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Polymorphisms in dopamine-associated genes and cognitive decline in Parkinson's disease

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Objectives: Cognitive decline is common in Parkinson's disease (PD), but the underlying mechanisms for this complication are incompletely understood. Genotypes affecting dopamine transmission may be of importance. This study investigates whether genotypes associated with reduced prefrontal dopaminergic tone and/or reduced dopamine D2-receptor availability (Catechol-O-methyltransferase [*COMT*] Val^{158}Met genotype and *DRD2* C^{957}T genotype) affect the development of cognitive deficits in PD.

Materials and methods: One hundred and 34 patients with idiopathic PD, participating in a regional, population-based study of incident parkinsonism, underwent genotyping. After extensive baseline investigations (including imaging and biomarker analyses), the patients were followed prospectively during 6-10 years with neuropsychological evaluations, covering six cognitive domains. Cognitive decline (defined as the incidence of either Parkinson's disease mild cognitive impairment [PD-MCI] or dementia [PDD], diagnosed according to published criteria and blinded to genotype) was studied as the primary outcome.

Results: Both genotypes affected cognition, as shown by Cox proportional hazards models. While the *COMT* ^{158}Val/Val genotype conferred an increased risk of mild cognitive impairment in patients with normal cognition at baseline (hazard ratio: 2.13, $P = .023$), the *DRD2* ^{957}T/T genotype conferred an overall increased risk of PD dementia (hazard ratio: 3.22, $P < .001$). The poorer cognitive performance in *DRD2* ^{957}T/T carriers with PD occurred mainly in episodic memory and attention.

Conclusions: The results favor the hypothesis that dopamine deficiency in PD not only relate to mild cognitive deficits in frontostriatal functions, but also to a decline in memory and attention. This could indicate that dopamine deficiency impairs a wide network of brain areas.

KEYWORDS
COMT, dementia, DRD2, mild cognitive impairment, neurodegeneration, Parkinson's disease, Parkinson's disease genetics, population-based

1 | INTRODUCTION

Cognitive decline affects the majority of patients with idiopathic Parkinson's disease (PD) and has a major impact on quality of life[1] and morbidity,[2] but the phenotype, pathophysiology, and genetics of the condition are incompletely understood.

Genetic factors are likely to contribute to cognitive dysfunction in PD, as reported in a small number of studies.[3–6] A functional

Catechol-O-methyltransferase (*COMT*) gene polymorphism (Val^{158}Met; rs4680) results in a COMT enzyme with reduced dopamine degradation activity. Human carriers of two *COMT* ^{158}Met-alleles (^{158}Met homozygotes) show about 40% lower enzymatic activity in the brain compared to ^{158}Val homozygotes,[7] and higher prefrontal dopamine activation as measured by PET.[8] The *COMT* ^{158}Val-allele correlates with lower scores in tests of working memory in healthy volunteers (showing complex relations to the same functions in PD), and with gray matter atrophy in dopamine-innervated brain areas in patients with dementia disorders.[9]

Also affecting dopamine transmission, the C^{957}T polymorphism of the Dopamine Receptor D2 (*DRD2*) gene (rs6277) affects messenger RNA stability,[10] thereby influencing the level of expression of D2 receptors in the brain. The ^{957}C/C genotype correlates with higher D2 receptor densities in extrastriatal, thalamic and neocortical areas,[11] and better episodic memory in healthy elders.[12] Hypofunction of extrastriatal dopamine receptor D2 subsystems, including in the insula, was recently found to contribute to cognitive decline in PD.[13, 14]

Variability in genes related to dopamine transmission can potentially clarify the role of dopamine deficiency in relation to cognitive decline in PD. Therefore, we investigated the above-mentioned polymorphisms and cognitive functions in prospectively followed patients with PD. As a measurement of structural integrity, we included a sensitive CSF biomarker for neurodegeneration of myelinated axons (neurofilament light chain; NFL).[15]

2 | MATERIALS AND METHODS

2.1 | Participants

All patients with PD participated in a prospective, population-based incidence study of unselected cases of new-onset idiopathic parkinsonism, from a geographically defined area in Sweden. The study design has been described previously in detail.[16] In brief, inclusion lasted from January 1, 2004, through April 30, 2009. Patients were followed by a movement disorder team at a University hospital, representing the only neurology clinic in the region. Patients with secondary parkinsonism (eg, drug induced parkinsonism) or dementia at baseline were excluded. Of 182 enrolled in the study, 144 patients of European ancestry were diagnosed as having PD, and of these, samples for *COMT* Val^{158}Met and *DRD2* C^{957}T genotyping were collected from 134 (Figure 1). The patients with PD who did not provide samples for genotyping (n = 10) were older than the others (82.3 vs 70.4 years) and had lower Mini-Mental State Examination (MMSE) scores, but were otherwise comparable. All patients were followed with standardized clinical examinations, including MMSE and motor assessments at least yearly for 6-10 years, except 14 non-demented patients that died and were followed shorter. A diagnosis of PD required two examiners (neurologists specialized in movement disorders) to agree that the clinical criteria for the diagnosis were fulfilled according to the UK Parkinson's Disease Society Brain Bank criteria (UK PDSBB).[17] Having a family member with PD was not, however, treated as an exclusion criterium. All except three of the 134 patients with PD were examined with FP-CIT SPECT (DAT-scan), and all had pathological uptake. In three of the PD cases, the diagnosis was confirmed by autopsy. For comparison, *COMT* Val^{158}Met and *DRD2* C^{957}T genotype and cognitive function in 30 adults, demographically similar, neurologically healthy controls with normal FP-CIT uptake on SPECT, were also determined. All participants provided written informed consent. The study was approved by the Regional Medical Ethics Board in Umeå, Sweden, and was performed in accordance with the Declaration of Helsinki.

