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Association of Family History and Polygenic Risk Score With Longitudinal Prognosis in Parkinson Disease

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Abstract

Background and Objectives

Evidence suggests that either family history or polygenic risk score (PRS) is associated with developing Parkinson disease (PD). However, little is known about the longitudinal prognosis of PD according to family history and higher PRS.

Methods

From the Parkinson's Progression Markers Initiative database, 395 patients with PD who followed up for more than 2 years were grouped into those with family history within first-degree, second-degree, and third-degree relatives (N = 127 [32.2%]) vs those without (N = 268 [67.8%]). The PRS of 386 patients was computed using whole-genome sequencing data. Longitudinal assessment of motor, cognition, and imaging based on dopaminergic degeneration was conducted during the regular follow-up period. Effects of family history, PRS, or both on longitudinal changes of cognition, motor severity, and nigrostriatal degeneration were tested using a linear mixed model. The risk of freezing of gait (FOG) according to family history was assessed using the Kaplan-Meier analysis and Cox regression models.

Results

During a median follow-up of 9.1 years, PD with positive family history showed a slower decline of caudate dopamine transporter uptake (β estimate of family history × time = 0.02, 95% CI = 0.002–0.036, $p = 0.027$). Family history of PD and higher PRS were independently associated with a slower decline of Montreal Cognitive Assessment (β estimate of family history × time = 0.12, 95% CI = 0.02–0.22, $p = 0.017$; β estimate of PRS × time = 0.09, 95% CI = 0.03–0.16, $p = 0.006$). In those 364 patients without FOG at baseline, PD with positive family history had a lower risk of FOG (hazard ratio of family history = 0.57, 95% CI = 0.38–0.84, $p = 0.005$).

Discussion

Having a family history of PD predicts slower progression of cognitive decline and caudate dopaminergic degeneration, and less FOG compared with those without a family history independent of PRS. Taken together, information on family history could be used as a proxy for the clinical heterogeneity of PD.

Trial Registration Information

The study was registered at clinicaltrials.gov (NCT01141023), and the enrollment began June 1, 2010.

Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder encompassing diverse motor and nonmotor symptoms.[1] Clinical heterogeneity of PD is well recognized, and clinical subtypes at diagnosis predict longitudinal progression and prognosis.[2,3] Genetic factors also

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Glossary

CI = confidence interval; **DAT** = dopamine transporter; **FOG** = freezing of gait; **GWA** = genome-wide association; **HR** = hazard ratio; **LMM** = linear mixed model; **LRP** = Lewy body-related pathology; **MoCA** = Montreal Cognitive Assessment; **OR** = odds ratio; **PD** = Parkinson disease; **PDD** = PD dementia; **PD^{f-}** = Parkinson disease without family history; **PD^{f+}** = Parkinson disease with family history; **PPMI** = Parkinson's Progression Markers Initiative; **PRS** = polygenic risk score; **SBR** = specific binding ratio; **SBRs** = striatal binding ratio.

contribute to the clinical heterogeneity in PD.[4] Pathogenic variants in the established monogenic cause of PD are associated with variable clinical phenotypes.[5] In addition, multiple common risk variants of PD were identified by genome-wide association (GWA) studies.[6,7] Polygenic risk score (PRS) calculated from these risk variants is related to the risk of developing PD, earlier age at onset,[8,9] and faster cognitive and motor decline.[10,11] However, one study reported slower dopaminergic degeneration in those with higher PRS scores.[12]

A family history of PD was reported in 15% of the patients[13] and is one of the strongest risk factors for PD.[14,15] Previous studies showed that a family history of PD is associated with the clinical heterogeneity of the disease. One study showed that positive family history of PD in first-degree relatives is associated with slower progression of motor symptoms and cognitive decline.[16] However, another study reported an association between a family history of PD and the development of PD dementia (PDD).[17] Therefore, the association between the presence of family history and longitudinal changes in clinical and imaging features of PD needs to be thoroughly investigated. Furthermore, the effect of family history in PD on longitudinal complications, such as freezing of gait (FOG), remains elusive.

