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Association of Parkinson Disease Risk Loci With Mild Parkinsonian Signs in Older Persons

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Abstract

IMPORTANCE—Parkinsonian motor signs are common in the aging population and are associated with adverse health outcomes. Compared with Parkinson disease (PD), potential genetic risk factors for mild parkinsonian signs have been largely unexplored.

OBJECTIVE—To determine whether PD susceptibility loci are associated with parkinsonism or substantia nigra pathology in a large community-based cohort of older persons.

DESIGN, SETTING, AND PARTICIPANTS—Eighteen candidate single-nucleotide polymorphisms from PD genome-wide association studies were evaluated in a joint clinicopathologic cohort. Participants included 1698 individuals and a nested autopsy collection of

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821 brains from the Religious Orders Study and the Rush Memory and Aging Project, 2 prospective community-based studies.

MAIN OUTCOMES AND MEASURES—The primary outcomes were a quantitative measure of global parkinsonism or component measures of bradykinesia, rigidity, tremor, and gait impairment that were based on the motor Unified Parkinson's Disease Rating Scale. In secondary analyses, we examined associations with additional quantitative motor traits and postmortem indices, including substantia nigra Lewy bodies and neuronal loss.

RESULTS—Parkinson disease risk alleles in the *MAPT* (rs2942168; *P* = .0006) and *CCDC62* (rs12817488; *P* = .004) loci were associated with global parkinsonism, and these associations remained after exclusion of patients with a PD diagnosis. Based on motor Unified Parkinson's Disease Rating Scale subscores, *MAPT* (*P* = .0002) and *CCDC62* (*P* = .003) were predominantly associated with bradykinesia, and we further discovered associations between *SREBF1* (rs11868035; *P* = .005) and gait impairment, *SNCA* (rs356220; *P* = .04) and rigidity, and *GAK* (rs1564282; *P* = .03) and tremor. In the autopsy cohort, only *NMD3* (rs34016896; *P* = .03) was related to nigral neuronal loss, and no associations were detected with Lewy bodies.

CONCLUSIONS AND RELEVANCE—In addition to the established link to PD susceptibility, our results support a broader role for several loci in the development of parkinsonian motor signs and nigral pathology in older persons.

Parkinson disease (PD) is a neurodegenerative disorder characterized by progressive rest tremor, bradykinesia, rigidity, and gait impairment; these motor symptoms are collectively referred to as *parkinsonism*.[1] At autopsy, PD pathology consists of α-synuclein protein inclusions, termed *Lewy bodies*, within the midbrain substantia nigra and associated degeneration of dopaminergic neurons. Data[2–4] suggest that nigral Lewy bodies and neuronal loss are also related to mild parkinsonian signs among persons without PD. In addition, clinical parkinsonism, which follows disruption of nigrostriatal pathways controlling movement,[5] can also be associated with other common age-related neuropathologies, including cerebrovascular lesions[6,7] and Alzheimer disease.[8] In fact, the manifestation of mild parkinsonian signs is common in older individuals, having been reported[9–11] to occur in up to 50% of some cohorts. Furthermore, mild parkinsonian signs are associated with substantial morbidity,[12,13] including risk of mild cognitive impairment,[14] dementia,[15,16] and mortality[11]; therefore, understanding the causes and risk factors are an important public health goal.

Genome-wide association studies (GWASs)[17–20] have successfully identified several common susceptibility loci for PD, and we investigated whether these alleles more broadly affect mild parkinsonian motor signs or nigral pathology in older persons. Our study was based on the hypothesis that overlapping genetic mechanisms may be responsible for PD, other causes of nigrostriatal pathology, and perhaps additional determinants of motor impairment that present as parkinsonism. We leveraged data from the Religious Orders Study (ROS)[21] and Rush Memory and Aging Project (MAP),[22] 2 complementary, community-based cohort studies of aging combining prospective, longitudinal clinical evaluations with brain donation at death. We found that 2 PD susceptibility loci, *MAPT* (OMIM 157140) and *CCDC62* (OMIM 613481), are associated with global parkinsonism,

and several others are associated with discrete parkinsonian features or additional motor traits, suggesting a broader effect on age-related motor impairment in the population. Unexpectedly, although variants at *NMD3* (OMIM 611021) were related to substantia nigra neuronal loss, none of the PD loci showed associations with nigral Lewy bodies.