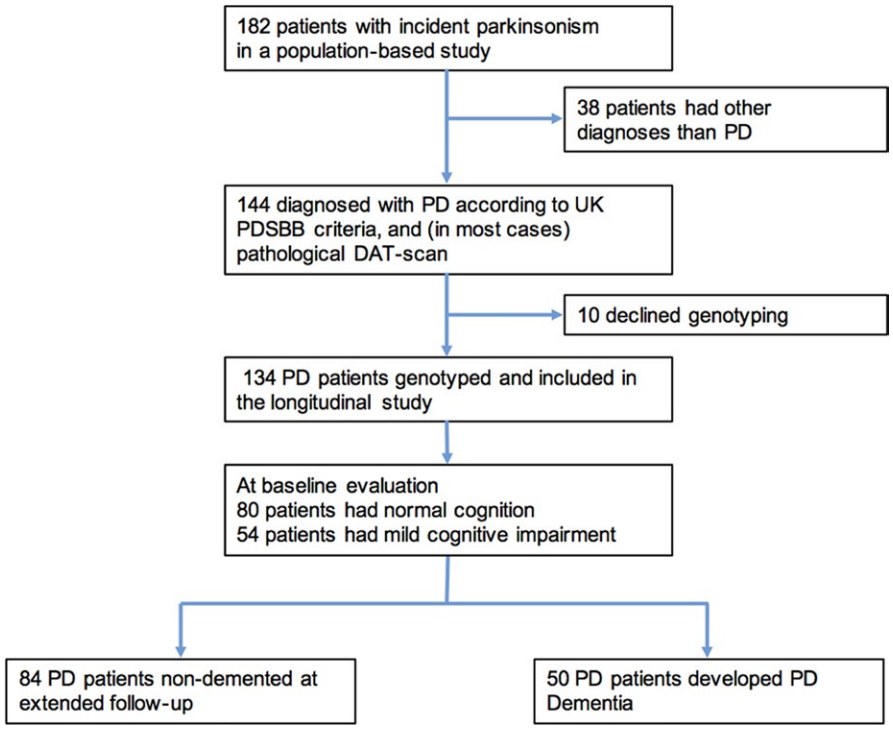

FIGURE 1 Flow of Parkinson's disease patients through the 10-year study period. PD, Parkinson's disease; UK PDSBB, UK Parkinson's Disease Society Brain Bank

2.2 | Genotyping and cerebrospinal fluid analysis

DNA was isolated from peripheral blood, using standard procedures. The polymorphisms of interest in the *COMT* and *DRD2* genes, rs4680 and rs6277, were genotyped using TaqMan Assay-by-design (Applied Biosystems, Foster City, CA, USA). The assay was performed according to manufacturer's instructions, and genotypes were analyzed using the allelic discrimination function of the TaqMan 7900 HT Fast Real-Time PCR system (Applied Biosystems, Foster City, CA, USA); 10% of the samples were run in duplicate, with 100% concordance. Genotype success rates of 98.3% (rs4680) and 100.0% (rs6277) were obtained. 103 of the patients with PD agreed to cerebrospinal fluid (CSF) collection by lumbar puncture at baseline, 1 year and/or 3 years. NFL concentration in CSF was measured with an ELISA method (NF-light® ELISA kit, UmanDiagnostics AB, Umeå, Sweden) as described by the manufacturer by board-certified laboratory technicians. The laboratory analyses were performed blinded from clinical data.

2.3 | Cognitive impairment

Extensive neuropsychological testing, covering specific cognitive domains and used for PD-mild cognitive impairment (MCI) and PD dementia (PDD) diagnostics, was performed at 0, 1, 3, 5, and 8 years.[18] MCI was diagnosed according to Movement Disorder Society criteria.[19] As the protocol included two tests of all cognitive domains but language, MCI was diagnosed on modified level 2 criteria, in keeping with previous research.[20] See Table 1 for tests used for MCI classification, the partition of the tests and criteria for PDD diagnoses. Structural MRI and routine laboratory tests were performed in all patients to exclude non-PDD causes of dementia. Diagnoses of PDD were determined by neurologists experienced in neurodegenerative disorders, blinded to the genotype of the patient. No patient with PD had the onset of dementia ≤1 year following motor onset (as in Lewy body dementia). All demented patients had PDD, according to published criteria.[21]