While profiling genetic variants and computation of PRS directly measure the genetic information, family history indirectly measures heritable susceptibility to the disease and provides additional information by reflecting the effect of rare variants or shared exposure to environmental factors.[181920] Although evidence suggests that either family history or PRS is associated with clinical heterogeneity of PD, simultaneous consideration of both pieces of information was not conducted in the previous studies. In this study, we collected questionnaire-based family history information and PRS from 395 newly diagnosed patients of PD from the Parkinson's Progression Markers Initiative (PPMI) database. We examined the independent effects of positive family history and PRS on the longitudinal prognosis of PD, including cognition, nigrostriatal degeneration, and motor complication. We hypothesized that the information on family history could be a proxy for the clinical heterogeneity of PD.

Methods

Study Participants

The data and study documentation used in this study were obtained from the PPMI cohort.[21] The PPMI is a multicenter observational study with clinical, imaging, and biological data to identify biomarkers of PD progression. Inclusion criteria for patients with idiopathic PD in the PPMI cohort were the following: (1) age 30 years or older, (2) untreated status with dopamine replacement medication, (3) within 2 years of diagnosis, (4) baseline Hoehn and Yahr scale (HY) < 3, (5) clinical features of the disease, and (6) having imaging evidence for dopaminergic deficit consistent with PD.[22] Data were downloaded from the PPMI repository in February 2023. To minimize a possible bias by the effects of known Mendelian monogenic variants on the analysis, we excluded those with known Mendelian monogenic variants in glucocerebrosidase (*GBA*; G2019S and R1441G), leucine-rich repeat kinase 2 (*LRRK2*; N370S, L483P, L444P, IVS2+1, and 84 GG), or synuclein alpha (*SNCA*; A53T).[23] Finally, we evaluated 395 patients with sporadic PD who followed up for more than 2 years. Participants were planned to follow-up at 3-month intervals during the first year followed by 6-month intervals.[22]

Standard Protocol Approvals, Registrations, and Patient Consents

All procedures in the study involving human participants were performed in accordance with the ethical standards committee at each participating institution, and written informed consent was obtained from all participants. The study was registered at clinicaltrials.gov (NCT01141023), and the enrollment began June 1, 2010.[22]

Clinical Assessment

At enrollment, age at the symptom onset of PD, sex, year of education, and apolipoprotein E ε4 (*APOE4*) carrier status were investigated. For each patient, motor severity was assessed using Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III score (UPDRS-III) and HY at every scheduled visit, and cognition was assessed using Montreal Cognitive Assessment (MoCA) at 12-month intervals. All participants underwent dopamine transporter (DAT) single-photon emission CT imaging using ^{123}I-N-(3-fluoropropyl)-2β-carboxymethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) following the PPMI imaging protocol at baseline and 12-, 24-, and 48-month visits. Processed data were normalized to the standard Montreal Neurologic Institute space, and the occipital cortex was used as a reference for quantitative analysis. The mean striatal binding ratio (SBRs) was calculated as $\frac{\textit{Target region} - \textit{Reference region}}{\textit{Reference region}}$. Count densities for the bilateral caudate and putamen were used to calculate SBRs. Development of FOG was defined to be present if any of UPDRS items 2.13 and 3.11 score ≥1 during the follow-up period.[24] The latency of FOG was calculated from the baseline date to the visit when FOG was first observed.

Family History of the Study Participants

The family history of the study participants was collected at the screening or the phase transition of the PPMI database. Both the total number of family numbers and those with PD or Parkinsonism were investigated using the case report form of the PPMI (eTable 1, links.lww.com/NXG/A656). Reported family members include first-degree (biological mother and father, full siblings, and children), second-degree (maternal or paternal grandparents, half-siblings, and maternal or paternal aunts and uncles), and third-degree relatives (first cousins). The participants were grouped as those with family history (PD^{f+}) if they had any first-degree, second-degree, or third-degree relatives with PD; otherwise, they were grouped as those without a family history (PD^{f-}).

Genotyping and Calculation of Polygenic Risk Scores

DNA samples were extracted from the whole blood of 386 patients and sequenced using an Illumina HiSeq X Ten Sequencer. Paired-end reads were aligned to the reference genome (hg38), and variants were called using the Genome Analysis Tool Kit.[25] We extracted the genotypes of the SNPs with the following quality control criteria: SNPs on non-autosomes, multiallelic, deviation from Hardy-Weinberg equilibrium (p < 1E-6), and high rates of missing genotypes (>0.05). PRS was computed using genotypes of 87 risk loci for PD after excluding 3 multiallelic loci.[6] Each PRS was calculated by summing the risk alleles weighted by log-transformed odds ratios (ORs). We also applied PRSice-2,[26] which predicts PRS by applying multiple p-value thresholds, using publicly available summary statistics of the GWA study, which excluded data conducted by 23 and Me.

