Genome-wide Analysis of Motor Progression in Parkinson Disease

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Abstract

Background and Objectives
The genetic basis of Parkinson disease (PD) motor progression is largely unknown. Previous studies of the genetics of PD progression have included small cohorts and shown a limited overlap with genetic PD risk factors from case-control studies. Here, we have studied genomic variation associated with PD motor severity and early-stage progression in large longitudinal cohorts to help to define the biology of PD progression and potential new drug targets.

Methods
We performed a GWAS meta-analysis of early PD motor severity and progression up to 3 years from study entry. We used linear mixed-effect models with additive effects, corrected for age at diagnosis, sex, and the first 5 genetic principal components to assess variability in axial, limb, and total Movement Disorder Society–Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) III scores.

Results
We included 3,572 unrelated European ancestry patients with PD from 5 observational cohorts and 1 drug trial. The average AAO was 62.6 years (SD = 9.83), and 63% of participants were male. We found an average increase in the total MDS-UPDRS III score of 2.3 points/year. We identified an association between PD axial motor progression and variation at the GJA5 locus at 1q12 ($\beta = -0.25$, SE = 0.04, $p = 3.4e^{-10}$). Exploration of the regulation of gene expression in the region (cis-expression quantitative trait loci [eQTL] analysis) showed that the lead variant was associated with expression of ACP6, a lysophosphatidic acid phosphatase that regulates mitochondrial lipid biosynthesis (cis-eQTL $p$-values in blood and brain RNA expression data sets: $<10^{-14}$ in eQTLGen and $10^{-7}$ in PsychEncode).

Discussion
Our study highlights the potential role of mitochondrial lipid homeostasis in the progression of PD, which may be important in establishing new drug targets that might modify disease progression.

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Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

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**Introduction**

Parkinson disease (PD) is a progressive neurodegenerative disorder with motor and nonmotor symptoms, clinically manifesting with rigidity, postural instability, and slowness of movement (bradykinesia). The motor deficits are linked to the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta, their projection to the striatum, and the accumulation of alpha-synuclein aggregates in Lewy bodies in the nigral and other neurons.1

PD is heterogeneous in its progression and onset. The predominant motor phenotype is influenced by age at onset, with tremor being more prominent in older patients, and the risk of dystonia at presentation increasing in younger individuals.2 With respect to progression, younger patients tend to have a slower rate of motor progression as measured using the Movement Disorder Society–Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) and Hoehn and Yahr assessments.3 Functional imaging studies have also shown a slower rate of decline in the loss of nigrostriatal terminals in early onset compared with late-onset PD.4

To date, most PD genetic studies have focused on the risk of developing PD.5 Relatively little is known about the genetic factors that contribute to variation in the onset and progression of motor and nonmotor symptoms. Studies of PD age at onset have shown that the genetic determinants of age at onset are different to the genetic factors determining case-control status, with the MAPT and GCH-1 loci associated with disease risk but not age at onset.6,8 With respect to common variability explaining differences in disease progression, Iwaki et al.9 performed a GWAS looking at 25 different outcome measures in a meta-analysis of 12 longitudinal cohorts, including mortality, dementia, disease severity, and patient disability. They reported an association between an intronic variant in SLC44A1, a mitochondrial choline transporter, and motor progression, reflected by reaching a Hoehn and Yahr score higher or equal than 3 (HY3). A more recent study10 took a different approach using a principal components (PC)–based measure that combined multiple assessments for composite motor and cognitive progression. They found a novel association between ATP8B2 and PC-based motor progression in a gene-based analysis.

These studies suggest that pathways specifically related to the progression of PD can be understood from genotype/phenotype analysis, which may ultimately lead to the development of new disease-modifying therapies. We modeled the early stages of motor Parkinson disease, using the total score from the MDS-UPDRS part III, a validated scale recommended for clinical trials to measure both response to levodopa treatment and the rate of change over time.11 We have also derived and analyzed separate axial and limb motor stages from the scale, as they may relate in part to distinct pathology.12 We have used a genome-wide association (GWA) approach to define genetic determinants associated with variation in motor progression and severity, identifying genetic variation that is significantly associated with change in the MDS-UPDRS, the primary outcome measure for many clinical PD trials. Finally, we have performed functional annotation and fine-mapping to understand how the nominated genetic variants are associated with the regulation of gene expression and the underlying biology of PD motor traits.