2.4 | Statistical analyses

Baseline differences in demographic, cognitive, and CSF variables between different *COMT* and *DRD2* genotype groups were tested by Kruskal-Wallis tests, ANOVA, and Fisher's exact test, as appropriate. Based on previous research, *a priori* hypothesized risk genotypes (*COMT* ^{158}Val/Val and *DRD2* ^{957}T/T) were compared with other genotypes, using Kaplan-Meier plots to investigate PD-MCI and PDD incidence. To allow for correction for age, sex, disease duration, and cognitive status at baseline, hazard ratios were estimated by Cox proportional hazards regression models. Proportionality of hazards was evaluated by log-log methods. To investigate potential domain-specific effects, neuropsychological test scores were merged into six domains (episodic memory, working memory, attention, executive function, visuospatial function, and language), following the partition suggested by the Movement Disorder Society (see Table 1).[19] The domain scores (measured by average standard deviations above or below the score mean at baseline; ie, Z-score) in five domains, throughout the study period, and CSF NFL concentrations (tested at 0, 1, and 3 years), were compared in the genotype groups by linear mixed models, run with and without adjustment (see Table 4). The use of mixed-effects models accounts for variability in length of follow-up and is flexible with missing data. Although used in MCI diagnostics, language was excluded from mixed model

TABLE 1 Tests used for Parkinson's disease cognitive impairment classification

Neuropsychological function	Test
Episodic memory	Free and Cued Selective Reminding Test (FCSRT)[a] Logical memory and Paired associative learning from Wechsler memory scale (WMS)[a] Brief visuospatial memory test (BVMT) total recall[a]
Working memory	Digit span forward, from Wechsler Adult Intelligence Scale (WAIS) III[b] Digit span backwards, from Wechsler Adult Intelligence Scale (WAIS) III[b]
Attention	Trail Making Test (TMT) A[c] and B[c]
Verbal function	Controlled Oral Word Association (COWA) Boston Naming Test (BNT)
Visuospatial function	The Benton Judgement of Line Orientation test[d] Pentagon copying from Mini-Mental State Examination (MMSE)
Executive function	Wisconsin card sorting test (WCST) – computer version 2[e] Mental Control from Wechsler memory scale (WMS) Category fluency (animals in 60 seconds)[e]

A domain score was calculated by the mean of standardized scores (Z-scores) in the tests of episodic memory[a], working memory[b], attention[c], visuospatial function[d], and executive function[e].

Subjects were classified as having mild cognitive impairment (PD-MCI) if: (i) impaired in a minimum of two tests in one domain (single domain MCI) or in a minimum of one test in two different domains (multiple domain MCI), (ii) impairments were ≥1.5 standard deviations below mean of normative data, (iii) self-perceived cognitive decline was reported by Questionnaire and/or directly by patient and/or family member, and (iv) no functional impairment in basic activities of living.

Parkinson's disease dementia (PDD) diagnoses were based on neuropsychological test results, objective and subjective cognitive decline, and by the occurrence of functional impairment in basic activities of living (ie, driving a car, social or personal care, medication management) due to cognitive decline.

analyses because of non-normal distribution of scores. Differences in episodic memory (if found) were further analyzed in free- and cued recall conditions. $P < .05$ was considered significant. Holm-Bonferroni correction for multiple comparisons was made in the Cox regression models and the mixed model analyses (see Tables 3 and 4). All statistical analyses were performed using a software program (SPSS 23.0; SPSS Inc).

3 | RESULTS

COMT Val^{158}Met genotype was successfully determined in 132 of the patients with PD who donated samples and *DRD2* C^{957}T genotype in 134 (all) of the patients with PD who donated samples. The genotypes had relatively even distributions among the participants. At baseline, there were no major differences in clinical characteristics or NFL concentrations in the different *COMT* and *DRD2* genotype groups (Table 2); 54 (40.3%) of the patients with PD had MCI at baseline. During follow-up, 50 patients (37.3%) developed PDD, and 28 patients (20,9%) converted from PD-normal to MCI. The genotyped patients had a median follow-up of 7.0 years (interquartile range: 6.0-9.0 years). There were no significant differences in medication dosages between the genotype groups during follow-up, as measured by mean levodopa equivalent dose scores. In the healthy control group, 25 participants carried *COMT* ^{158}Met-alleles and 19 participants carried *DRD2* ^{957}C-alleles.

3.1 | *COMT* genotype in PD

As shown in Figure 2A, the *COMT* ^{158}Val/Val genotype increased the risk of any cognitive decline in PD during follow-up (decline from PD-normal to PD-MCI or from PD-MCI to PDD, $P = .006$). However, as shown by Cox regression (Table 3) and in Figure 2B, the increased risk of cognitive decline was driven by a higher incidence of PD-MCI among carriers of two *COMT* ^{158}Val alleles (*COMT* ^{158}Val/Val homozygotes). The *COMT* ^{158}Val/Val homozygotes had 2.1 times higher hazard for developing PD-MCI compared to PD patients with other *COMT* ^{158} genotypes, after correction for age, sex, disease duration, and baseline cognitive status ($P = .023$), but the *COMT* ^{158}Val/Val genotype was not a risk factor for PDD. Analyses of survival times with no cognitive impairment showed that the increased risk of cognitive decline in *COMT* ^{158}Val/Val carriers occurred between baseline and the fifth year of follow-up. There was no measurable effect related to *COMT* genotype in the analysis of single cognitive domains (estimated by linear Mixed Models). The concentration of NFL in cerebrospinal fluid (CSF) did not significantly differ between the different *COMT* genotype groups. The *COMT* genotype had no effects on cognitive functions in the healthy controls (data not shown).