Statistical Analysis

Statistical analyses of the demographic and clinical data were performed using R Statistical Software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria). The independent t test and χ^2 test were used to compare demographic variables between PD^{f+} and PD^{f-}. To evaluate the effect of positive family history, PRS, or both on longitudinal changes in clinical outcomes, we used linear mixed models (LMMs) for MoCA, UPDRS-III, and subregional DAT uptake. Predictors included time (follow-up years from baseline), dichotomized family history, and interaction between positive family history and time (family history × time) for model 1; time, PRS, and PRS × time for model 2; and time, family history, PRS, family history × time, and PRS × time for model 3. Random intercepts and random slopes were included in the models to allow the subject-specific cognitive changes. Each interaction term was used to measure the effect of positive family history or PRS on the rate of change of clinical outcomes. Age at diagnosis, symptom duration, and sex were adjusted in LMMs for UPDRS-III and subregional DAT uptake. Years of education were further adjusted in LMMs for MoCA.

Kaplan-Meier curves were used to visually compare the time to onset of FOG according to family history. Then, risks for developing FOG were further computed using Cox proportional hazard models to estimate hazard ratios (HRs) according to the presence of family history with adjustment of age at the diagnosis, symptom duration, sex, years of education, and baseline UPDRS-III (model 1). Model 2 further included PRS as covariates.

Data Availability

All data generated or analyzed during this study are available from the PPMI website.[21]

Results

Baseline Characteristics

The baseline demographics and clinical characteristics of the participants are presented in Table 1. Among 395 patients, 32.2% (N = 127) reported a family history of PD within third-degree relatives. Baseline age, proportion of male sex, years of education, symptom duration, and proportion of *APOE4* carrier status were comparable between the 2 groups. Follow-up duration was significantly longer in the PD^{f+} group than the PD^{f-} group (mean [SD] years, 9.0 [2.3] vs 7.8 [2.7]; p < 0.001). Clinical assessment, including UPDRS score, HY, MoCA score, and subregional DAT uptake were comparable between the 2 groups.

Table 1 Demographics and Clinical Characteristics of the Participants

	Family history (−) (N = 268)	Family history (+) (N = 127)	*p* Value
Age, y	62.2 (±9.5)	60.2 (±10.4)	0.057
Male, no. (%)	171 (63.8)	90 (70.9)	0.204
Education, y	15.7 (±2.9)	16.0 (±2.7)	0.397
Symptom duration, y	1.9 (±1.9)	2.2 (±2.2)	0.186
Follow-up duration, y	7.8 (±2.7)	9.0 (±2.3)	< 0.001
APOE4 carrier, no (%)	65 (24.3)	29 (22.8)	0.855
MDS-UPDRS part I score	4.3 (±3.3)	4.2 (±2.9)	0.849
MDS-UPDRS part II score	5.9 (±4.3)	5.5 (±3.8)	0.475
MDS-UPDRS part III score	20.9 (±8.8)	20.3 (±9.0)	0.539
Hoehn and Yahr scale			0.081
1	118 (44.0)	61 (48.0)	
2	150 (56.0)	64 (50.4)	
3	0 (0.0)	2 (1.6)	
MoCA	27.1 (±2.3)	27.1 (±2.3)	0.923

Abbreviations: Aβ = β-amyloid; *APOE4*, apolipoprotein E ε4; MoCA = Montreal Cognitive Assessment; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale.
Plus-minus values are the mean ± SD. Results from the t test or χ^2 test were used as appropriate.

Polygenic Risk Score Between PD^{f+} and PD^{f-} Groups

The PD^{f+} group had higher PRS based on 87 risk variants of PD ($p = 0.026$; Figure 1A). A trend for higher PRS computed using PRSice-2 in the PD^{f+} group than the PD^{f-} group was observed ($p = 0.052$; Figure 1B).