Methods

Participants and Clinical Evaluations

Study participants from ROS[21] and MAP[22] did not have a diagnosis of dementia at enrollment, agreed to annual clinical evaluations, and signed an informed consent and an Anatomic Gift Act form to donate their brains at death. They did not receive financial compensation. The studies were approved by the institutional review board of Rush University Medical Center. A total of 1698 individuals (ROS, 810, and MAP, 888) with genotyping data were available for analyses of global parkinsonism, and the nested autopsy cohort included 821 participants at the time of these analyses. The ROS[21] and MAP[22] participants received a uniform structured clinical evaluation that includes medical history, neurologic examination, and neuropsychological performance tests. Diagnosis of PD (n = 46) was based on self-reported history, including L-dopa treatment at any time before or during the study.[2] Parkinsonism was assessed by trained nurses at study entry and was based on 26 items from a modified version of the motor section of the Unified Parkinson's Disease Rating Scale (mUPDRS).[23] Four previously established parkinsonian sign scores (bradykinesia, rigidity, tremor, and gait disturbance) were derived from these 26 items, and a summary global parkinsonian sign score was constructed by averaging these 4 scores, as detailed in prior publications.[2,23] Clinical evaluations also included testing of upper and lower extremity motor function, including quantitative assessments of gait (time and number of steps to walk 2.4 m and turn 360°), Purdue pegboard, and finger tapping, as previously described.[7,12]

Postmortem Procedures

The mean (SD) postmortem interval was 8.3 (7.4) hours. As part of comprehensive neuropathologic evaluations, diagnostic blocks were dissected from the midbrain, including the substantia nigra.[24] Nigral neuronal loss was assessed in the substantia nigra in the mid to rostral midbrain near or at the exit of the third nerve using hematoxylin-eosin stain and 6-μm sections using a semiquantitative scale (0–3).[2] Lewy bodies were identified with antibodies to α-synuclein using alkaline phosphatase as the chromogen.[24] A tissue diagnosis of PD was based on the presence of nigral Lewy bodies and moderate or severe nigral neuronal loss.[25] Postmortem indices of Alzheimer disease pathology and cerebrovascular disease were collected as previously described.[6,26]

Genotyping and Single-Nucleotide Polymorphisms

Genome-wide genotyping and quality-control procedures have been reported.[27] Genotype imputation was performed using BEAGLE software, version 3.3.2 (http://faculty.washington.edu/browning/beagle/beagle.html). We used reference haplotype panels from 87 Centre d' Etude du Polymorphisme Humain individuals of Northern European ancestry in the 1000 Genomes Project (1000 Genomes Project Consortium interim phase I

haplotypes, 2010–2011 data freeze).[28,29] For selection of candidate single-nucleotide polymorphisms (SNPs), we initially consulted the PDGene website(http://www.pdgene.org),[30] which performs meta-analyses of available GWAS data and ranks susceptibility loci with the strongest statistical evidence of association. The available PDGene meta-analysis results were last updated in November 2011; therefore, a select number of additional candidate SNPs were supplemented based on published studies.[17–20] All of the PD susceptibility loci evaluated in this study have been reported to have genome-wide significant associations with PD ($P < 5 \times 10^{-8}$) in case-control studies.[17–20] In our imputed data set, we did not have confident estimates of genotypes for SNPs at the *MMP16* (chr8:89442157) or *SYT11-GBA* (chr1: 154105678) loci, so these were excluded from our analyses. The list of SNPs, reference alleles, frequency in our study cohort, and relevant references are included in the Supplement (eTable 1 and eReferences).

