) ($p = 0.03$) and possibly COMT Met/Met ($p = 0.06$) carriers exhibited faster annual decline on the MMSE. Additionally, APOEε4+ carriers showed faster decline in many of the neuropsychological test scores. No such differences in neuropsychological outcomes were seen for the COMT genotypes.

CONCLUSION—This work supports a growing set of research identifying overlapping etiology and pathology between synucleinopathies, such as PD, Alzheimer's disease, and tauopathies, especially in the context of cognitive dysfunction in PD. We provide support for the argument that APOE ε4+ and COMT Met/Met genotypes can be used as predictors of faster cognitive decline in PD.

Corresponding author information: Beate Ritz, UCLA, Epidemiology, Box 951772, Los Angeles, CA 90095, Telephone: 310-206-7438, Fax: 310-206-6039, britz@ucla.edu.

Keywords

APOE; COMT; MAPT; Parkinson's disease; cognition; cognitive decline

Introduction

Parkinson's disease (PD) is a disorder pathologically characterized by progressive depletion of dopaminergic neurons in the substantia nigra and the accumulation of alpha-synuclein containing aberrant protein aggregates, Lewy bodies, in the midbrain. It is typically described in terms of motor dysfunction, including resting tremor, bradykinesia, rigidity, and postural instability; however, in recent years, non-motor features of PD have received more concentration, including cognitive decline, a major concern for patients and caregivers [1, 2].

Cognitive impairment and dementia are well established disorders in PD, with prevalence estimates for dementia between 22% and 48%, and up to 75% of PD patients who live more than 10 years after diagnosis expected to develop dementia, especially older patients [3]. Yet, the course and severity of cognitive symptom progression is variable and, to date, rather unpredictable. Few factors have been repeatedly associated with increased rates of cognitive decline or dementia, including age and severity of PD symptoms [3–6]. Recent genetic research is starting to further elucidate genetic contributions to cognitive impairment in PD, though replication is necessary.

Apolipoprotein E *(APOE)*, catechol-O-methyl transferase *(COMT)*, and microtubule-associated protein tau *(MAPT)* have been examined as to their contributions to cognitive decline or dementia in PD. *APOE* investigations were inspired by the gene's involvement in Alzheimer's disease (AD) etiology and speculations about common pathologies of protein aggregation in neurodegenerative disorders [7, 8]. A growing body of research supports the involvement of amyloid-β (Aβ) plaques (a feature of AD) in the etiology of dementia in PD, including observations that PD patients with dementia have a higher cortical Aβ plaque burden than PD patients without dementia [9]. The association between *APOE* and cognitive impairment in PD was further supported by a longitudinal PD patient cohort that for the first time reported more rapid cognitive decline, defined in terms of changes in dementia rating scale scores, in APOE ε4 carriers [10]. *COMT* is involved in cortical dopamine degradation; the functional polymorphism Val158Met alters the activity of catechol-*O*-methyl-transferase (a dopamine-regulating enzyme in the prefrontal cortex) [11]. This polymorphism is linked to executive function performance in both healthy individuals and PD patients and has more recently been associated with the development of cognitive dysfunction in PD [6, 12]. The *MAPT* H1 haplotype has been widely associated with PD susceptibility in multiple independent populations and GWAS results [13, 14]. The haplotype is believed to increase expression of tau, which aggregates to form neurofibrillary tangles (a feature of AD) and also forms filamentous pathological inclusions, hallmarks of several neurodegenerative disorders known as tauopathies [15, 16]. The H1 haplotype was further linked to the development of dementia in a PD patient longitudinal cohort [17].

Results of longitudinal investigations into associations between these genes and cognitive function in PD however are rare and inconsistent in their implication [10, 18–20]. Here, we

aim to first establish whether these genes contribute to PD susceptibility in our case control study and second investigate the relationship between the genes and cognitive decline in our PD patient cohort, followed on average 7.5 years into disease course.

Methods

Study Population

We rely on 634 PD patients and 879 controls of the Parkinson's Environment and Gene (PEG) population-based case-control study for susceptibility analysis. PEG enrolled cases and controls from three Central California counties from 2001–2014. All patients were seen by movement disorder specialists (JB, YB) at least once at baseline, many on multiple occasions, and confirmed as having probable idiopathic PD based on published criteria [21]. The subject selection methods for the case-control study can be found in the supplemental text.

For progression analysis, we use a patient only longitudinal cohort, following 246 patients from the original case-control study. All patients from the first round of PEG recruitment (2001–2007; n=373) were invited to participate in the longitudinal cohort follow-up study (for more detail see Ritz et al 2012 [22]). The patients were early in their disease course (diagnosed within 3 years of recruitment) when follow-up began. Briefly, at first attempted re-contact, 108 patients (29%) could not be re-examined (64 were deceased, 6 too ill, 17 withdrew, and 21 could not be contacted). We successfully examined 265 (71%) patients during follow-up, but 13 of these participants were re-classified as not having PD upon further examination. Of the remaining patients, 246 provided the data necessary for the cognitive progression analyses.

