Genetic Associations With Rapid Motor and Cognitive Deterioration in Parkinson’s Disease

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Research

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Abstract

**Background:** Parkinson's disease (PD) is caused by the interplay of genetic and environmental factors during brain aging. About 90 single nucleotide polymorphisms (SNPs) have been recently discovered associating with PD, but their associations with PD clinical features have not been fully characterized yet.

**Methods:** Clinical data of 377 patients with PD who enrolled in Parkinson's Progression Markers Initiative (PPMI) study were obtained. Patients with rapid cognitive or motor progression were determined through clinical assessments over five years follow-up. In addition, genetic information of 50 targeted SNPs was extracted from the genetic database of NeuroX for the same cohort. Genetic associations with rapid motor and cognitive dysfunction of PD were analyzed using SPSS-logistic regression.

**Results:** Among 377 patients with PD, there are more male (31%) than female (17%) prone to have rapid motor progression ($p<0.01$), who demonstrate 16 points increase in the motor part assessment of MDS-UPDRS. There is no gender difference in rapid cognitive deterioration. Four SNPs (rs11724635, rs12528068, rs591323, rs17649553) were associated with fast cognitive decline ($p<0.05$) and the extended 50 SNPs researches excellent predicative value of area under curve (AUC) at 0.961. Three SNPs (rs823118, rs10797576, rs12456492) were associated with faster motor progression ($p<0.05$), and the extended 50 SNPs and gender researches fair prediction of AUC at 0.736. There were multiple genetic associations with initial clinical presentations of PD at baseline as well.

**Conclusions:** Genetic factors contribute to the disease progression as well as the clinical features at the disease onset.

Background

Parkinson disease (PD) is the second most common neurodegenerative disorder in the elderly, which is characterized by motor disabilities such as tremor, bradykinesia, rigidity as well as non-motor symptoms including hyposmia, REM sleep behavior disorder (RBD), cognitive impairment and so on[1, 2]. Both motor and non-motor disabilities are significant to patients’ quality of life and increase financial burden to the families and the society[3]. In addition to various combination of motor and non-motor presentations, the disease progression of each patient varies quite differently[4]. The rate of motor progression is the major factor related to prognosis and quality of life[5, 6]. Among non-motor symptoms, cognitive impairment and dementia are frequent problem encountered in PD especially at advanced stages of PD[1, 7]. At least 75% patients with PD who survive for more than 10 years will develop dementia[8]. Despite the high prevalence, our understanding of related mechanism is still limited. Therefore, identifying factors affecting the progression of motor and cognitive impairment of PD is particularly important for the discovery of PD pathogenesis, disease therapy and patient’s care.

Genetic contributions to PD and its susceptibility to the onset of PD have been well acknowledged[2, 9-11]. Meta-analysis of genome-wide association studies (GWAS) in 2017 and 2019 have successfully
identified more than 40 independent single nucleotide polymorphisms (SNPs) and 90 SNPs associated with PD\cite{12,13}. These 90 variants explained 16–36\% of the heritable risk of PD depending on prevalence\cite{13}. Recent studies showed that patients carrying a certain gene mutation have distinct clinical presentations and disease progression from sporadic PD\cite{14,15}. In addition, PD susceptibility genes have been associated with PD clinical features, such as the age of onset, progression of other non-motor symptoms of PD\cite{16-21}. However, these studies were either based on cross-sectional PD cohorts or with limited genetic variants involved, so as to made incremental advances to the field. Although recent genome-wide association study (GWAS) revealed genetic contributions to PD motor and cognitive progression in longitudinal PD cohorts\cite{22}, the clinical classification applied in that study might conceal significant genetic findings. This study aims to investigate genetic associations with rapid motor and cognitive decline in a longitudinal PD cohort based on recent GWAS identified PD risk SNPs\cite{12,13}.