3.2 | *DRD2* genotype in PD

As shown in Figure 2D, the *DRD2* ^{957}T/T genotype increased the risk of any cognitive decline in PD, measured by incidence of either PD-MCI

TABLE 2 Baseline characteristics of 134 Parkinson's disease patients in relation to *COMT* Val^{158}Met- and *DRD2* C^{957}T genotype

Variable	*COMT* ^{158}Met/Met genotype (n = 42)	*COMT* ^{158}Val/Met genotype (n = 64)	*COMT* ^{158}Val/Val genotype (n = 26)	*P*-value
Age	70.3 (9.0)	69.3 (10.3)	72.9 (9.1)	.273
Disease duration in months, median (IQR)	25.4 (12.6-36.1)	13.4 (8.1-24.4)	16.9 (10.0-35.3)	.042
Sex, M:F (% male)	23:19 (54.8%)	41:23 (64.1%)	15:11 (57.7%)	.614
UPDRS III, median (IQR)	26 (13-36)	25 (18-34)	29 (24-37)	.340
MMSE	28.6 (1.4)	28.7 (1.4)	28.7 (1.3)	.959
CSF NFL concentration, ng/L, [number with baseline sample]	1247 (760) [32]	1499 (1601) [45]	1508 (738) [18]	.638
Variable	**DRD2 ^{957}C/C genotype (n = 31)**	**DRD2 ^{957}T/C genotype (n = 66)**	**DRD2 ^{957}T/T genotype (n = 37)**	***P*-value**
Age	71.9 (9.7)	69.1 (10.2)	71.5 (9.3)	.286
Disease duration in months, median (IQR)	24.0 (10.2-41.0)	12.7 (8.0-30.0)	20.6 (12.2-31.0)	.138
Sex, M:F (% male)	18:13 (58.1%)	40:26 (60.6%)	22:15 (59.5%)	.971
UPDRS III, median (IQR)	28 (21-35)	23 (16-31)	26 (19-39)	.166
MMSE	28.5 (1.6)	28.8 (1.3)	28.4 (1.6)	.377
CSF NFL concentration, ng/L, [number with baseline sample]	1465 (762) [23]	1269 (848) [50]	1762 (1928) [27]	.247

Values are expressed as means (standard deviation) unless otherwise stated. Disease duration was defined by time from onset of first motor symptom to diagnosis of PD. COMT, catechol-O-methyltransferase; DRD2, dopamine receptor D2; PD, Parkinson's disease; IQR, interquartile range; UPDRS III, Unified Parkinson's Disease Rating Scale, part III (motor function); MMSE, Mini-Mental State Examination; CSF, cerebrospinal fluid; NFL, neurofilament light chain protein.