Assessment of Cognitive Progression

Trained interviewers recorded information on demographic and risk factors, and physical exams were performed by movement disorder specialists (JB, YB) at baseline and during each follow-up, confirming PD diagnosis and assessing disease progression. Cognitive function was assessed at each exam time with the Mini-Mental State Exam (MMSE). The MMSE is a widely used 30-point test assessing cognitive function, including tests of orientation, attention, memory, language, and visual-spatial skills. A 26-point telephone version of the MMSE exam, validated to estimate the in-person MMSE, was administered in lieu of an in-person exam for 3 patients at baseline exams and 6 at the first follow-up; for these participants, validated weights were applied to make scores comparable with the 30-point in-person interview [23].

Additionally, within 6 months (95% of participants) to 18 months (5% of participants) of the two follow-up exams, a subgroup of these patients, those who scored 26 or higher on the MMSE (n = 183) underwent extensive neuropsychological exams by staff trained and supervised by our neuropsychologist (RR). Of the 183 patients who completed the neuropsychological battery during the first follow-up exam, 146 completed a second round of neuropsychological exams on average 2.2 years later (standard deviation (SD) =0.5). Tests included Wechsler Memory Scale (WMS) III: Logical Prose Recall Story A,

immediate (IR) and delayed recall (DR) and Visual Reproduction (IR and DR); Wechsler Adult Intelligence Scale III: Digit Span Forward and Backwards, Digit Symbol Coding, Letter Number Sequencing (LNS), Similarities; Trail-Making Test, The Stroop Color Word Test (Comalli-Kaplan Version), Verbal Fluency Tests (FAS, animal and vegetables), Shortened Version of the Boston Naming Test (BNT), Hopkins Verbal Learning Test (HVLT-R) (IR and DR), Der Benton Visual Retention Matching-Recognition Test, and WMS-R Visual Reproduction (IR and DR). Besides the standard scorings, two additional scoring indices were calculated to reduce effects of speed on performance on executive functions: Trail-Making Executive Index: Trails B Time -Trails A Time and Stroop Executive Index: Interference Time -Color Naming Time. Primary domains assessed by scores from these tests are shown in Table 5.

SNP Selection and Genotyping Methods

We selected five SNPs for this analysis, *APOE* rs429358 and rs7412 to differentiate ε2, ε3, and ε4 carrier status [20], the functional *COMT* polymorphism Val158Met (rs4680), *MAPT* rs1052553 (C_7563736_10) to differentiate the H1 and H2 haplotype clades, and rs1724425 near the *MAPT* gene, based on previous association with PD in a subset of our population [24]. Note, we have also genotyped *MAPT* rs1800547, another SNP previously used to distinguish the H1 and H2 haplotype clades, but do not present results as rs1800547 and rs1052553 are nearly in full linkage disequilibrium (R^2=0.97) and thus rs1800547 provides no additional information.

DNA was extracted from blood or saliva samples at the UCLA Biologic Specimen Core Facility. Genotyping was performed as part of several research projects, utilizing different methods, thus not all eligible subjects had data available for some SNPs. All genotyping for *APOE* SNPs rs429358 and rs7412 and *COMT* rs4680 was done using the Fluidigm BioMark system (Fluidigm Corporation, South San Francisco, CA). Initial (2009) and fill-in (2014) genotyping of the both *MAPT* SNPs (rs1052553 and rs1724425) was conducted at UCLA where PCR assays were conducted with TaqMan Universal Master Mix (Applied Biosystems).

Statistical Methods

We assessed Hardy-Weinberg equilibrium in controls for all SNPs using a chi-square test. For PD susceptibility analyses, we used unconditional logistic regression, calculating odds ratios (ORs) and 95% confidence intervals (CIs) to assess genetic marginal effects, assuming a general genetic model for individual SNP analyses, and adjusting for age (continuous), sex, smoking status (ever/never), and European ancestry (yes/no).

We used repeated-measures regression analyses (Proc MIXED; SAS 9.4, SAS Institute, Cary, NC) to assess longitudinal associations between genotype and cognitive progression scores (MMSE, battery exam scores), reporting the regression coefficient (β) for the interaction between the genotype and age, which represents the difference in annual change in score across genotype. We adjusted for the same potential confounders and additionally controlled for years of education, Levodopa use (yes/no), and geriatric depression score (GDS) at each exam; age refers to the age at each exam, centered at the mean age at time of

baseline exam (68.9 years). In order to address both variable length of follow-up time for subjects and variation in time between exam and differences in baseline exam scores, we employed linear mixed-effects models, treating both the intercept and regression coefficient for age (in lieu of follow-up time due to collinearity) as random effects. We also conducted sensitivity analysis restricting to patients diagnosed over the age of 60 and of European ancestry only.

We used SAS 9.4 (SAS Institute Inc., Cary, NC) and Mendel [25] for all analysis.

Results

Demographic and general characteristics of the case-control population are described in Table 1 and baseline characteristics by genotypes for the longitudinal patient cohort in table 3. All SNPs investigated are in HWE. Marginal associations for PD with the SNPs are reported in table 2; neither *APOE* carrier status or *COMT* rs4680 were risk factors for PD, while we estimated 30 to 70% decreases in risk in recessive homozygotes for the *MAPT* SNPs.