Statistical Analysis

The SNP dosage values were coded additively in terms of the reference alleles specified in the Supplement (eTable 1). Our primary analyses examined the association of SNPs with the quantitative summary measure of global parkinsonism or the component parkinsonian signs (bradykinesia, gait, rigidity, and tremor). Linear regression models were used to relate SNPs with global parkinsonism as well as the quantitative measures of bradykinesia and gait; the scaled outcomes were square root–transformed to better approximate the assumptions of normality. Logistic regression was used for analyses of tremor and rigidity. Unadjusted *P* values are presented throughout; $P < .0028$ was considered significant after adjusting for multiple hypothesis testing ($\alpha = .05$ divided by 18 SNPs). Because this correction for multiple tests is conservative and each of these susceptibility polymorphisms has been independently validated as a PD susceptibility locus, we additionally considered an unadjusted value of $P < .05$ as suggestive evidence of association in our analyses. Secondary analyses included additional clinical motor traits and postmortem indices, as described above. Linear regression was used for all quantitative motor outcomes (Purdue pegboard, finger taps, gait speed, gait steps, turn speed, and turn steps). Consistent with prior studies,[2,6] for analyses of postmortem indices, linear regression was used for global Alzheimer disease pathology, and logistic regression was used to evaluate the extent of nigral neuronal loss (ordinal), the presence of nigral Lewy bodies, or the presence of macroscopic or microscopic infarcts. All analyses were adjusted for patient age (baseline or death) and sex.

Results

There were 1698 participants with baseline assessments of global parkinsonism and available genotyping included in our primary analysis. The distribution, quality, and severity of parkinsonian signs were previously reported for the ROS and MAP cohorts.[2,23] Demographic and clinical characteristics for the study cohort are reported in Table 1. Eighteen SNPs were selected on the basis of prior identification of PD susceptibility loci from GWAS meta-analyses (Supplement [eTable 1]).[30]

Association of PD Susceptibility Variants With Parkinsonism

We evaluated the 18 PD risk variants with global parkinsonism at baseline evaluations (Table 2), a quantitative summary measure of parkinsonian motor features based on the mUPDRS. We found *MAPT* (rs2942168; *P* = .0006) to be significantly associated with parkinsonism, and another locus, *CCDC62* (rs12817488; *P* = .004), was suggestively associated. The observed associations between baseline global parkinsonism and both *MAPT* (*P* = .0004) and *CCDC62* (*P* = .004) remained after excluding 46 participants with a clinical diagnosis of PD (Supplement [eTable 2]), suggesting that our findings are driven by the mild parkinsonian signs broadly ascertained in the cohort. Surprisingly, the direction of effects for the associations with global parkinsonism in our cohort was opposite from that reported for association with PD susceptibility. Specifically, rs2942168^{A} and rs12817488^{G}, at *MAPT* and *CCDC62*, respectively, were associated with increased parkinsonism at baseline assessments in our cohorts (Supplement [eFigure 1]), whereas these alleles were protective against PD in other published studies.[18,30]

Although recognized as a distinct syndrome, the clinical manifestations of parkinsonism are often heterogeneous. For example, tremor- and gait-predominant forms of PD are recognized,[31] and it has been suggested[32] that such heterogeneity might be genetically encoded. We therefore also evaluated associations between PD susceptibility loci and 4 discrete domains of motor impairment that comprise the global parkinsonism trait derived from the relevant components of the mUPDRS: bradykinesia, rigidity, tremor, and gait impairment (Table 3 and Supplement [eTable 3]). Both *MAPT* (*P* = .0002) and *CCDC62* (*P* = .003) were predominantly associated with bradykinesia at baseline study evaluations. These analyses also implicated associations between other PD risk alleles and parkinsonian features: *SREBF1* was associated with gait impairment (*P* = .005), *SNCA* with rigidity (*P* = .04), and *GAK* with tremor (*P* = .03). Therefore, the global parkinsonism summary score may obscure more-selective genetic associations with the component domains. Similar to *MAPT* and *CCDC62*, the associations observed for *SREBF1* and *GAK* with parkinsonian features is opposite from the direction of effect reported in GWASs[19,30,33]; that is, the risk alleles for PD susceptibility (rs11868035^{G} and rs1564282^{T}, respectively) were protective in our cohort. We suggest that differences between the makeup of our cohort and the case-control populations included in PD GWASs may contribute to these reversals (see the Discussion section).