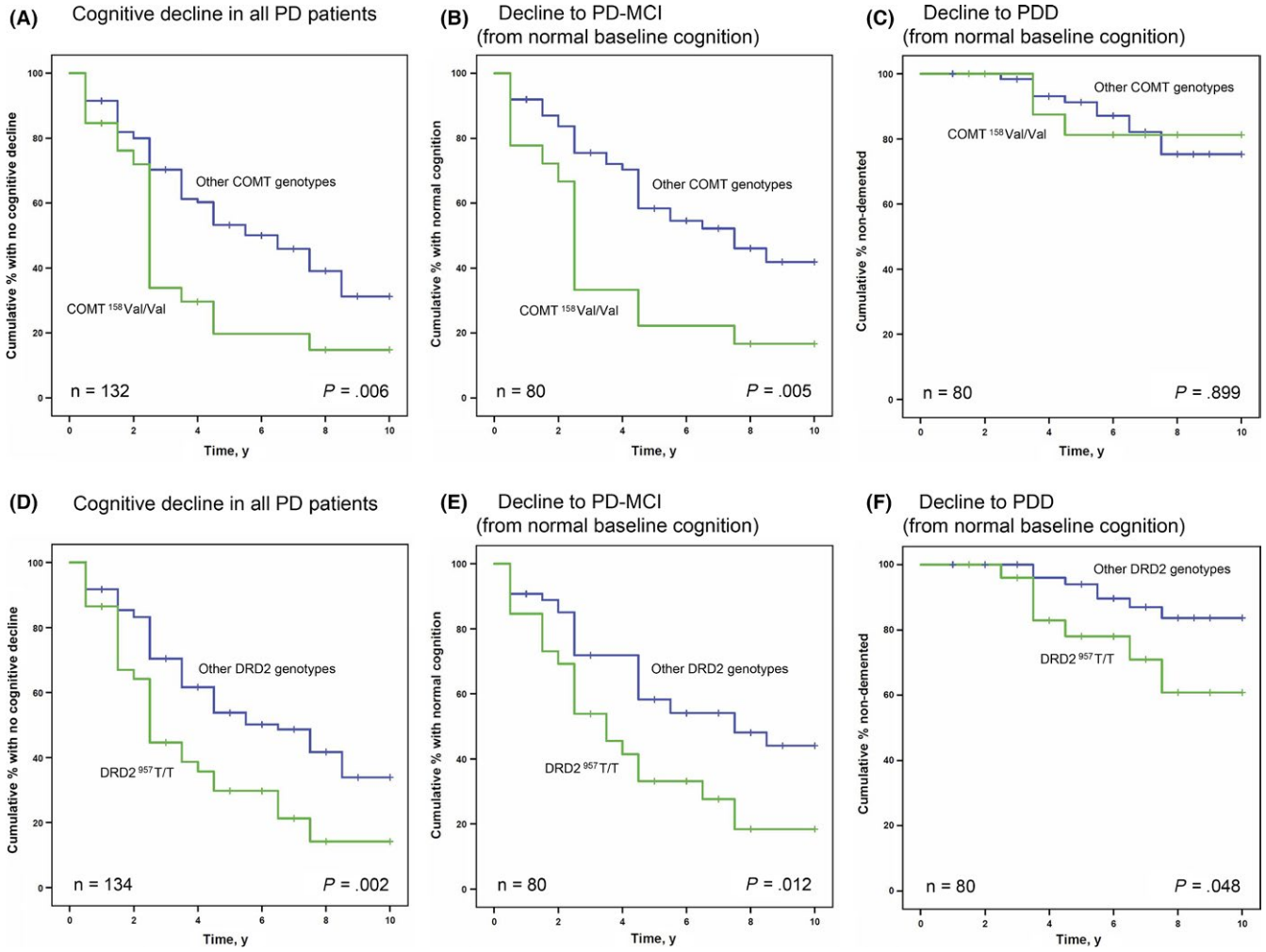

FIGURE 2 Effect of the *COMT* Val^{158}Met and *DRD2* C^{957}T genotypes on cognitive decline in Parkinson's disease. Kaplan-Meier plots showing the incidence of cognitive decline in relation to *COMT* (A–C) and *DRD2* (D–F) genotype. The specific incidence of PD-MCI and PDD (B, C, E, and F) is shown here only for the patients who had a normal cognitive function at baseline (n = 80). PD, Parkinson's disease; COMT, catechol-O-methyltransferase; DRD2, dopamine receptor D2; MCI, mild cognitive impairment; PDD, Parkinson's disease dementia

or PDD (P = .002). More specifically, carrying a *DRD2* ^{957}T/T genotype increased the hazard for developing PDD 3.2 times, in comparison with PD patients with other *DRD2* genotypes (P < .001; Table 3), after correction for age, sex, disease duration, and baseline cognitive status. The ^{957}T/T genotype was also a risk factor for PD-MCI development among patients with normal cognition at baseline (n = 80, P = .018, Table 3). Conversely, carriers of any *DRD2* ^{957}C alleles had a lower risk of all types of cognitive decline (Figure 2FD-; Table 3). Analysis of test scores in specific cognitive domains showed that carriers of the *DRD2* ^{957}T/T genotype had significantly poorer performances in episodic memory (on average 0.25 standard deviations lower scores, P = .007) and in attention (on average 0.58 standard deviations lower scores, P < .001) after correction for confounding factors (Table 4). Patients with PD with a *DRD2* ^{957}T/T genotype tended to perform slightly worse in all domains, but apart from the differences in episodic memory and attention, effects were non-significant after correction for multiple comparisons. Detailed analysis of episodic memory showed opposite effects of *DRD2* genotype in free versus cued recall. While PD patients with the *DRD2* ^{957}T/T genotype had a significantly poorer performance in free recall (P = .021), they performed better in cued recall (P = .026). NFL concentrations in CSF did not differ between the *DRD2* genotypes.

In the group of healthy control participants, *DRD2* ^{957}T/T carriers performed poorer in tests of attention at an uncorrected statistical threshold (on average 0.47 standard deviations lower scores, P = .031, after correction for age, sex, time of testing, and years of education), similar to the performance in patients with PD. The difference was, however, non-significant corrected for multiple comparisons.

4 | DISCUSSION

By prospectively following a population-representative cohort of patients with PD with neuropsychological evaluations for up to 10 years, we found that two common, functional polymorphisms in genes related to dopamine transmission (the *COMT* and *DRD2* genes), affect the evolution of cognitive deficits, and alter the risks of MCI and PDD.

TABLE 3 Cognitive decline in 134 Parkinson's disease patients, in relation to *COMT* Val[158]Met- and *DRD2* C[957]T genotype

	H.R. (95% CI)	*P*-value
Any cognitive decline (MCI or PDD)		
↑No. of *COMT* [158]Val-alleles	1.51 (1.11-2.06)	.009[a]
↑No. of *DRD2* [957]T-alleles	1.64 (1.17-2.31)	.004[a]
COMT [158]Val/Val vs. any Met allele	1.79 (1.06-3.03)	.030[a]
DRD2 [957]T/T vs. any C allele	2.31 (1.41-3.79)	<.001[a]
COMT [158]Val/Val or *DRD2* [957]T/T	2.46 (1.54-3.91)	<.001[a]
MCI development[b]		
COMT [158]Val/Val vs. any Met allele	2.13 (1.11-4.08)	.023[a]
DRD2 [957]T/T vs. any C allele	2.12 (1.14-3.94)	.018[a]
PDD development		
COMT [158]Val/Val vs. any Met allele	1.11 (0.51-2.45)	.791
DRD2 [957]T/T vs. any C allele	3.22 (1.64-6.30)	<.001[a]