Longitudinal Changes of Striatal DAT Uptake According to Family History

In LMMs for caudate DAT uptake, the PD^{f+} group had a significantly slower decline of DAT uptake than the PD^{f-} group (β estimate of family history × time = 0.02, 95% confidence interval [CI] = 0.002–0.036, $p = 0.027$; Figure 2A and model 1 in eTable 2, links.lww.com/NXG/A656), while the rate of changes of putaminal DAT uptake was comparable between the 2 groups (β estimate of family history × time = 0.01, 95% CI = −0.001 to 0.017, $p = 0.100$; Figure 2B and model 1 in eTable 2). PRS was not associated with the longitudinal changes of DAT uptake in caudate and putamen (model 2 in eTable 2). When both family history and PRS were simultaneously considered, only family history was associated with a slower decline of DAT uptake (β estimate of family history × time = 0.02, 95% CI = 0.001–0.035, $p = 0.042$; model 3 in eTable 2).

Longitudinal Changes of Motor and Cognitive Measures According to Family History

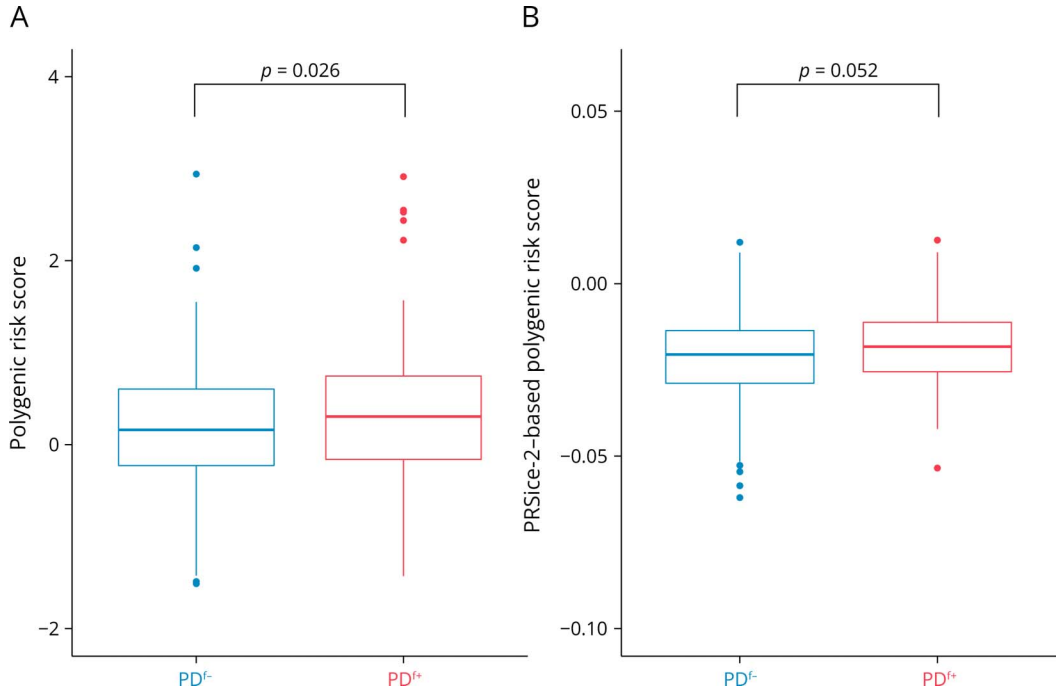
Over time, the total MoCA scores of all participants deteriorated after consideration of possible confounders (β estimate of time = −0.20, 95% CI = −0.26 to −0.14, $p = < 0.001$; model 1 in Table 2). The existence of family history was associated with slower declines of MoCA scores (β estimate of family history × time = 0.12, 95% CI = 0.02–0.22, $p = 0.017$). Higher PRS was also associated with slower declines of MoCA score (β estimate of PRS × time = 0.09, 95% CI = 0.03–0.16, $p = 0.006$; model 2). When both family history and PRS were simultaneously considered (model 3), there were independent effects of family history (β estimate of family history × time = 0.12, 95% CI = 0.02–0.22, $p = 0.024$) and PRS (β estimate of PRS × time = 0.08, 95% CI = 0.02–0.15, $p = 0.014$) on the decline rate of MoCA scores.

In LMMs for motor severity scores, UPDRS-III was increased longitudinally (β estimate of time = 2.14, 95% CI = 1.91–2.37, $p = < 0.001$; model 1 in eTable 3, links.lww.com/NXG/A656). However, neither family history, PRS, nor both did not modify the longitudinal decline rate of UPDRS-III (eTable 3).