The mean follow-up for our patients in this analysis was 5.2 years (table 3) and the mean PD duration at last follow-up 7.5 years. We saw no statistically significant differences in demographic or baseline health indicators MMSE, GDS, and UPDRS-III scores across genotypes (table 3). Of the 246 patients followed longitudinally, 65 (26%) had 2 exams (on average 3.6 years from baseline exam), 174 (71%) had 3 exams (on average exam 1 was 3.5 years from baseline, and exam 2 was 2.2 years from exam 1), and 7 (3%) participants had 4 exams (on average exam 1 was 1.2 years from baseline, exam 2 was 1.8 years from exam 1, and exam 3 was 3.3 years from exam 2). The 108 patients lost to follow-up after baseline were significantly older at time of diagnosis and interview than those we followed. Additionally, those lost scored worse in terms of our baseline measures (UPDRS, MMSE, and GDS) (table 3); however, genotype distributions were not significantly different between the two groups (supplemental table 1).

Using repeated measures regression models, treating age and the intercept as random effects, both *APOE* 4 carriers (ε4+) and *COMT* Met/Met carrier status were associated with faster annual decline in MMSE (ε4+*age: β=−0.068, p=0.03; Met/Met*age: β=−0.052, p=0.06), relative to all other genotypes (table 4). The reported regression coefficient (β) for the interaction term between genotype and age represents the difference in annual change in MMSE score; for example, a coefficient of −0.068 for the ε4+ group indicates the ε4 carriers decline 0.068 points faster on the MMSE per year than those belonging to the ε4- group, which is twice as fast a yearly decline compared with *APOE* ε4-patients. Results were stronger and gained significance when we restricted our sample to those diagnosed with PD when they were older than 60 years of age and of European ancestry (table 4). The interaction associations were still present when including both *APOE* ε4, *COMT* Val158Met, and the two interactions in the same model (ε4+*age: β=−0.091, p=0.04; Met/Met+*age: β=−0.069, p=0.07; data not shown). No associations for progression (within subject) were detected for either *APOE* ε2 or based on MAPT genotypes; however the *MAPT* H1/H1 haplotype main effect (between subject) suggested a lower MMSE score (β=

−0.47, p=0.09; supplemental table 2) and this association was significant in the subgroup of patients diagnosed at age 60 or older (β=−0.63, p=0.04; data not shown). Supplemental table 2 presents the full model solutions for each variant and the MMSE as the dependent variable.

Results using outcomes from the neuropsychological battery are listed in table 5; again, we show the interaction β between genotype and age, the difference in annual change in battery test measures between genotypes. APOE ε4+ carriers show faster decline in many of the test scores. Supplemental table 3 shows the full model solutions for covariates and the Stroop and Trails Executive Indices only. No such differences in neuropsychological outcomes were seen for the *COMT* genotypes (data not shown).

Discussion

In our prospective, longitudinal study of a population-based cohort of PD patients from central California, which followed patients on average 7.5 years into disease, we confirm associations between the *MAPT* H1 haplotype and PD susceptibility and – importantly, suggest that *APOE* and possibly also *COMT* influence decline in global cognitive functioning as measured by the MMSE in PD patients. We consider the size of our estimates for both *COMT* Met/Met and *APOE* ε4+ carriers and decline in the MMSE meaningful, as APOE ε4+ and Met/Met carriers equate with a decline similar in size or more than the decline we estimate for aging alone, meaning those carrying the *APOE* or *COMT* vulnerable genotypes are declining in MMSE score twice as fast or more than those without them (*APOE* ε4+: β_{age}=−0.067, p<.0001, $\beta_{\varepsilon 4+ \times age}$=−0.068, p=0.03; *COMT* Met/Met: β_{age}= −0.039, p=0.10, $\beta_{Met/Met \times age}$=−0.052, p=0.06; supplemental table 2). While we did not detect evidence for faster progression in cognitive decline with the *MAPT* H1 haplotype, we found suggestive associations for the H1/H1 genotype carriers and lower MMSE scores (between-subject main effect β=−0.47, p=0.09), suggesting across all exams those with the H1/H1 genotype had a lower MMSE score though they did not progress differently than those with the H2 haplotype.

To provide insight into the nature of the cognitive decline, we conducted an extensive battery of neuropsychological tests in a subset of this PD patient population with relatively intact global cognitive status (initial MMSE ≥ 26) to find performance differences over a 2.2 year period on average. We observed more rapid cognitive decline among *APOE* ε4+ carriers across multiple neuropsychological measures. Our findings are consistent with the longitudinal study of Morley et al. 2012 [10], who followed a group of PD patients with a more heterogeneous range of cognitive status than ours. These authors report declines in multiple cognitive domains, as assessed by the Mattis Dementia Rating Scale V2 (DRS-2), in *APOE* ε4+ carriers. While the DRS-2 used by Morley et al. [10] has been shown to be sensitive to dementia in PD, because of potential ceiling effects, its usefulness in studies of PD patients with milder deficits is limited [26]. Our findings extend upon the results by Morley et al. [10] by following a select group of PD patients with relatively intact global cognition who completed an extensive neuropsychological battery.