**Methods**

The workflow for all methods applied in the manuscript is available on a Zenodo repository (doi.org/10.5281/zenodo.7258985).

**Study Design and Quality Control at the Sample and Genetic Level**

We studied 6 observational and interventional longitudinal PD cohorts with either genotyping or whole genome sequencing (WGS) data available, totaling 4,971 patients (eTable 1, links. lww.com/NXG/A624). We selected cohorts which included longitudinal MDS-UPDRS part III assessments from the MDS-UPDRS11 and applied quality control (QC) at the clinical data level (eFigure 1). To study the motor progression of PD, we derived limb and axial phenotypes from the MDS-UPDRS part III scale based on previously accepted definitions.13 In addition, we used the MDS-UPDRS III total score as an overall measure of PD motor state (eTable 2). We included data up to 36 months from the baseline visit, within longitudinal observational and therapeutic cohorts, as we had high rates of data completion up to 36 months. Imputation of patients’ missing motor outcomes was performed when possible14 (eMethods; eTable 3).

We applied genetic QC at the sample and variant level followed by imputation in the Michigan Imputation Server (RRID:SCR_017579)15 and postimputation QC (eMethods; eFigure 1, links. lww.com/NXG/A624). Table 1 summarizes the demographics of the data after QC.

Previous studies have reported that levodopa improves motor state examination and may possibly slow disease progression.16 Because the motor improvement is noticeable a few hours after treatment, and affects the MDS-UPDRS measure, we have

**Glossary**

eQTL = expression quantitative trait loci; GD = Gaucher disease; GWA = genome-wide association; LD = linkage disequilibrium; LMMs = linear mixed-effect models; MDS-UPDRS = Movement Disorder Society–Unified Parkinson’s Disease Rating Scale; PD = Parkinson disease; QC = quality control; TSS = transcription start site; WGS = whole genome sequencing.
Table 1

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<tr>
<th>Study</th>
<th>N patients(^a)</th>
<th>N Observations(^b)</th>
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<th>ON/OFF</th>
<th>No. (%) male</th>
<th>Age at Baseline, y</th>
<th>Age at Diagnosis, y</th>
<th>N patients</th>
<th>N observations</th>
<th>Visit interval, mo</th>
<th>ON/OFF</th>
<th>No. (%) male</th>
<th>Duration(^c), y</th>
<th>Total rate of change per year</th>
<th>Mean ± SD</th>
<th>Total rate of change centered</th>
<th>Mean ± SD</th>
<th>Limb rate of change centered</th>
<th>Mean ± SD</th>
<th>Axial rate of change centered</th>
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</table>

Abbreviations: AAD = Age at Diagnosis; AAB = Age at Baseline; N = Number; \(^a\) N patients = number of patients with PD after QC was applied; \(^b\) N observations = number of observations including MDS-UPDRS part III motor assessment after QC was applied; \(^c\) Duration = disease duration from onset to study entry.

### Statistical Approaches

To study the effect of genetics on motor progression as well as on baseline variability, we used linear mixed-effect models (LMMs) which can be used to study longitudinal measures as the variability in the outcome can be studied at 2 levels, within groups (i.e., individual patient longitudinal visits) or between groups (across patients). We studied the changes in disease limb and axial motor severity and progression associated with genetic variants under an additive genetic effect (eMethods, links.lww.com/NXG/A624). In the disease severity model, we studied the additive genetic effect of SNPs on the average motor outcome. In the disease progression model, we studied the genetic additive effect of SNPs on the outcomes’ rate of change (eMethods). Both progression and severity models met the LMMs model assumptions (eFigure 3). We quantified the power of LMMs to investigate the effect of SNPs in changes in the motor signs of PD (eMethods). To run the disease progression model, we used lmerTest R package (v. 3.1-3; RRID:SCR_015656) and the Satterthwaite approach to approximate degrees of freedom and derive \(\beta\)-values and fitted them using restricted maximum likelihood (REML), as it produces acceptable type-1 error rates.\(^{17}\) In addition, we used SCEBE\(^{18}\) algorithm (v. 0.1.0) with REML and lme4 R package (v. 1.1-30; RRID:SCR_015654) to decrease the computational expense of adding unexplained variability at the slope level in the disease severity model (eMethods). We validated SCEBE in 2 separate cohorts (eFigure 4). All tests were two-tailed. We used METAL software (version released on the 25/03/2011; RRID:SCR_002013) for meta-analysis of genome-wide association summary statistics, using a fixed effects model weighted by \(\beta\) coefficients and the inverse of the standard errors.\(^{19,20}\) We also applied QC to the meta-analysis results (eMethods). Statistical significance was assessed at the genome-wide level (\(p = 5 \times 10^{-8}\)).