Hazard Ratios (H.R.) are for risks within 6-10 years, after correction for age, disease duration, sex, and baseline cognitive status (normal or MCI).
[a]Significant ($P < 0.05$) after Holm-Bonferroni correction.
[b]Risk of PD-MCI was analyzed in the 80 patients who had normal cognition at baseline, while the other outcomes were analyzed in all patients.
COMT, catechol-O-methyltransferase; DRD2, dopamine receptor D2; MCI, mild cognitive impairment; PDD, Parkinson's disease dementia; ↑, higher number (0, 1, or 2).

Biomarkers predictive of cognitive dysfunction in idiopathic PD are of value because of the serious impact of such complications. Furthermore, common variations in genes with known biological effects have been favored as a mean to test causality of disease mechanisms in observational studies.[22] The present study extends earlier observations of a relationship between frontostriatally based cognitive functions and genes associated with dopamine transmission and is, to our knowledge, the first to demonstrate the *DRD2* [957]T/T genotype as a risk factor for PDD. The observed effects were not explained by differences in demographic factors such as age or by differences in medication.

Converging evidence points to a multifactorial etiology of cognitive dysfunction in PD. Patients with early PD underrecruit an extensive frontostriatal brain network as a consequence of dopaminergic hypofunction,[23] contributing to cognitive impairments. In later disease phases, accumulating cortical Lewy bodies, Alzheimer disease-type brain pathology and hypofunction in non-dopaminergic (ie, acetylcholinergic) transmitter systems contribute to PD dementia (PDD).[24] According to the "dual syndrome hypothesis," the early, dopamine dysfunction-related impairments of frontostriatal, executive functions in PD are stable and do not strongly relate to dementia, while the more "posterior" deficits in visuospatial function or memory relate to cortical pathology that is predictive of PDD.[25] The present findings potentially modify this hypothesis. In particular, the finding of *DRD2*

TABLE 4 Longitudinal cognitive function and cerebrospinal fluid data in 134 Parkinson's disease patients, in relation to *COMT* Val[158]Met- and *DRD2* C[957]T genotype

Cognitive domain	Mean difference, measured in SDs (95% CI)	*P*-value
COMT [158]Val/Val genotype vs. any Met allele		
Episodic memory	−0.05 (−0.25-0.15)	.598
Working memory	−0.14 (−0.53-0.25)	.482
Attention	−0.18 (−0.20-0.56)	.350
Executive function	−0.19 (−0.51-0.13)	.245
Visuospatial function	−0.20 (−0.62-0.22)	.343
DRD2 [957]T/T genotype vs. any C allele		
Episodic memory	−0.25 (−0.43 to −0.07)	.007[a]
Free recall	−0.42 (−0.78 to −0.07)	.021[a]
Cued recall	0.36 (0.04-0.67)	.026[a]
Working memory	−0.33 (−0.69-0.01)	.060
Attention	−0.58 (−0.91 to −0.26)	<.001[a]
Executive function	−0.31 (−0.61 to −0.02)	.034
Visuospatial function	−0.38 (−0.75 to −0.01)	.044
Cerebrospinal fluid NFL concentration	**Difference, ng/L (95% CI)**	***P*-value**
COMT [158]Val/Val genotype vs. any Met allele	3.8 (−433.0-440.7)	.986
DRD2 [957]T/T genotype vs. any C allele	265.2 (−125.7-656.1)	.181

Fixed effects estimates for differences at 0, 1, 3, 5, and 8 years (for NFL concentration at 0, 1, and 3 years), after correction for age, sex, disease duration, time of testing, and years of education.
[a]Significant ($P < 0.05$) after Holm-Bonferroni correction.
COMT, catechol-O-methyltransferase; DRD2, dopamine receptor D2; SD, standard deviation; NFL, neurofilament light chain protein.

^{957}T/T genotype as a risk factor for dementia (with the strongest detrimental effects seen in attention and episodic memory) suggests that dopamine hypofunction in PD may have effects beyond "frontostriatal" brain functioning including, possibly, alterations of distributed, dopamine-dependent attention- and/or memory networks.