Association of PD Susceptibility Variants With Additional Motor Traits

There is no single testing battery universally accepted for documenting mild motor symptoms in older adults, and some motor traits not assessed by the mUPDRS may be more sensitive in detecting prodromal PD.[34] We therefore examined whether other motor performance measures assessed in these cohorts were associated with PD susceptibility alleles. These analyses identified many additional associations (Table 4 and Supplement [eTable 4]). For example, compared with the mUPDRS gait assessment, additional associations were discovered based on performance in a timed 2.4-m gait trial. Specifically, SNPs at *PARK16* (rs11240572; *P* = .005), *FAM47E* (rs6812193; *P* = .02), and *GPNMB* (rs156429; *P* = .008) were each associated with the number of steps taken, whereas only *PARK16* (*P* = .02) was associated with overall gait speed. Compared with gait, measures of

upper extremity speed and dexterity showed overall fewer associations: *MCCC1* was associated with completion of the Purdue pegboard task (rs11711441; $P = .02$), whereas *CCDC62* was associated with finger taps (rs12817488; $P = .04$). Notably, the *MAPT* SNP, which was related to the mUPDRS assessments, was not associated with any of the quantitative motor measures. Our results suggest the possibility that distinct motor traits may have variable sensitivity and/or specificity to detect the effects of individual risk alleles. However, findings from a broad battery of motor performance measures, including the mUPDRS, collectively support the hypothesis that many PD susceptibility loci may contribute to motor impairment in older persons without PD.

Association of PD Susceptibility Variants With Nigral Pathology

We next investigated whether PD susceptibility loci are associated with nigral pathology, including α-synuclein Lewy bodies and neuronal loss, which are characteristic of PD and also have been linked to parkinsonian motor signs in older persons without PD.[2] Among our study cohort, a subset of 821 deceased individuals was available with genotyping and a complete, uniform neuropathologic evaluation (Table 1). Interestingly, the *NMD3* locus was related to the severity of nigral neuronal loss (rs34016896; $P = .03$) (Table 5) based on semi-quantitative assessment of pigmented dopaminergic neurons on hematoxylin-eosin–stained tissue sections from the midbrain. Surprisingly, none of the PD susceptibility loci showed associations with the presence of Lewy body pathology in the substantia nigra (Supplement [eTable 5]) based on α-synuclein immunohistochemistry. The prevalence of nigral Lewy body pathology in our cohort(19.7%) is consistent with that seen in similar older community-based cohorts.[35] In addition to synuclein pathology, parkinsonism can result from other common neuropathologies, including Alzheimer disease[36,37] and cerebrovascular lesions.[6] However, PD risk alleles were associated with neither a quantitative measure of global Alzheimer disease pathology nor the presence of macroscopic or microscopic infarct pathology (Supplement [eTable 6]).

Discussion

Mild parkinsonian signs are common in the aging population, with estimates as high as 50% in persons older than 85 years based on the cohort studied and the definition used.[9–11] These signs are not benign; their severity is associated with substantial morbidity,[12,13] including cognitive decline,[14] dementia,[15,16] and risk of death.[11] In an effort to expand our understanding of risk factors for parkinsonian signs, we investigated 18 genetic variants implicated in PD susceptibility for links with parkinsonism in 2 large community-based cohorts. Our findings suggest that several loci, including *MAPT* and *CCDC62*, may have a broader role in age-related motor impairment in the population beyond their established connection to PD. Analyses of individual parkinsonian features and related quantitative motor measures implicated several additional loci, including *GAK*, *SREBF1*, and *SNCA*. Although mild clinical signs have been described in otherwise healthy carriers of dominant mutations in families with mendelian PD,[38] to our knowledge, genetic risk factors for mild parkinsonian signs in the broader population have not previously been reported. In sum, our findings begin to reveal the genetic architecture of mild parkinsonian signs and point to an overlap with determinants of PD susceptibility.