### Fine-Mapping and Functional Annotation

We performed a conditional and a stepwise model selection procedure to determine whether there were independently associated SNPs in each locus of interest. To nominate causal variants, we applied fine-mapping. To further understand regulatory mechanisms in nominated loci, we mapped each locus against (1) cell type–specific and “bulk” genome enhancer marks, (2) enhancer-transcription start site (TSS) interaction marks from FANTOMS, and (3) brain cell type–specific transcriptional regulatory marks and distal enhancer-promoter interactions.\(^{21,22}\) To determine whether causal variants could be linked to the motor phenotypes by dysregulation of gene expression, we performed colocalization against cis-expression quantitative trait loci (eQTL) data sets.\(^{23-25}\) Software and packages to conduct the analyses and access the data are described in eMethods. In addition, we used FUMA, a web-based platform that integrates a wide range of compared individuals from cohorts in the same state at each assessment. If cohorts had data in the “OFF” state available, we used longitudinal “OFF” vs “OFF” MDS-UPDRS part III scores, otherwise “ON” vs “ON” comparisons were made. In addition, we performed sensitivity analyses adjusting the motor scores by levodopa dosage (eMethods, eFigure 2).
functional annotation data (RRID:SCR_017521; version 1.3.8)\textsuperscript{26} We used LocusZoom (RRID:SCR_009257; version 0.12)\textsuperscript{27} to display the linkage disequilibrium (LD) structure of a given locus against the locus lead SNP, as well as the protein coding genes and rRNAs nearby.

**Standard Protocol Approvals, Registrations, and Patient Consents**

Each participant provided written informed consent for participation. TPD has multicenter research ethics approval from the West of Scotland Research Ethics Committee: IRAS 70980, MREC 11/AL/0163 (ClinicalTrials.gov, NCT02881099). OPDC has multicenter research ethics approval from the South Central Oxford Research Ethics Committee 16/SC/0108. PD STAT has been approved by the North East-Newcastle and North Tyneside 2 Research Ethics Committee (ClinicalTrials.gov NCT02787590). The DIGPD study was sponsored by Assistance Publique Hôpitaux de Paris, approved by French regulatory authorities and an ethics committee and conducted according to good clinical practices (ClinicalTrials.gov NCT01564992).

**Data Availability**

We have made our summary statistics available (doi.org/10.5281/zenodo.7257484). TPD data are available on access request from trackingparkinsons.org.uk/about-1/data/. The PDBP and PPMI data were accessed from Accelerating Medicines Partnership: Parkinson’s Disease (AMP-PD), and data are available on registration at amp-pd.org/. OPDC data are available on request from the Dementias Platform UK (portal.dementiasplatform.uk/Apply). DIGPD data are available on request to the principal investigator (JC Corvol, Assistance Publique Hôpitaux de Paris; clinicaltrials.gov/ct2/show/NCT01564992). PD STAT is available on request to the principal investigator (C Carroll, Plymouth University. penctu.psmd.plymouth.ac.uk/pdstat/#:~:text=PD%20STAT%20-%20Simvastatin%20%20a,brain%20from%20injury%20or%20loss). HapMap phase 3 data (HapMap3) is available for download at ftp://ftp.ncbi.nlm.nih.gov/hapmap/. Cis-QTL data were obtained from eQTLGen (eqtlgen.org/cis-eqtls.html) and PsychENCODE (resource.psychencode.org). MetaBrain cis-eQTL data can be accessed on request form (metabrain.nl/cis-eqtls.html). eQTL data from eQTL catalog can be ftp-accessed (ebi.ac.uk/eqt/Data_access/). FANTOMS CAGE-seq and Nott brain cell type–specific enhancer-promoter interactome data were accessed through echolocatoR (github.com/RajLabMSSM/echolocatoR).