In healthy subjects, the high-activity *COMT* ^{158}Val-allele has generally been found to impair executive functions such as working memory and cognitive flexibility.[26,27] In PD, studies by Williams-Gray et al. showed that in later disease phases (>1.6 years after diagnosis), the Val-allele correlated with impairments in executive functioning (as measured by the "Tower of London" test), similar to findings in controls, while in early disease (<1.6 years after diagnosis), the effect was opposite.[4,28] This was suggested to result from an inverted U-shaped relation between cortical dopamine levels and prefrontal function, where a transient up-regulation of prefrontal dopamine would cause "overdosing" in Met-carriers in early PD, while the same patients would have an advantage in later disease phases, when progressive degeneration of dopaminergic systems produce more marked dopamine deficits. The present finding of mild cognitive impairments (MCI, as diagnosed according to the Movement Disorder Society) in *COMT* ^{158}Val/Val carriers with PD could relate to the fact that the mean age at baseline was higher than in the CamPaIGN cohort, possibly making the studied population more vulnerable to a high prefrontal dopamine clearance. The invariably detrimental effect of the ^{158}Val/Val genotype on cognition in the present study is also compatible with structural effects in the brain, for example an increased gray matter atrophy in dopamine-innervated areas, such as reported in previous studies.[9]

In relation to DRD2 function, patients with PD often experience memory problems characterized by an inability to recall information. This may partly relate to dopamine deficiency. The hippocampus is strongly interconnected with dopaminergic neurons in the midbrain,[29] and several lines of evidence have established the importance of D2 receptor function in attention and memory.[30] Specifically, the DRD2 system is linked to transient memory updating processes.[31,32] A reduction in D2 receptors has been found in PD[13] and in imaging studies, memory deficits in PD are correlated with reduced extrastriatal D2 receptor binding in the medial temporal lobe, including the insula, in parts of the so-called salience network.[14] The present findings of poorer performances in attention and episodic memory and an increased risk of dementia in *DRD2* ^{957}T/T carriers with PD could, potentially, relate to reduced function or increased vulnerability in D2-dependent "salience networks" of the brain (eg, in medial, temporal structures). In this respect, the opposite effect on episodic memory in free recall compared to cued recall, related to the *DRD2* ^{957}T/T genotype, is intriguing. This might suggest that the typical memory impairment in PD (memory deficits that improve with external cues) is a hypodopaminergic trait, specifically related to reduced function in D2 receptor signaling. This would be consistent with the proposed role of D2 receptors in flexible memory updating, and the corresponding memory deficit could gradually become more detrimental in PD compared to effects induced by COMT enzyme heterogeneity (related to the *COMT* Val^{158}Met polymorphism).

Interestingly, the *DRD2* ^{957}C/C genotype (and the *DRD2* gene locus) has previously been found to be associated to susceptibility to schizophrenia in younger populations.[33,34] The seemingly opposite effects of the *DRD2* ^{957}C allele in different populations (increasing the risk of schizophrenia in young populations, while protecting against cognitive decline in PD) may be an example of genetic pleiotropism. The precise mechanisms behind the *DRD2*-genotype-induced effects on cognition were not determined by this study but merits further investigation.

While the effects on cognition were different for the *COMT* and *DRD2* genotypes, none of the genotypes affected cerebrospinal fluid NFL concentration (which has been found predictive of PDD).[35] This suggests that the *COMT* and *DRD2* genotypes did not affect cognition through gross effects on neurodegeneration, at least not as measured by injury of myelinated axons. This is consistent with the trend of a similarly poorer performance in tests of attention in the healthy control persons with a *DRD2* ^{957}T/T genotype, which may indicate that the *DRD2* genotype-related effect on attention is not specific to degenerating dopaminergic systems, but rather is an effect on functions common to both disease-affected and normal brains. The effect may, however, be amplified in PD. It could also be of interest to investigate the studied genotypes in Lewy Body Dementia.

A limitation was the small number of healthy controls and patients and the theoretical classification of cognitive tests in cognitive domains, which is, however, not standardized in clinical research settings. Our study also has strengths, namely a population-based and longitudinal design, evaluation of incident cases, and the use of an extensive neuropsychological test battery at several times during the follow-up period. The risk of incorrect PD diagnosis was minimized by the long follow-up periods, the finding of pathologic uptake on DAT-scan examination in all (100%) of the examined patients with PD, and by confirmation of the diagnosis by autopsy in a small number of cases.

In conclusion, although confirmation in independent, larger studies is needed, our results suggest that the *COMT* ^{158}Val/Val genotype (which is known to produce a decrease in synaptic dopamine availability) increases the risk of MCI in PD and that the *DRD2* ^{957}T/T genotype is a risk factor for PDD. These findings provide new insights into the mechanisms of cognitive dysfunction in PD. In the clinical setting, the *DRD2* ^{957}T/T genotype could possibly be used as a marker for PDD risk.

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CONFLICT OF INTERESTS

David Bäckström, Magdalena Eriksson, Gabriel Granåsen, Sofia Mayans, Eva Elgh, Henrik Zetterberg, Kaj Blennow, Lars Forsgren – Reports no disclosures. Jan Linder reports receiving honoraria for lectures from

GSK, Lundbeck, Boehringer Ingelheim, Abbott, AbbVie, Solvay, Orion Pharma, UCB, Nordic InfuCare, Medtronic, and IPSEN and serving on advisory boards for Boehringer Ingelheim, Lundbeck, and GSK.