Compared with the published[17–20,30] effects on PD risk, we found an opposite direction of effect for several variants on global parkinsonism in our cohort. There are several potential explanations for this unexpected result. First, compared with PD GWASs, our cohort was distinguished by older participants, community-based recruitment, and a prospective study design. In fact, patients manifesting mild parkinsonian signs in our cohort were nearly 20 years older, on average, than the typical cases included in PD GWASs.[18] Thus, if a given variant is associated with accelerated PD clinical manifestation, recruitment of an older, largely neurologically healthy sample may exclude such alleles, leading to an apparent opposite, protective effect. Simulations have demonstrated[39] that similar effect reversals can arise from gene interaction effects after distortion of allele frequencies of unknown interacting variants. Another potential contributor might be that the proxy SNPs under consideration are in incomplete linkage disequilibrium with the true causal variants.[40] Finally, although global parkinsonism in our cohort and PD diagnosis were assessed using similar metrics (mUPDRS), these traits may have divergent genetic architectures. For example, mild parkinsonian signs in the older population are likely to be more pathologically heterogeneous than are those for PD. Few individuals (1.1%) in our cohort carried a diagnosis of PD, and these patients could be excluded from the analysis without significantly affecting the results. Thus, although our findings suggest an intriguing overlap between genetic risk for PD and parkinsonism, additional studies will be required to understand the mechanisms responsible for this association.

Although the development of parkinsonism, including mild parkinsonian signs, is not specific for a particular pathologic process, the clinical manifestations have traditionally been neuroanatomically linked to dysfunction in nigrostriatal pathways.[5] Parkinsonism in our cohort, similar to that in other clinicopathologic studies, has been associated with PD-related α-synuclein pathology[2,41] as well as Alzheimer disease pathologic changes[36,37] and brain infarct burden.[6] We hypothesized that such heterogeneous brain lesions might similarly result in dopaminergic neuronal dysfunction and/or loss and the development of parkinsonian motor signs. In ROS and MAP, for example, a previous study[2] showed that the association of Lewy body pathology and global parkinsonism can be statistically mediated by nigral neuronal loss. However, in the present study, neither of the loci identified in association with parkinsonism (*MAPT* and *CCDC62*) showed evidence of an association with nigral neuronal loss in our sample of 821 autopsies. Of the other PD risk alleles, only *NMD3* was associated with nigral neurodegeneration, and none of the evaluated SNPs was associated with nigral Lewy bodies, Alzheimer disease pathology, or cerebrovascular lesions. In a prior study,[42] the *MAPT* H1 haplotype showed evidence of an association with cortical Lewy body pathology; however, the study cohort is difficult to compare with the ROS/MAP cohort because it was largely from a clinic-based population sample with dementia, and nigral Lewy bodies were not considered independently. Surprisingly, although the PD-associated H1 haplotype tag SNP at *MAPT*, rs2942168, was significantly associated with global parkinsonism, it was not associated with nigral pathology in our cohort. Statistical power may be limited in the reduced sample size of the autopsy cohort, and it is also possible that our current neuropathologic procedures underestimate the true anatomic extent of Lewy bodies and spectrum of nigral neuronal loss, hindering our capability to detect such associations. Furthermore, it is now recognized that α-synuclein

pathology is found throughout the neuraxis in PD affecting the autonomic ganglia, spinal cord, brainstem, limbic, and cortical regions.[43] It is possible that more comprehensive characterization of such widespread neuropathologic changes might allow the detection of genetic associations with the nervous system lesions underlying mild parkinsonian signs.