**Methods**

**Participants**

*Parkinson's Progression Markers Initiative (PPMI)* is an observational international, multi-centre cohort study using advanced imaging, biologic sampling and clinical and behavioral assessments to identify biomarkers of PD progression, funded by Michael J. Fox Foundation (MJFF)\cite{23}. Application to data usage was approved by the scientific committee of PPMI, and this study involved database usage was approved by the Ethics Board of the Beijing Tiantan Hospital, Capital Medical University of China (KY 2018-031-02). A total 377 patients with clinical diagnosis of PD were selected in this study. All patients had been clinically assessed by Unified Parkinson's Disease Rating Scale (UPDRS), including UPDRS-III for motor function, Montreal Cognitive Assessment (MoCA) for cognitive function, and Rapid Eye Movement Behaviour Disorder Questionnaire (RBDQ), the University of Pennsylvania Smell Identification test (UPSIT), Scales for Outcomes in Parkinson’s disease - Autonomic (SCOPA-AUT), and Geriatric Depression Scale (GDS) for RBD, hyposmia, autonomic dysfunction, and depression respectively at baseline and annual examination basis up to five years.

**Baseline Evaluations**

As studies suggested, cutoff values of 26, 5, 9, 5 were chosen for MoCA, RBDQ, SCOPA-AUT and GDS for the presence of the problems in cognition, RBD, autonomic dysfunction and depression \cite{24-26}. Age at onset less than 55 years old was chosen as the cut-off value for early onset of PD\cite{27}.

**Five-Year Follow-Up Evaluation**

**Determine PD Subgroup with Rapid Motor Progression:** UPDRS is currently the most authoritative scale for evaluating PD motor symptoms. A number of studies have shown that the progression of motor symptoms is a non-linear pattern in the course of the disease\cite{28}. Thus, we selected analyzing phase change in UPDRS-III score to define motor progression. 3.2-point (95\% CI 2.8 to 3.6) change per year in
UPDRS-III score represents a rapid motor progression \[^{[29]}\]. Thus, we identified fast motor progressors if they had more than 16-point increase in the UPDRS-III score from baseline to the follow-up at year 5, and 99 patients (26\%) were defined as fast motor progressors.

**Determine PD Subgroup with Rapid Cognitive Dysfunction:**

MoCA is a sensitive and widely used tool for cognitive function measurement in PD. Research showed that a four-point decrease in MoCA score is reliable to define cognitive decline with 90\% confidence \[^{[30]}\]. Thus, from baseline to the follow-up year 5, we recognized 21 patients (5.6\%) with fast cognitive decline meet with the definitive standard ie. having more than four-point decrease in MoCA.

**Genotyping and Selection of SNPs**

Samples from PPMI were genotyped using NeuroX array. The NeuroX array is an Illumina Infinium iSelect HD Custom Genotyping array containing 267,607 Illumina standard contains exonic variants and an additional 24,706 custom variants designed for neurological disease studies. Out of the variants, approximately 12,000 are designed to study PD and are applicable to both large population studies of risk factors and investigations of familial disease with known mutations \[^{[31, 32]}\]. All samples and genotypes underwent stringent quality controls (QC). Genetic data were cleaned using PLINK v1.9 beta. SNPs with missing genotype rate over 10\%, minor allele frequency less than 0.02, and Hardy-Weinberg equilibrium (HWE) test \( p \) value less than \( 1 \times 10^{-6} \) were excluded. Eventually 50 SNPs information were extracted as no further GWAS PD significant \( (p \leq 5 \times 10^{-8}) \) were found in NeuroX or excluded by filtering (Supplementary Table 1).

**Statistical Analysis**

IBM SPSS Statistics 26 was used for this study. To assess genetic associations with rapid motor or cognitive decline, logistic regression was used to estimate odds ratios (OR) with 95\% CI, \( p \)-values of each genetic variable, and the predictive values of total 50 SNPs with each phenotype were calculated. Receiver operating curve (ROC) analysis was used to assess the significant and total 50 SNPs for predicing the rapid cognitive and motor deterioration, and area under curves (AUC) were used to evaluate the predictive models. For the genetic association studies based on the initial clinical data collection, binary logistic regression was used for presence or absence of non-motor symptoms analysis with disease duration as a covariant as well, and linear regression was used for the onset age analysis.