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REFERENCES

1. Reginold W, Duff-Canning S, Meaney C, et al. Impact of mild cognitive impairment on health-related quality of life in Parkinson's disease. *Dement Geriatr Cogn Disord*. 2013;36:67-75.
2. Fletcher P, Leake A, Marion MH. Patients with Parkinson's disease dementia stay in the hospital twice as long as those without dementia. *Mov Disord*. 2011;26:919.
3. Kalinderi K, Bostantjopoulou S, Fidani L. The genetic background of Parkinson's disease: current progress and future prospects. *Acta Neurol Scand*. 2016;134:314-326.
4. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain*. 2009;132:2958-2969.
5. Winder-Rhodes SE, Evans JR, Ban M, et al. Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. *Brain*. 2013;136:392-399.
6. Ferreira M, Massano J. An updated review of Parkinson's disease genetics and clinicopathological correlations. *Acta Neurol Scand*. 2017;135:273-284.
7. Chen J, Lipska BK, Halim N, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am J Hum Genet*. 2004;75:807-821.
8. Wu K, O'Keeffe D, Politis M, et al. The catechol-O-methyltransferase Val(158)Met polymorphism modulates fronto-cortical dopamine turnover in early Parkinson's disease: a PET study. *Brain*. 2012;135:2449-2457.
9. Gennatas ED, Cholfin JA, Zhou J, et al. COMT Val158Met genotype influences neurodegeneration within dopamine-innervated brain structures. *Neurology*. 2012;78:1663-1669.
10. Duan J, Wainwright MS, Comeron JM, et al. Synonymous mutations in the human dopamine receptor D2 (DRD2) affect mRNA stability and synthesis of the receptor. *Hum Mol Genet*. 2003;12:205-216.
11. Hirvonen MM, Lumme V, Hirvonen J, et al. C957T polymorphism of the human dopamine D2 receptor gene predicts extrastriatal dopamine receptor availability in vivo. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33:630-636.
12. Li SC, Papenberg G, Nagel IE, et al. Aging magnifies the effects of dopamine transporter and D2 receptor genes on backward serial memory. *Neurobiol Aging*. 2013;34:358. e1-10.
13. Christopher L, Duff-Canning S, Koshimori Y, et al. Salience network and parahippocampal dopamine dysfunction in memory-impaired Parkinson disease. *Ann Neurol*. 2015;77:269-280.
14. Christopher L, Marras C, Duff-Canning S, et al. Combined insular and striatal dopamine dysfunction are associated with executive deficits in Parkinson's disease with mild cognitive impairment. *Brain*. 2014;137:565-575.
15. Bacioglu M, Maia LF, Preische O, et al. Neurofilament light chain in blood and csf as marker of disease progression in mouse models and in neurodegenerative diseases. *Neuron*. 2016;91:494-496.
16. Linder J, Stenlund H, Forsgren L. Incidence of Parkinson's disease and parkinsonism in northern Sweden: a population-based study. *Mov Disord*. 2010;25:341-348.
17. Gibb WR, Lees AJ. The significance of the Lewy body in the diagnosis of idiopathic Parkinson's disease. *Neuropathol Appl Neurobiol*. 1989;15:27-44.
18. Elgh E, Domellöf M, Linder J, Edström M, Stenlund H, Forsgren L. Cognitive function in early Parkinson's disease: a population-based study. *Eur J Neurol*. 2009;16:1278-1284.
19. Litvan I, Goldman JG, Tröster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord*. 2012;27:349-356.
20. Yarnall AJ, Breen DP, Duncan GW, et al. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. *Neurology*. 2014;82:308-316.
21. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007;22:1689-1707; quiz 837.
22. Ebrahim S. DAVEY SMITH G. Mendelian randomization: can genetic epidemiology help redress the failures of observational epidemiology? *Hum Genet*. 2008;123:15-33.
23. Ekman U, Eriksson J, Forsgren L, Mo SJ, Riklund K, Nyberg L. Functional brain activity and presynaptic dopamine uptake in patients with Parkinson's disease and mild cognitive impairment: a cross-sectional study. *Lancet Neurol*. 2012;11:679-687.
24. Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. *Lancet Neurol*. 2012;11:697-707.
25. Kehagia AA, Barker RA, Robbins TW. Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis. *Neurodegener Dis*. 2013;11:79-92.
26. Egan MF, Goldberg TE, Kolachana BS, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A*. 2001;98:6917-6922.
27. Dickinson D, Elvevåg B. Genes, cognition and brain through a COMT lens. *Neuroscience*. 2009;164:72-87.
28. Williams-Gray CH, Hampshire A, Barker RA, Owen AM. Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. *Brain*. 2008;131:397-408.
29. Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron*. 2005;46:703-713.
30. Floresco SB, Magyar O. Mesocortical dopamine modulation of executive functions: beyond working memory. *Psychopharmacology*. 2006;188:567-585.
31. Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology*. 2004;29:1943-1961.
32. Nyberg L, Andersson M, Forsgren L, et al. Striatal dopamine D2 binding is related to frontal BOLD response during updating of long-term memory representations. *NeuroImage*. 2009;46:1194-1199.
33. Liu L, Fan D, Ding N, et al. The relationship between DRD2 gene polymorphisms (C957T and C939T) and schizophrenia: a meta-analysis. *Neurosci Lett*. 2014;583:43-48.
34. Consortium SWGOTPG. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014;511:421-427.
35. Bäckström DC, Eriksson Domellöf M, Linder J, et al. Cerebrospinal fluid patterns and the risk of future dementia in early, incident Parkinson disease. *JAMA Neurol*. 2015;72:1175-1182.

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