**Code Availability**

Code used in the analysis is available from github.com/AMCalejandro/EMPD (doi.org/10.5281/zenodo.7258985). Analysis was performed using open-source tools as described in the Methods section.

**Results**

We explored the overall rate of change in MDS-UPDRS part III total, limb, and axial scores (Table 1). There was variation across studies. We specifically studied the amount of change for the motor measures in each study by comparing the final score with the baseline score, divided by the baseline score, for MDS-UPDRS-total, axial, and limb. We found that the axial score rate of change was the highest in TPD, OPDC, PD STAT, and PDBP. The limb rate of change was the highest in PPMI and DIGPD. PD STAT and PDBP had a lower rate of changes, which may be due either to longer disease duration or to selection effects related to the inclusion of “benign” PD in patients with longer disease duration. We assessed this by fitting an LMM using data from TPD and found a significant interaction between time and disease duration related to MDS-UPDRS total progression (β = –0.11, SE = 0.04, p = 0.01). Longer disease duration was associated with a lower total rate of change in MDS-UPDRS, which appears to be nonlinear with extended disease durations. Overall, we confirmed that the MDS-UPDRS–derived measures increased, reflecting worsening motor impairment, from study entry up to 3 years (Figure 1). The MDS-UPDRS part III total yearly rate of change ranged between 2.37 and 3.01 points/year, which is consistent with previous reports\textsuperscript{28}

Our power calculation showed that the current LMM was well powered to detect high effect sizes (β ≥ 0.2) for a wide range of different MAFs, with a limit for variants with an allele frequency ≤1% (eFigure 5, links.lww.com/NXG/A624). We performed a GWAS on each cohort to study PD motor progression and meta-analyzed results separately using a genomic control to correct the test statistics of those cohorts that had genomic inflation (λ > 1 & λ < 1.2) (eTable 4).

We evaluated disease progression and disease severity models for total, limb, and axial progression. We did not find any significant genetic association with the PD limb motor progression or severity. For axial motor progression, we found 1 haplotype block that reached genome-wide significance (GJAS in chromosome 1) (Figure 2A; eFigure 6, links.lww.com/NXG/A624). This association was also found, at a lower significance level, with the MDS-UPDRS part III total. Given that there was no association with PD limb motor progression and severity, this relates to the inclusion of axial components in the overall MDS-UPDRS-III total score. Although the lead variant in the GJAS locus was not captured in the PPMI WGS data, we found proxy variants that were present in all cohorts. The lead proxy variant was rs12037169 (β = –0.25, SE = 0.06, p = 3.93e\textsuperscript{–5}) (Table 2). The association test statistic and directionality of each of these variants was consistently replicated across cohorts (eTable 5; Figure 2B).

To test whether levodopa was a major confounder of our study of motor progression, we corrected the patient motor scores using an equation described in eMethods (links.lww.com/NXG/A624) that best predicted the effect of levodopa dose on MDS-UPDRS part III total over time to correct the motor scores by levodopa usage. To weight the effect of levodopa usage on the limb and axial motor states, we used data from Tracking Parkinson’s Levodopa challenge\textsuperscript{29} with MDS-UPDRS part III scores recorded before and after treatment and used these
weights to correct the motor scores by levodopa usage. We did not find significant changes either in the SNPs significance level or the direction of effects. In addition, rs120371169 remained significantly associated with axial motor progression (eTable 5).

Hoehn and Yahr (HY), a measure of a patient’s disability, measures motor progression including loss of balance and provides an alternative measure to the axial score from MDS-UPDRS part III. To further validate the GWS association linked to PD axial motor progression, we ran the disease progression statistical model to study the contribution of SNPs to motor changes over time using HY as our longitudinal outcome. We found an LD block approaching genome-wide significance within GJA5 locus, the same locus found to be significantly associated with axial motor progression (eFigure 7, links.lww.com/NXG/A624). The lead variant was rs36005900 ($\beta = -0.08$, SE = 0.0078, $p = 5.7e^{-7}$). We found the directionality of the effects to be the same as in the axial motor progression GWAS. In addition, rs36005900 is in LD with the lead variant reported in the same locus for MDS-UPDRS III axial motor progression ($D’ = 0.8$, $R^2 = 0.6$).