Strengths of our study include the community-based, prospective cohort design and systematic collection of clinical and pathologic data. Although our analyses included nearly 1700 participants and more than 800 brains in the autopsy cohort, these samples are not large enough to definitively exclude associations with global parkinsonism or nigral pathology. Additional potential limitations include an older population, which might limit generalizability to the broader adult population. We also did not consider less common or rare variant susceptibility factors for PD, such as the established polymorphisms at *LRRK2* and *GBA*, which will be an important future area of investigation. It will also be essential to replicate and confirm our findings in additional community- and population-based cohorts with a similar collection of clinical and neuropathologic data.

Conclusions

Our results suggest that PD susceptibility loci may have a broader effect on the development of parkinsonian motor signs in older individuals. Larger sample sizes will enable future meta-analyses with improved power to reveal additional genetic risk factors for mild parkinsonian signs and related pathology in the aging population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Cohort Characteristics

Measure	Mean (SD)
Baseline clinical characteristics	
No. of cases	1698
Baseline age, y	78.5 (7.5)
Educational level, y	16.4 (3.6)
Male sex, No. (%)	523 (30.8)
PD diagnosis, No. (%)	19 (1.1)
mUPDRS	
Global parkinsonism score	8.8 (7.8)
Bradykinesia score	12.1 (12.1)
Gait score	16.2 (15.7)
Rigidity, No. (%)	471 (27.7)
Tremor, No. (%)	643 (37.9)
Other motor traits	
Purdue pegboard score	0.97 (0.21)
Finger taps score	0.99 (0.14)
Gait speed score	1.04 (0.30)
Gait steps score	0.98 (0.21)
Turn speed score	1.06 (0.35)
Turn steps score	0.98 (0.25)
Postmortem indices	
No. of autopsies	821
Age at death, y	88.4 (6.4)
Nigral neuronal loss, moderate to severe, No. (%)	117 (14.2)
Lewy bodies present in nigra, No. (%)	162 (19.7)
Global Alzheimer disease pathology score	0.74 (0.63)
Macroscopic infarcts, No. (%)	294 (35.8)
Microscopic infarcts, No. (%)	230 (28.0)

Abbreviations: mUPDRS, motor Unified Parkinson’s Disease Rating Scale; PD, Parkinson disease.

Table 2

Associations With Baseline Global Parkinsonism[a]

Locus	SNP	Model, Estimate (SE, *P* Value)
PARK16	rs11240572	−0.06 (0.15, .70)
STK39	rs2102808	0.007 (0.06, .91)
ACMSD	rs6710823	0.23 (0.21, .28)
MCCC1	rs11711441	0.01 (0.06, .82)
NMD3	rs34016896	0.04 (0.04, .41)
SNCA	rs356220	−0.0003 (0.05, .99)
GAK	rs1564282	−0.03 (0.06, .67)
BST1	rs4698412	0.01 (0.04, .78)
FAM47E	rs6812193	−0.07 (0.04, .11)
HLA-DRB5	rs3129882	0.03 (0.04, .46)
GPNMB	rs156429	0.02 (0.04, .58)
FGF20	rs591323	−0.01 (0.05, .77)
CCDC62	rs12817488	**0.30 (0.11, .004)**
LRRK2	rs1491942	−0.005 (0.05, .93)
SETD1A	rs4889603	−0.004 (0.04, .92)
MAPT	rs2942168	**0.17 (0.05, .0006)**
SREBF1	rs11868035	−0.07 (0.05, .16)
RIT2	rs12456492	−0.004 (0.04, .96)

Abbreviation: SNP, single-nucleotide polymorphism.

[a]Based on linear regression models examining the level of global parkinsonism to Parkinson disease SNP genotypes. Estimates (SE, *P* value) were based on the effect of increasing the dosage of the SNP reference allele after adjustment for age and sex. Boldface type denotes results with $P < .05$.