While we found evidence suggesting an association between *COMT* Val158Met and MMSE decline, we did not see differences in the rate of decline between genotypes in any of the neuropsychological measures. The neuropsychological measures were obtained over a shorter period of time than the MMSEs, as the battery was only conducted at the follow-up exams and not at baseline; thus a longer time frame may be needed to identify influences of the Met/Met genotype on performance on these measures in patients with relatively intact global cognitive status. Alternatively, the influence of *COMT* Val158Met may be mediated by disease duration as has been proposed Williams-Gray et al. [6], with Met alleles negatively influencing cognition early in disease, likely through modulation of cortical dopamine levels, but not later in disease. Specifically, they found an increasing number of Met alleles to be associated with cognitive deficits, but only in incident (<1.6 years) and not prevalent cases [6]. Our patients' disease duration was on average 5.4 years (SD=2.5) when we conducted the first neuropsychological testing and it is possible that any change in executive function influenced by *COMT* had already occurred. Additionally, the smaller sample size of patients assessed with two neuropsychological exams (n=146) and smaller effect sizes may have limited our statistical power in detecting any differences.

Our study shows more rapid cognitive decline in PD patients who are *APOE* ε4+ carriers than non-carriers on multiple neuropsychological measures. Difficulties in cognitive domains represented by these scores have been reported as part of the varied cognitive symptomatologies seen in PD patients, both with and without dementia [9, 27, 28]. We found that the cognitive domains primarily at risk for rapid decline in PD *APOE* ε4+ carriers are working memory, select language functions (such as encoding prose, word retrieval, abstraction), visual tracking, and processing speed. A consistent *APOE* ε4+ associated increased rate of decline was seen on verbal executive measures (verbal fluency scores), but a selectively increased decline was not identified on one of the executive measures derived from visual tasks highly dependent upon processing speed. On the Stroop test, both time to name colors and time to read words increased more rapidly for *APOE* ε4+ carriers, indicating slower processing speeds for these tasks. However, while the interference task, naming color of an incongruent word, was slower in the *APOE* ε4+ carriers than non-carriers at the first testing, the *APOE* ε4+ carriers did not show a more progressive slowing on this task over time. It is possible that the effect of *APOE* ε4+ on this particular executive measure had peaked at the time of the first testing, as we estimated large main effect for *APOE* 4+ (β=30.5, p=0.004; supplemental table 3), or that its continued influence follows a different temporal pattern than we assessed. On the Trails-Making Test, another multi-component, visual-timed task, APOE ε4+ carriers as compared with non-carriers performed progressively worse (slower) on both the simpler number tracking task (Trails A) and the more demanding task requiring cognitive shifting of two concepts (Trails B). We did not confirm a strong effect on verbal learning, as assessed by the HVLT, reported previously in a cross-sectional study [29]. In terms of verbal learning tasks, *APOE* ε4+ only influenced a delayed discrimination recognition score. Also, the statistically significant finding for delayed recall of logical prose was due to the rapid decline seen in the initial learning of the prose, not the loss of information over time. Because of our small sample, all of our findings need to be re-examined and replicated in future studies with larger sample sizes and longer follow-up. Nevertheless, our study provides further evidence that PD patients without

dementia who are carriers of *APOE* ε4 are at risk for more rapid decline in multiple cognitive domains relative to non-carriers.

APOE, *MAPT*, and *COMT* have been investigated in terms of their contribution to cognition in PD patients previously. Though longitudinal analyses have not been consistent, interestingly each of the variants examined has previously been associated with brain function measured with functional magnetic resonance imaging (fMRI) [18, 30, 31]. These studies found that *APOE* status influences the magnitude of activation associated with memory encoding, such that *APOE* ε4+ carriers display lower activation, the *MAPT* H1 haplotype modulates parietal activations associated with spatial rotations, while *COMT* Val158Met modulates the effect of levodopa therapy on planning-related activations in the frontoparietal network, such that Met/Met carriers experience more activation on low-dose dopaminergic medication relative to Val/Val homozygotes on high-dose medications [30]. However, these later differences were described for incident patients, and as discussed, it has been suggested that the *COMT* Met allele action depends on PD disease duration, and may not be observed at longer disease duration [6]. Smaller studies also found differing levels of brain activation by *COMT* Val158Met and the *MAPT* H1/H2 haplotype [18, 31], though it is unclear whether these can be attributed to sample size issues or differences in disease duration or stages at time of imaging which might have influenced these results.