Risk of Freezing of Gait According to the Family History

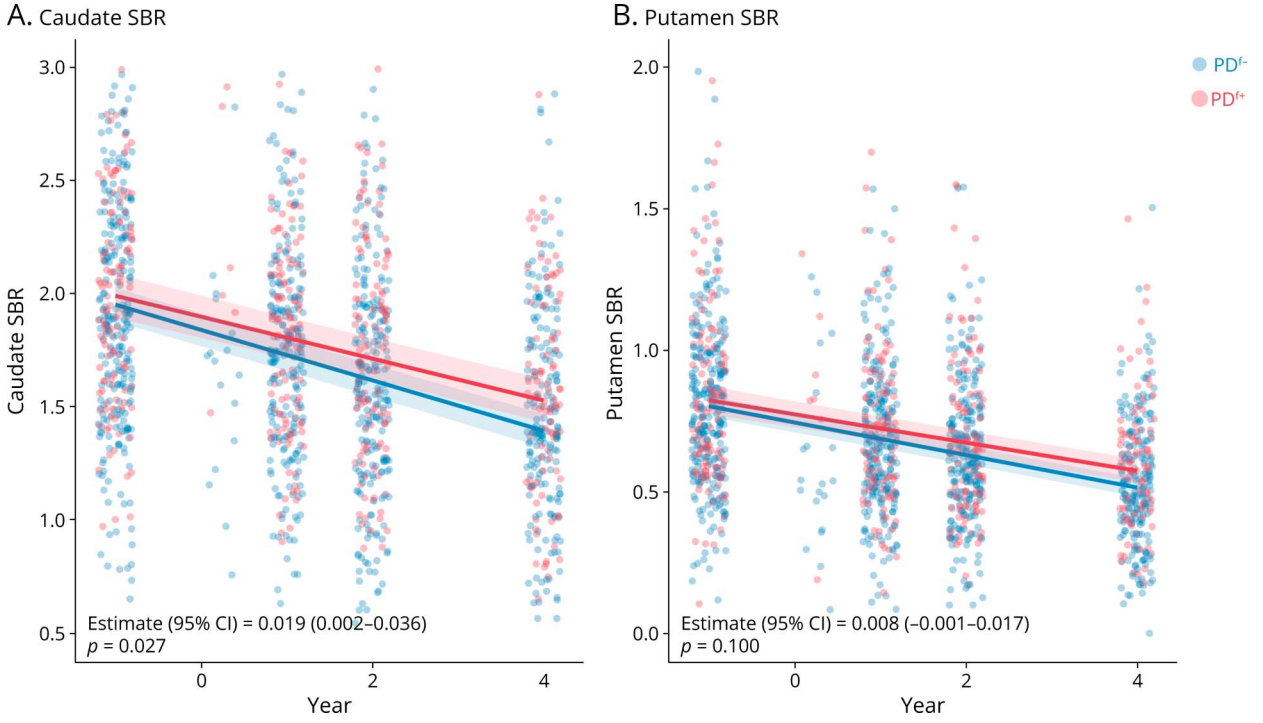
Among 364 patients without FOG at baseline, FOG developed in 105 in PD^{f-} and 79 in PD^{f+} during the follow-up period. A log-rank test of Kaplan-Meier analysis revealed that the PD^{f-} group had a higher risk of FOG than the PD^{f+} group ($P_{log\text{-}rank} = 0.004$; Figure 3). The Cox regression model revealed that the PD^{f+} group had a lower risk of FOG development than the PD^{f-} group after adjusting for age at the

Figure 1 Distribution of Polygenic Risk Score for Parkinson Disease According to Family History



Distribution of polygenic risk score based on 87 variants of recent genome-wide association study (A) and computed using PRSice-2 (B). PD^{f-} = Parkinson disease without family history; PD^{f+} = Parkinson disease with family history.