We then investigated whether there were independently associated SNPs at the GJA5 locus. We did not find any signal other than the lead SNP in the selection procedure under a conditional and stepwise selection approach using GCTA-COJO. Under a single causal variant assumption, we then performed statistical fine-mapping. We did not resolve consensus SNPs (a SNP nominated to be causal by 2 different fine-mapping tools) at the GJA5 locus. We found a total of 12 SNPs with support for causality of changes in motor axial progression, nominated from at least 1 fine-mapping tool (eTable 6, links.lww.com/NXG/A624). We did not find an overlap between the GJA5 locus haplotype block and regulatory marks from functional annotation data sets described in eMethods.

We also explored eQTLs data sets through the FUMA platform. We found that many of the GWAS-significant SNPs within the GJA5 locus were significant cis-eQTLs for ACP6, in PsychEncode, and eQTLGen. In particular, we found that the lead variant was a significant eQTL in PsychEncode, and eQTLGen, and also rs12037169, the proxy significant variant found in all cohorts, was a significant cis-eQTL in eQTLGen (eTable 7, links.lww.com/NXG/A624). We then performed a colocalization analysis to evaluate whether there was colocalization between the GWAS axial progression results and eQTL GWAS for gene expression at the GJA5 locus (eMethods). We used cis-eQTL data from eQTLGen and Metabrain cortex tissue cis-eQTLs data sets and performed a colocalization test for any gene within ±1 Mb from the GJA5 lead SNP. We did not find direct colocalization evidence for any gene, including ACP6. We found PPH3 (indicating separate significant

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**Figure 1 MDS-UPDRS III Motor Scores Trajectories**

Trajectory of the MDS-UPDRS III-derived motor scores across cohorts. In the x-axis, the time point at which the MDS-UPDRS III assessment was measured. Each plot shows the motor scores trajectories on each cohort highlighted in the label. The y-axis represents the average scores for each of the motor states. The bars represent the SD of the average motor scores.
associations for GWAS and eQTL analysis) to be the highest for the ACP6 gene using default SNP priors (eQTLGen = 0.98, MetaBrain = 0.88). The PPH3 remained the highest for these 2 genes (PPH3 > 0.8), after we adjusted the priors according to the number of overlapping SNPs (eMethods).

In a separate analysis, we also studied the genome-wide effect that SNPs had on average changes of limb and axial motor states using the disease severity model (see eMethods, links. lww.com/NXG/A624). We did not find any haplotype block that reached genome-wide significance. However, there were 2 distinct signals approaching genome-wide significance associated with changes in the average axial motor scores (MAD1L1 in chromosome 7 and LINC00511 in chromosome 17) (eFigure 8A). The lead SNP in MAD1L1 was rs4721411 (Beta = 0.54, SE = 0.11, p = 1.6e−7), and the lead variant in the long noncoding RNA LINC00511 was rs36082764 (Beta = −0.62, SE = 0.11, p = 6.3e−8) (Table 2). We found the association test

### Table 2 Lead SNPs on the Disease Progression and Severity GWAs

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We explored eQTL databases from FUMA. We found the lead variant in MAD1L1 as well as the fine-mapped nominated causal variant to be a significant cis-eQTL in BIOS and eQTLGen (eTable 8, links.lww.com/NXG/A624). We then performed a colocalization analysis to evaluate whether there is a shared causal variant between the 2 traits (eMethods). We did not find direct colocalization evidence for any gene within ±1 Mb from the GWAS lead SNPs. There was no cis-eQTL data available for SOX9. In the MAD1L1 locus, the posterior probability H3 (PPH3) (association with both phenotypic and expression traits, but distinct causal variants) was the highest (PPH3 in MAD1L1: eQTLGen = 0.97, MetaBrain = 0.98, PsychENCODE = 0.75).

To understand how ACP6, MAD1L1, and SOX9 might contribute to Parkinson disease motor function, we have described their biological function based on previous research (eResults, links.lww.com/NXG/A624).