In population studies, though not unanimous, multiple independent populations have implicated *APOE* ε4+ in cognitive dysfunction or dementia in PD. Though these investigations were primarily cross-sectional in nature and did not assess progression longitudinally. A 2009 meta-analysis of 17 independent studies showed significant over-representation of *APOE* ε4+ in PD patients with dementia versus patients without (OR=1.74, 95%=1.36, 2.23), though longitudinal follow-up of 109 PD patients from the United Kingdom (UK) (CamPaIGN cohort) included in this meta-analysis showed no association between *APOE* ε4+ and change in MMSE score after 3 years of follow-up or time to dementia after 10 years of follow-up [19, 20]. The Pennsylvanian longitudinal study of 212 PD patients previously discussed, Morley et al., report similar results to ours: *APOE* ε4+ carriers had a faster rate of decline in DRS-2 score [10]. The UK CamPaIGN cohort, however, did detect a faster rate of MMSE decline in *MAPT* H1/H1 carriers [17] and time to dementia [19], which was not replicated in the Pennsylvania cohort after 2–4 years of follow-up [10]. While the H1 haplotype did not influence the rate of decline in our patients, our analysis suggested a possible main effect for the H1 haplotype on MMSE score, meaning between subjects, patients with the H1 haplotype had lower scores. *COMT* Val158Met in the Pennsylvania cohort was not associated with the rate of decline in DRS-2, and the CamPaIGN UK cohort did not find an association with time to dementia [19]. Though, as discussed, cross-sectional analysis of 425 PD patients, which includes the CamPaIGN cohort, found that an increasing number of Met alleles was associated with lower ‘Tower of London’ scores, a measure of executive function, but only in incident patients, not patients more than 1.6 years into their disease [6]. Again, we found Met/Met carriers declined faster in terms of MMSE score, but detected no differences in rate of decline in any of our neuropsychological battery test scores, not seeing any associations with measures specific to executive function.

Differences between our cohort and the Pennsylvanian and UK CamPaIGN PD patient cohorts could explain the heterogeneity in findings. Follow-up in the UK cohort started early disease course (mean 0.3 years from diagnosis, SD=0.3), with the 129 PD patients recruited from 3 UK districts, and more than 10 years of follow-up after the initial recruitment (mean=7.2 years; SD=2.8)[6, 19]. Small sample size may have limited power to detect associations involving *APOE* in this cohort. The Pennsylvanian cohort recruited 212 PD patients to the Udall Center of Excellence in Parkinson's Disease Research (Philadelphia, PA), with prevalent disease (mean duration of PD at baseline=6.7 years), and a median follow-up of 3 years (IQR=2–4 years)[10]. As the authors discuss, this may influence the ability to detect certain associations, if the genetic mechanism differs between early-versus late-onset cognitive decline in PD [10].

Other variants have been implicated in cognitive decline or dementia in PD, including loss of function mutations and the E326K SNP in the glucocerebrosidase gene (*GBA*) [32], or PD related genes, like leucine-rich repeat kinase 2 (*LRRK2*), where mutations are the most common cause of familial PD and may influence the cognitive profile of patients [33]. We screened our patients for these variations, but identified only 5 GBA mutation carriers and no carriers of *LRRK2* G2019S or R1441C/G/H mutations; thus not allowing us to assess cognitive variation.

Our population-based and prospective design provides a good opportunity to investigate cognitive decline in PD: all patients recruited were confirmed as idiopathic PD by movement disorder specialists, early in disease course when follow-up began (within three years of diagnosis), and population based, thus, we expect our results to be generalizable to many PD populations. Additionally, we were able to follow the majority of our longitudinal cohort more than seven years into disease, and exams were conducted by the same movement disorder specialists and neuropsychology team members. However, as one would expect in a general population based study, we were not able to follow-up with all patients enrolled at baseline (n=360); 108 (29%) of initial patients could not be followed, mostly because the patient was too ill or already deceased (n=70), though 17 refused and we could not re-contact 21. Those lost were older and scored worse on baseline health indicators UPDRS and MMSE, consequently selection bias is possible (table 3), however they did not differ in *APOE*, *MAPT*, or *COMT* genotype distributions (supplemental table 1). Finally, given that we do not have follow-up data on a non-PD population, we cannot tell whether the longitudinal findings are specific to cognitive decline in PD or whether the same type of decline would be observed among *APOE* ε4+ carriers in a matched control population. However, multiple longitudinal studies have tracked cognitive decline in cognitively normal, elderly populations, with results from no effect of *APOE* ε4+ on change of MMSE [34, 35] to ε4+ carriers showing a greater decline in MMSE score than non-carriers (mean: −1.4 points over 6 years)[36]. Given the null findings and that the reported decline is less than the mean decline seen in ε4+ of our PD population, it is possible that *APOE* ε4 is involved in PD related cognitive impairment specifically.

Ultimately, this work supports a growing set of research identifying overlapping etiology and pathology between synucleinopathies, such as PD, Alzheimer’s disease, and tauopathies, especially in the context of cognitive dysfunction in PD. We replicate previous

findings for the *MAPT* H1 haplotype and increased PD susceptibility, and provide new support for the argument that *APOE* ε4+ and *COMT* Met/Met genotypes can be used as predictors of faster cognitive decline in PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

General Characteristics of the case-control study population, n=1505[a]

Characteristic	Controls (n=877)	Cases (n=628)
Age, median ± SD[b]	66 ± 11.6	68 ± 10.4
Male sex, n (%)	422 (0.48)	394 (0.63)
Cigarette smoking, n (%)		
Never	412 (0.47)	326 (0.53)
Ex	355 (0.41)	270 (0.43)
Current	109 (0.12)	26 (0.04)
European Ancestry, n (%)		
Yes	596 (0.68)	475 (0.76)
No	278 (0.32)	153 (0.24)
Education, Mean years ± SD	13.7 ± 4.2	13.5 ± 4.5

[a]Excludes 6 cases and 2 controls that failed genotyping of all SNPs

[a]Age at interview for controls and PD diagnosis for cases

Table 2

Genetic associations between *APOE*, *COMT*, and *MAPT* and PD susceptibility; assumed a general genetic model.