Figure 2 Trajectories of Longitudinal Nigrostriatal Dopaminergic Degeneration According to Family History of Parkinson Disease



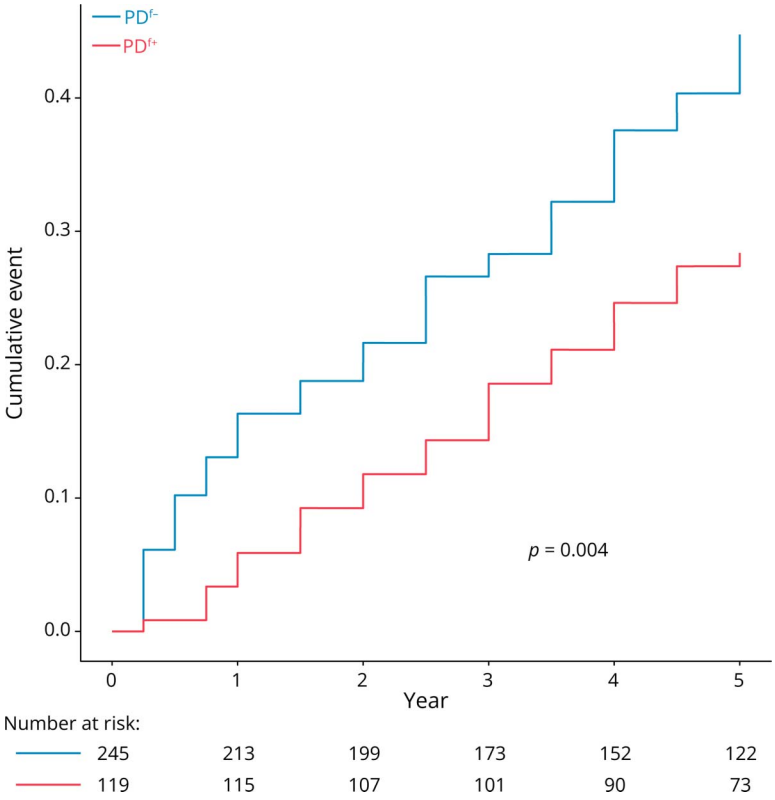
Data are the results of linear mixed model analysis for longitudinal caudate (A) and putamen (B) dopamine transporter uptake using the time (y), family history, and time × family history as predictors. Estimate, CI, and *p* values are the statistics of interaction terms between family history and year. The covariates included age, sex, and symptom duration. CI = confidence interval; SBR = specific binding ratio; PD^{f-} = Parkinson disease without family history; PD^{f+} = Parkinson disease with family history.

Table 2 Association Between Family History and PRS and Longitudinal Changes of Cognitive Score

	Model 1		Model 2		Model 3	
Predictors	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age	−0.07 (−0.09 to −0.04)	<0.001	−0.06 (−0.09 to −0.04)	<0.001	−0.06 (−0.09 to −0.04)	<0.001
Sex, male	−0.72 (−1.15 to −0.30)	0.001	−0.68 (−1.11 to −0.25)	0.002	−0.69 (−1.12 to −0.26)	0.002
Education	0.12 (0.05 to 0.19)	0.001	0.12 (0.05 to 0.20)	0.001	0.12 (0.05 to 0.19)	0.001
Symptom duration	−0.01 (−0.11 to 0.10)	0.912	−0.001 (−0.107 to 0.104)	0.979	−0.004 (−0.110 to 0.101)	0.939
MDS-UPDRS part III	−0.03 (−0.049 to −0.002)	0.031	−0.03 (−0.049 to −0.002)	0.036	−0.03 (−0.049 to −0.002)	0.037
Time	−0.20 (−0.26 to −0.14)	<0.001	−0.19 (−0.24 to −0.13)	<0.001	−0.22 (−0.29 to −0.16)	<0.001
Family history	0.27 (−0.16 to 0.71)	0.216			0.23 (−0.20 to 0.67)	0.296
Family history × time	0.12 (0.02 to 0.22)	0.017			0.12 (0.02 to 0.22)	0.024
PRS			−0.03 (−0.31 to 0.26)	0.858	−0.04 (−0.33 to 0.24)	0.771
PRS × time			0.09 (0.03 to 0.16)	0.006	0.08 (0.02 to 0.15)	0.014

Abbreviation: CI = confidence interval; HR, hazard ratio; MoCA = Montreal Cognitive Assessment; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PRS = polygenic risk score.
Data are the results of linear mixed models for longitudinal cognitive scores measured by MoCA. Predictors for model 1 were time (y), family history, and time × family history; those for model 2 were time, PRS, and time × PRS; and those for model 3 were time, family history, PRS, time × family history, and time × PRS. The covariates included age, sex, education, symptom duration, and baseline MDS-UPDRS part III score.