Table 3

Associations With Parkinsonian Features[a]

Locus	Estimate (SE, *P* Value)			
	Bradykinesia	**Gait**	**Rigidity**	**Tremor**
MAPT	**0.31 (0.08, .0002)**	**0.16 (0.08, .04)**	0.13 (0.10, .18)	0.14 (0.09, .13)
CCDC62	**0.52 (0.18, .003)**	**0.33 (0.16, .04)**	−0.14 (0.21, .50)	0.25 (0.19, .19)
SNCA	0.05 (0.08, .50)	0.03 (0.07, .73)	**−0.19 (0.09, .04)**	−0.13 (0.09, .14)
GAK	0.02 (0.11, .84)	−0.10 (0.10, .31)	−0.16 (0.12, .19)	**0.26 (0.12, .03)**
SREBF1	0.07 (0.08, .40)	**−0.21 (0.08, .005)**	−0.11 (0.10, .26)	−0.14 (0.09, .12)

[a]Based on linear (bradykinesia and gait) or logistic (rigidity and tremor) regression models examining the level of parkinsonian features to Parkinson disease single-nucleotide polymorphism genotypes. Estimates (SE, *P* value) were based on the effect of increasing the dosage of the single-nucleotide polymorphism reference allele after adjustment for age and sex. Boldface type denotes results with $P < .05$.

Table 4

Association With Other Motor Traits[a]

Locus	Estimate (SE, *P* Value)					
	Purdue Pegboard	**Finger Taps**	**Gait Speed**	**Gait Steps**	**Turn Speed**	**Turn Steps**
MAPT	−0.003 (0.008, .76)	−0.005 (0.007, .45)	−0.004 (0.01, .76)	−0.001 (0.008, .89)	−0.001 (0.02, .95)	−0.02 (0.01, .18)
CCDC62	−0.02 (0.02, .31)	**−0.03 (0.02, .04)**	−0.04 (0.03, .12)	−0.03 (0.02,T.13)	−0.04 (0.04, .35)	−0.03 (0.03, .25)
PARK16	0.01 (0.03, .62)	−0.006 (0.02, .79)	**0.09 (0.04, .02)**	**0.07 (0.03, .005)**	0.08 (0.06, .21)	0.05 (0.04, .29)
MCCC1	**0.02 (0.01, .02)**	−0.01 (0.008, .22)	−0.01 (0.02, .43)	0.001 (0.01, .92)	**−0.057 (0.02, .01)**	**−0.03 (0.02, .03)**
FAM47E	−0.007 (0.007, .30)	−0.003 (0.006, .56)	0.02 (0.01, .08)	**0.017 (0.007, .02)**	0.002 (0.012, .92)	−0.004 (0.01, .67)
GPNMB	−0.003 (0.007, .64)	0.006 (0.006, .28)	−0.02 (0.01, .08)	**−0.018 (0.007, .008)**	−0.039 (0.02, .02)	−0.02 (0.01, .18)
SETD1A	0.0004 (0.007, .96)	−0.007 (0.006, .24)	0.002 (0.01, .84)	**0.01 (0.007, .048)**	0.01 (0.02, .42)	0.02 (0.01, .17)

[a]Based on linear regression models examining the level of motor performance tasks to Parkinson disease single-nucleotide polymorphism genotypes. Estimates (SE, *P* value) were based on the effect of increasing the dosage of the single-nucleotide polymorphism reference allele after adjustment for age and sex. Boldface type denotes results with $P < .05$.

Table 5

Associations With Nigral Pathology[a]

Locus	Estimate (SE, *P* Value)	
	Lewy Bodies	**Nigral Loss**
MAPT	0.07 (0.15, .64)	−0.20 (0.12, .10)
CCDC62	−0.42 (0.33, .20)	−0.39 (0.26, .13)
NMD3	0.08 (0.14, .55)	**0.25 (0.11, .03)**

[a]Based on logistic regression models examining the presence of Lewy bodies or severity of nigral neuronal loss to Parkinson disease single-nucleotide polymorphism genotypes. Estimates (SE, *P* value) were based on the effect of increasing the dosage of the single-nucleotide polymorphism reference allele after adjustment for age and sex. Boldface type denotes results with $P < .05$.