Genotype	Cases (%)	Controls (%)	Adjusted OR (95% CI)[a]	P Value
APOE Status (rs429358 − rs7412)[b]				
ε2−	506 (0.88)	728 (0.88)	1.00 (ref)	--
ε2+	69 (0.12)	95 (0.12)	0.96 (0.69, 1.35)	0.83
ε4−	450 (0.78)	629 (0.76)	1.00 (ref)	--
ε4+	125 (0.22)	194 (0.24)	0.88 (0.68, 1.14)	0.32
COMT rs4680				
Met/Met (AA)	84 (0.25)	127 (0.26)	1.00 (ref)	--
Met/Val (AG)	174 (0.51)	229 (0.47)	1.16 (0.82, 1.64)	0.40
Val/Val (GG)	83 (0.24)	127 (0.26)	0.95 (0.64, 1.42)	0.81
MAPT rs1052553				
H1/H1 (AA)	415 (0.68)	529 (0.64)	1.00 (ref)	--
H1/H2 (AG)	184 (0.30)	257 (0.31)	0.88 (0.70, 1.12)	0.31
H2/H2 (GG)	10 (0.02)	38 (0.05)	0.31 (0.15, 0.65)	0.002
MAPT rs1724425				
CC	232 (0.38)	266 (0.32)	1.00 (ref)	--
CT	282 (0.46)	411 (0.50)	0.77 (0.61, 0.98)	0.03
TT	95 (0.16)	153 (0.18)	0.68 (0.49, 0.93)	0.02

[a]Adjusted for age (continuous), sex, smoking status (ever/never), European ancestry (yes/no)

[b]Both *APOE* carrier status indicators do not include individuals with a CT genotype at both loci, as based on inferred haplotypes, these individuals are TC:TC (ε1/ε3) not CT:TC (ε2/ε4) at rs429358 and rs7412 respectively.

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Table 3

Baseline characteristics of the longitudinal cohort by genotype.

Characteristic Mean ± SD or %	Cohort (N=246)	Lost to follow-up (N=108)	*APOE*				*COMT* rs4680		*MAPT*	
			ε4+ (N=54)	ε4− (N=179)	ε2+ (N=23)	ε2− (N=210)	Met/Met (N=63)	Val/Met Val/Val (N=168)	H1/H1 (N=161)	H1/H2 H2/H2 (N=82)
Age at interview	68.9 ± 9.8	73.5 ± 10.1*	68.2 ± 10.3	69.2 ± 9.6	69.0 ± 9.5	68.9 ± 9.8	68.7 ± 10.0	68.8 ± 9.8	69.0 ± 9.2	68.9 ± 10.7
Age at diagnosis	67.0 ± ± 9.9	71.4 ± 10.0*	65.9 ± 10.3	67.3 ± 9.8	66.8 ± 9.9	67.0 ± 9.9	67.1 ± 10.2	66.9 ± 9.9	67.0 ± 9.3	67.1 ± 10.8
Age at Onset	65.8 ± 10.4	69.7 ± 10.7*	65.4 ± 8.9	66.0 ± 10.8	66.2 ± 10.7	65.8 ± 10.4	66.8 ± 3.4	65.5 ± 10.9	66.0 ± 9.9	65.7 ± 11.0
PD Duration										
Baseline	2.0 ± 1.5	2.3 ± 1.5	2.4 ± 1.8	2.0 ± 1.4	2.2 ± 1.5	2.1 ± 1.5	1.8 ± 1.5	2.1 ± 1.8	2.1 ± 1.5	2.0 ± 1.5
Follow-up	7.5 ± 2.6	--	8.0 ± 2.5	7.5 ± 2.6	7.7 ± 2.5	7.6 ± 2.6	7.2 ± 2.7	7.7 ± 2.6	7.4 ± 2.6	7.9 ± 2.7
Follow-up	5.2 ± 2.1	--	4.9 ± 2.3	5.3 ± 2.1	5.4 ± 2.1	5.1 ± 2.2	5.2 ± 2.1	5.3 ± 2.1	5.0 ± 2.2	5.6 ± 1.9
Sex, % male	56.9	58.3	58.3	56.8	51.6	58	52.4	56.6	57.1	57.3
European Ancestry, % yes	80.1	80.6	80.0	79.6	87.1	78.8	87.3	82.7	75.2	89.0
Smoker, % never	54.9	48.2	54.6	53.3	61.3	53.3	57.1	54.8	57.8	48.8
Years of education	13.7 ± 4.4	12.8 ± 3.1*	14.6 ± 4.0	13.4 ± 4.6	15.0 ± 3.7	13.6 ± 4.5	14.3 ± 4.6	14.1 ± 3.4	13.4 ± 4.6	14.3 ± 4.1
MMSE	28.1 ± 2.3	26.9 ± 3.0*	28.3 ± 2.1	28.0 ± 2.4	27.9 ± 2.6	28.1 ± 2.3	28.2 ± 2.6	28.3 ± 1.9	28.1 ± 2.4	28.0 ± 2.0
GDS	3.2 ± 3.3	4.2 ± 2.9*	3.9 ± 4.0	3.1 ± 3.1	2.6 ± 2.6	3.4 ± 3.4	3.3 ± 3.4	3.1 ± 3.2	3.2 ± 3.3	3.2 ± 3.3
UPDRS III	19.6 ± 9.6	25.7 ± 13.2*	21.3 ± 10.2	19.4 ± 9.4	16.8 ± 8.5	20.1 ± 9.7	20.2 ± 9.3	18.8 ± 9.1	19.1 ± 9.4	20.8 ± 9.8
Bradykinesia	6.6 ± 4.0	8.8 ± 5.2*	7.2 ± 4.2	6.6 ± 4.0	5.7 ± 3.8	6.8 ± 4.1	6.5 ± 3.9	6.4 ± 3.9	6.3 ± 4.0	7.3 ± 3.9
Rigidity	3.2 ± 2.4	3.9 ± 2.8*	3.4 ± 2.3	3.2 ± 2.4	2.4 ± 1.6	3.4 ± 2.4*	3.4 ± 2.5	3.0 ± 2.3	3.1 ± 2.2	3.4 ± 2.8
Tremor	1.7 ± 1.8	1.9 ± 2.1	2.0 ± 2.6	1.6 ± 1.4	1.7 ± 1.5	1.7 ± 1.8	1.6 ± 1.9	1.6 ± 1.5	1.7 ± 1.9	1.6 ± 1.5
Postural reflex impairment	2.9 ± 2.0	4.8 ± 3.3*	3.2 ± 2.0	2.9 ± 2.0	2.7 ± 2.3	3.0 ± 2.0	3.1 ± 2.1	2.8 ± 2.0	2.9 ± 2.0	3.0 ± 2.0
Levodopa Use, % yes	67.3	75.4	82.7	62.4*	63.6	67.5	68.3	70.0	64.5	75.0