Figure 3 Kaplan-Meier Curve Analysis for Freezing of Gait



Kaplan-Meier curve showing the risk of development of freezing of gait by the presence of family history in patients with newly diagnosed Parkinson disease. PD^{f-} = Parkinson disease without family history; PD^{f+} = Parkinson disease with family history.

diagnosis, symptom duration, sex, years of education, and baseline UPDRS-III (HR of family history = 0.57, 95% CI = 0.38–0.84, p = 0.005; model 1 in Table 3). When PRS was further considered, the effect of family history on developing FOG remained significant (HR of family history = 0.54, 95% CI = 0.36–0.81, p = 0.003; model 2 in Table 3).

Discussion

In this study, we evaluated the association between family history and PRS with the longitudinal prognosis of PD. The major finding of our study is as follows: first, positive family history was associated with a slower decline of caudate DAT uptake. Second, positive family history and higher PRS were independently associated with slower cognitive decline. Third, positive family history was associated with a lower risk of developing FOG. Our study suggests that those with a family history of PD had better longitudinal outcomes. Furthermore, collecting information on positive family history has a clinical implication for predicting longitudinal outcomes.

Our first major finding is that positive family history was associated with a slower decline of caudate DAT uptake. Given that family history is one of the strongest risk factors for developing PD[15,27] and positive family history was associated with a marker of vulnerability to nigrostriatal dysfunction,[28] it may be counterintuitive that the nigrostriatal degeneration of the caudate is slower in those with family history. However, this is in line with prior PPMI-based study which showed less dopaminergic degeneration in PD patients with higher PRS.[12] Furthermore, PD patients with a genetic variants on *LRRK2* and *GBA* also showed a favorable trajectory of dopaminergic degeneration.[29,30] The observed phenomenon may be attributed to the reduced spread of Lewy body-related pathology (LRP) from the substantia nigra pars compacta, where axonal terminals project to the putamen. On the contrary, the longitudinal change of putaminal DAT uptake was comparable between PD^{f+} and PD^{f-}. This could be the floor effect because putaminal DAT uptake is already decreased at the time of diagnosis of PD. Taken together, although the risk of developing PD is higher if there is a family history, the progression of the disease itself may be slower.

Our second major finding is that positive family history and higher PRS were independently associated with slower cognitive decline. This is consistent with a previous study which revealed that positive family history in PD was associated with slower deterioration of motor and cognitive scores.[16] Caudate has an abundant connection to various neocortical regions of the brain consisting of corticostriatal circuits, and patients with PD dementia showed a considerable loss of lateral dopaminergic system to frontal, parietal, and temporal cortical regions.[31] Regarding relatively preserved caudate DAT availability in patients with a family history, a slower decrement in

Table 3 Cox Regression Analyses for Freezing of Gait According to the Presence of Family History

	Model 1		Model 2	
Predictors	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age	1.02 (1.00–1.04)	0.016	1.02 (1.00–1.04)	0.016
Sex, male	1.33 (0.92–1.92)	0.132	1.33 (0.91–1.93)	0.138
Symptom duration	0.91 (0.80–1.02)	0.107	0.92 (0.82–1.05)	0.208
MDS-UPDRS part III	1.03 (1.01–1.05)	0.012	1.03 (1.01–1.05)	0.011
Family history	0.57 (0.38–0.84)	0.005	0.54 (0.36–0.81)	0.003
PRS			1.08 (0.84–1.39)	0.538

Abbreviations: CI = confidence interval; HR = hazard ratio; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PRS = polygenic risk score.
Data are the results of the Cox regression model for the presence of freezing of gait. The predictor for model 1 was family history; and those for model 2 were family history and PRS. covariates included age, sex, symptom duration, and baseline MDS-UPDRS part III score.

MoCA score might be associated with a slower decrement in caudate DAT availability. However, another study showed that patients with a family history of PD had more frequent dementia; however, regarding latency to develop dementia, PD family history showed no effect on dementia development.[17] Although we could not evaluate the effect of family history or PRS on the prevalence of dementia, as the determination of dementia was not conducted in the initial phase of the PPMI, family history and higher PRS were associated with slower cognitive decline. As pathologic correlates of cognitive decline in PD are LRP in the neocortex,[32] our data suggest slower propagation of LRP in those with a genetic predisposition.