Discussion

To understand the biology of motor progression in PD, we performed a large well-powered GWAS of PD motor progression. We have found 1 haplotype block at the GJA5 locus that is significantly associated with axial PD motor progression. This association was consistently replicated across individual cohorts included in our motor progression GWAS meta-analysis and was replicated in an analysis of H/Y supporting our findings. Further exploration of the GWAS significant signals in eQTL databases suggests that the GWAS hits may control the expression of ACP6, an enzyme that regulates lipid metabolism in mitochondria.\(^3^0\) Changes in ACP6 concentrations are found in Gaucher disease (GD), although there is no clear link between ACP6 levels in and GD progression. ACP6 has a high astrocyte specificity,\(^3^1\) and mitochondrial dysfunction has been widely associated with PD etiology.\(^3^2\)

We used the MDS-UPDRS III (PD motor examination) scale, a sensitive measure of motor progression over time which has been widely studied in observational and interventional studies of PD. A study of patients with untreated de novo PD in the PPMI study, followed up for 5 years to assess the progression of MDS-UPDRS, showed a linear increase of 2.4 points per year in MDS-UPDRS part III total score.\(^2^8\) In this study, we observed a similar yearly rate of change for the total MDS-UPDRS score across the studies we included in our analysis (2.3 points/year on average) (Table 1). We have used linear mixed-effect models to investigate the common genetic variability associated with the severity and progression of distinct PD motor aspects. This concept may be consistent with PD subtype studies having a differential motor severity and progression.\(^3^3-3^8\) Another aspect of this differential approach to PD symptomatology is that limb and axial PD motor components may have a different cellular and pathophysiologic basis, with axial and limb motor symptoms related to cholinergic and dopaminergic dysfunction, respectively.\(^3^9,4^0\)

We corrected all models by AAO and sex and PCs as confounding variables. We performed a fixed effects meta-analysis as opposed to a pooled analysis to further account for between cohorts heterogeneity, as cohorts we included had different inclusion and exclusion criteria and were either genotyped with different microarrays or whole genome sequenced. Our results are not confounded by levodopa response, as defined in our sensitivity analysis (eFigure 1, eTable 1, links.lww.com/NXG/A624). In this data set, we have identified common genetic variability which determines axial, but not limb motor progression.

The lack of association between common genomic variation and the MDS-UPDRS limb subscale could be due to a combination of limited power and the levodopa effect in early disease. A study reported that measures of mobility, tremor, gait, and posture were consistent and reliable measures of PD progression.\(^4^1\) Because these measures are well represented in the axial score (except for tremor), this may be better powered to assess progression. Moreover, the limb signs may be more sensitive to levodopa use than the axial signs, making it possible that true genetic associations with limb motor progression were masked. Finally, we found the individual cohorts with the largest sample size had a higher axial rate of change compared with the limb rate of change (Table 1). A separate GWAS meta-analysis assessing the PD genetic contribution to the disease motor severity and subsequent functional annotation identified MAD1L1 and SOX9 as candidate genes associated with PD axial motor severity. Nevertheless, these potential associations did not reach genome-wide significance, and further analysis in distinct PD cohorts is needed for validation.

Strengths of our study include the large sample size and replication of our results across cohorts and across different measures of axial motor progression. Potential limitations of our identification of ACP6 as the relevant gene at the GJA5 locus include the lack of colocalization between the phenotype and expression GWAS, although these analyses are currently limited by the sample size of eQTL data sets and the lack of cell-specific gene expression data.
We hypothesize that expression of ACP6 is important in the function in cell groups relevant to axial progression in PD including the pedunculopontine nucleus and that therapies directed toward mitochondrial lipid metabolism may be relevant to the disease modification. Further replication in independent cohorts genotyped in the global Parkinson’s genetics program (GP2.org) will help to determine the importance of this region, and further analysis of this biochemical pathway may provide new insights into the pathogenesis of PD progression.

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### Appendix
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Genome-wide Analysis of Motor Progression in Parkinson Disease
Alejandro Martínez Carrasco, Raquel Real, Michael Lawton, et al.
Neurol Genet 2023;9;
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