*P-value <0.05; p-values from t-test for continuous variables and chi-square for categorical variables

Table 4

Relationship between genotype and change in MMSE using linear mixed effects model.

	Entire Study Population (n=246)		Age of diagnosis 60+ (n=213)		European ancestry only and age of diagnosis 60+ (n=172)	
Genotype	**Interaction β***	**p-value**	**Interaction β***	**p-value**	**Interaction β***	**p-value**
APOE						
ε4+[a]	−0.068	0.03	−0.101	0.02	−0.087	0.05
ε2+[a]	0.017	0.72	0.058	0.33	0.044	0.43
MAPT						
H1/H1 [b]	0.023	0.40	0.048	0.20	0.024	0.50
rs1724425 CT/TT[c]	−0.004	0.90	0.033	0.38	0.025	0.50
***COMT* rs4680**						
Met/Met[d]	−0.052	0.06	−0.067	0.08	−0.079	0.04

[a]Relative to all other *APOE* genotypes

[b]Relative to H1/H2 and H2/H2

[c]Relative to rs1724425 CC

[d]Relative to all other rs4680 genotypes

*eg (age*genotype) effect of genotype on MMSE change over time, between group annual difference in MMSE decline

Models adjusted for age (continuous), sex, smoking status (ever/never), European ancestry (yes/no), years of education, Levodopa use (yes/no), PD duration prior to baseline (0–3 years), and GDS score (continuous)

Table 5

Relationship between APOE ε4 and neuropsychological outcomes, using linear mixed model and showing mean scores of each measure at both exam (n=138).