Our third major finding is that positive family history was associated with a lower risk of developing FOG. The underlying pathomechanism of FOG in PD is not well understood. However, genetic variants could partly explain the heterogeneity of FOG in PD, as monogenic variants in *LRRK2* or *GBA* showed higher frequency of developing FOG.[33,34] By contrast, some genetic variations showed a protective effect on the development of FOG.[35] It is also suggested that the combination of dysfunction in both nigral and extranigral systems may contribute to the development of FOG.[36,37] A lower risk of developing FOG in patients with a family history might be attributable to the slower decrease in the caudate DAT availability, given that decreased caudate DAT uptake was associated with FOG.[38,39] Furthermore, mixed pathology of cortical amyloidopathy is also associated with FOG.[38] Taken together, those with a family history of PD might have some protective variants of FOG or have less pathologic burden other than LRP.

On the contrary, longitudinal progression of motor severity measured by the total UPDRS-III score was not associated with family history nor PRS. Evidence on the effect of family history or PRS on motor progression remains elusive. A prospective cohort-based study showed slower progression in PD patients with a family history.[16] Different measurement of motor severity in the previous study, which was qualitative and was based on the patient's subjective report, may explain the different results. Regarding PRS, another study reported that higher PRS was associated with faster motor and cognitive decline.[11] As we excluded those with monogenic variants in *GBA*, *LRRK2*, or *SNCA* and used different risk loci for calculating PRS, different results of PRS on motor progression could be achieved between studies. It may counterintuitive that not UPDRS-III but only subscores for FOG is deteriorated in the PD^{f-} group compared with the PD^{f+} group. However, this finding is consistent with a previous longitudinal study, which evaluated the clinical predictors for FOG.[40] In the study, there was no significant interaction effect between time and group divided by the developing FOG, suggesting that longitudinal changes of total UPDRS-III were not different between those who experienced FOG and those who did not. Given that the proportion of nonaxial symptoms, such as rigidity, bradykinesia, and tremor, is higher than that for axial symptoms in UPDRS-III and that overall motor severity of PD is thought to be associated with dopaminergic depletion in the putamen,[41] we hypothesized that PD patients with family history may have less progression in axial symptoms which is not explained by nigrostriatal degeneration involving putamen.

Our study did not observe the association of PRS with nigrostriatal degeneration and the development of FOG. This relative lack of effect of PRS than family history could be explained by the fact that variants used for the computation of PRS were those from GWA studies of normal controls vs patients with PD, exploring the risk variants of the disease.[6] As recent studies evaluated the variants associated with endophenotypes of the disease,[42-44] future studies are warranted to derive genetic risk scores for targeting to predict disease progression in PD. For this reason, the meaning of PRS varies depending on the study in which the value was calculated, and the variability in the calculated value increases depending on the patient group participating in the study. As shown in our study, the clinical usability of family history and PRS are independent of each other, and this pattern has been reported in other diseases, such as diabetes and stroke.[45,46] Thus, further development of a combined model to account for both family history and PRS could be useful in explaining the clinical heterogeneity of PD.[47]

Our study has some limitations. First, assessing family history data of patients with PD is not always straightforward. It can vary depending on the assessing method and informants. Prior studies regarding the validity of family history data in PD revealed substantial family information bias in the family history method, overreporting family history of PD in patients with PD, or their proxies.[48] However, our study investigated patients with PD only, eliminating the possible bias of family information. Moreover, the PPMI cohort implemented a

detailed form for family history data. Second, the inhomogeneous follow-up duration between the two groups is evident in our study, with the PD^{f+} group having a longer follow-up duration than the PD^{f-} group. However, despite longer follow-up, PD^{f+} patients had less development of FOG and a slower decline in MoCA and caudate DAT uptake. Considering the higher possibility of worsening as the follow-up duration lengthens, this finding could further assure our results. In this study, we showed that those with a family history had less cognitive decline and a lower risk of FOG related to important milestones of the disease progression in PD.[3,49] Thus, collecting information on family history has a clinical implication as a marker for disease heterogeneity in PD.

Study Funding

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Disclosure

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