		Longitudinal Associations		Cross Sectional Analysis (Mean Scores ± SD)			
				Follow-up 1		Follow-up 2	
Primary Domain	**Neuropsychological Measures**	**Interaction β[a]**	**p-value**	**ε4+ (N=31)**	**ε4− (N=107)**	**ε4+ (N=31)**	**ε4− (N=107)**
	Age at Exam	--	--	69.1 ± 9.8	72.0 ± 9.7	71.5 ± 9.6	74.1 ± 8.5
	PD Duration	--	--	5.9 ± 2.4	5.4 ± 2.5	8.1 ± 2.4	7.6 ± 2.6
Language Attention	Digit Forward (/16)	−0.02	0.70	8.8 ± 2.4	9.5 ± 2.1	9.3 ± 2.3	9.5 ± 2.3
	Digit Backward (/14)	−0.05	0.15	5.8 ± 2.2	6.4 ± 1.9	5.3 ± 2.0	5.9 ± 2.1
Language Attention / Working Memory	Letter Number Sequencing	−0.10	0.03	7.3 ± 3.8	8.4 ± 3.0*	6.0 ± 3.2	7.8 ± 2.6**
	Logical Prose - IR (/25)	−0.17	0.04	12.6 ± 4.4	12.9 ± 4.6	11.1 ± 5.2	13.0 ± 4.5**
	Logical Prose - IR - Themes (/7)	−0.03	0.22	5.0 ± 1.3	4.8 ± 1.6	4.2 ± 1.8	5.1 ± 1.5**
Language / Concept Formation	Similarities (/33)	−0.24	0.01	20.2 ± 6.2	22.0 ± 5.4	18.0 ± 8.2	21.1 ± 5.9*
	Boston Naming Test (/30)	−0.17	0.002	26.3 ± 3.2	26.8 ± 3.0	24.7 ± 4.7	26.3 ± 3.3*
	Verbal Fluency (VF) - Phonemic (FAS)	−0.40	0.07	30.0 ± 13.1	31.4 ± 11.2	26.2 ± 12.3	30.4 ± 12.6
Language / Processing Speed / Executive Function	VF - Semantic (Animals)	−0.26	0.01	16.2 ± 6.0	15.7 ± 5.5	13.0 ± 6.2	14.6 ± 5.6
	VF - Semantic (Vegetables)	−0.13	0.04	10.1 ± 3.0	10.8 ± 3.7	8.6 ± 4.4	9.9 ± 3.7
	Stroop Color Naming Time†	1.11	0.001	83.5 ± 17.5	76.1 ± 15.6**	88.7 ± 19.7	79.2 ± 19.7**
Language / Processing Speed / Executive Function	Stroop Word Reading Time†	0.71	0.01	62.9 ± 15.2	57.2 ± 11.8**	69.2 ± 20.5	60.2 ± 13.7**
	Stroop Interference Time†	2.66	0.02	197.0 ± 84.3	155.3 ± 53.5**	200.3 ± 101.4	166.3 ± 58.3
	Stroop Executive Index†	1.57	0.12	113.4 ± 81.6	79.5 ± 45.4**	114.6 ± 48.8	88.6 ± 89.9
	Trail-Making A Time (0–150 sec)†	1.01	0.03	53.1 ± 22.9	54.8 ± 27.8	70.3 ± 39.0	54.9 ± 24.6*
Visual Tracking / Processing Speed / Executive Function	Trail-Making B Time (0–300 sec)†	3.09	0.02	186.0 ± 91.2	152.5 ± 80.2*	191.6 ± 98.0	154.9 ± 81.8*
	Trails Executive Index†	2.35	0.03	134.2 ± 80.9	98.6 ± 65.0**	128.6 ± 77.0	101.0 ± 65.0*
Visual Tracking / Processing Speed / Working Memory	Digital Symbol (/133)	−0.59	0.01	41.4 ± 16.0	44.2 ± 14.4	34.8 ± 14.5	40.7 ± 14.6*
Verbal Learning / Verbal Memory Recall / Verbal Memory Recognition	HVLT Total trials 1–3 (/36)	−0.14	0.18	22.7 ± 5.8	23.1 ± 5.9	18.8 ± 7.5	20.9 ± 6.4
	DR (/12)	−0.06	0.26	7.5 ± 3.3	8.0 ± 3.0	5.8 ± 3.9	6.7 ± 3.3

Primary Domain	Neuropsychological Measures	Longitudinal Associations		Cross Sectional Analysis (Mean Scores ± SD)			
		Interaction β[a]	p-value	Follow-up 1		Follow-up 2	
				ε4+ (N=31)	ε4− (N=107)	ε4+ (N=31)	ε4− (N=107)
Verbal Memory Recall	*Retention % (0–150)*	−0.33	0.50	82.1 ± 36.2	83.4 ± 23.3	68.5 ± 35.9	75.2 ± 31.2
	Recognition Discrimination Index (−12 to 12)	−0.07	0.05	9.7 ± 1.7	9.9 ± 1.8	8.7 ± 2.5	9.3 ± 2.3
	Logical Prose - DR (/25)	−0.20	0.03	11.6 ± 5.6	11.5 ± 5.1	9.6 ± 5.6	11.4 ± 4.8*
	Logical Prose - DR - Themes (/7)	−0.03	0.27	4.8 ± 1.5	4.9 ± 1.7	4.3 ± 2.0	4.9 ± 1.7*
	% Retention (DR/IR)	−0.001	0.78	0.89 ± 0.3	0.88 ± 0.2	0.84 ± 0.3	0.87 ± 0.2
	Der Benton Visual Retention Matching Recognition (/15)	−0.06	0.14	11.5 ± 2.2	11.5 ± 2.4	10.2 ± 3.0	11.5 ± 2.4**
Visual Attention / Learning / Memory Recognition / Visual Memory Recall	Visual Reproduction - IR (/104)	−0.34	0.25	60.0 ± 15.7	64.3 ± 17.4	52.4 ± 23.5	60.0 ± 20.4*
	Visual Reproduction - DR (/104)	−0.41	0.22	33.7 ± 21.8	40.8 ± 21.0	33.8 ± 22.7	35.4 ± 20.9
	% Retention (DR/IR)	−0.004	0.35	0.53 ± 0.3	0.62 ± 0.3*	0.61 ± 0.3	0.55 ± 0.3

Abbreviations: IR=Immediate recall; DR=delayed recall; VF=verbal fluency

*p<0.10

**p<0.05; p-values based on two-tailed t-test

†On these tasks, positive scores indicate worse performance

[a]eg (age*genotype) effect of genotype on outcome change over time, between group annual difference in outcome decline

Longitudinal models adjusted for age (continuous), sex, smoking status (ever/never), European ancestry (yes/no), years of education, Levodopa use (yes/no), PD duration prior to baseline (0–3 years), and GDS score (continuous)