**Bioinformatics Analysis**

STRING (version 11) website-based software was used to detect protein-protein interaction networks in supporting functional discovery in this polygenetic association datasets to generate common molecular pathways among different genetic products \[^{[33]}\].

**Results**
Clinical Observations

**Baseline data observation:** Of the 377 patients from PPMI database, 249 were men (66.0%) and the ratio of male vs female was 1.95. The median age at diagnosis was 61 years, 351 patients (93.1%) had hyposmia, detected by UPSIT test. As for other non-motor tests, median scores of SCOPA-AUT, GDS (Short version), RBDQ were 12, 5, and 4, respectively (Table 1). There were no significant gender differences in age of onset, progression of cognitive impairment, RBD symptoms, hyposmia symptoms, autonomic dysfunction, and depressive symptoms of this PD cohort \( p > 0.05 \).

**Longitudinal observation:** The median UPDRS-III motor score change was 8 by the fifth year follow up in this cohort. 99 (26%) patients had fast motor progression with median UPDRS-III motor score change of 22 by the 12th visit at the 5th year. 21 patients (5.6% of the cohort) had fast cognitive decline with median MoCA change of 5. there are more male (31%) than female (17%) prone to have rapid motor progression \( p < 0.01 \), but there is no gender difference in cognitive deterioration (Table 1).

Genetic Associations

**Genetic associations with longitudinal disease progression:** Four SNPs (rs11724635, rs12528068, rs591323, rs17649553 located in the loci of BST1, RIMS1, FGF20, and MAPT respectively) associated with fast cognitive decline \( p = 0.025, p = 0.008, p = 0.019, p = 0.024 \), respectively). Three SNPs (rs823118, rs10797576, rs12456492 located in the loci of NUCKS1, SIA1L2, RIT2 respectively) were associated with faster motor progression \( p = 0.028, p = 0.039, p = 0.018 \), respectively) (Table 2).

**Genetic associations with clinical features at the baseline:** Three SNPs (ITPKB rs4653767, FGF20 rs591323, GALC rs8005172) were associated with early onset age of PD \( p = 0.042, p = 0.014, p = 0.020 \), respectively); IP6K2 rs12497850 and LRRK2 rs76904798 were associated with cognitive impairment \( p = 0.006, p = 0.007 \), respectively); SCN2A rs353116 was associated with hyposmia \( p = 0.002 \); NDUFAF2 rs2694528 and USP25 rs2823357 were associated with RBD \( p = 0.021, p = 0.006 \), respectively), SATB1 rs4073221 and GAK rs11248051 were associated with autonomic dysfunction \( p = 0.034, p = 0.043 \), respectively), and FGF20 rs591323 was associated with depression \( p = 0.034 \) (Supplementary Table 2).

ROC curve analysis

ROC curve analysis was performed to evaluate the predictive values of all and significant different SNPs for the outcomes of rapid motor and cognitive dysfunction (Figure 1). AUC of fast cognitive decline is 0.772 (95% CI 0.726 to 0.813) predicted by the significantly related SNPs (rs11724635, rs12528068, rs591323, rs17649553) (Table 2), while it reaches 0.961 (95% CI 0.937 to 0.978) with all 50 SNPs information input (Figure 1). The AUC of rapid motor progression is 0.628 predicted by the significantly related SNPs (rs823118, rs10797576, rs12456492) (Table 2), and it reaches 0.736 (95% CI 0.684 to 0.776) while considering all 50 SNPs and gender.
Genetic factors also demonstrated fair predication properties (AUC=0.7-0.8) early onset age (0.744) and cognitive impairment (0.729) performances at baseline visit (Supplementary figure 1). In addition, genetic factors also associate with other quantitative traits of PD at the initial visit, such as hyposmia (0.851), RBD (0.719), autonomic dysfunction (0.711), and depression (0.756) (supplementary figure 2). p value of each ROC curve is less than 0.001.

Analysis of molecular pathways related to rapid motor and cognitive decline

STRING analysis showed the number of edges was 77 vs the expected of 11, average node degree was 3.28, and there was significant more interactions in this protein network ($p < 1.0e-16$). There were no direct interactive molecular pathways related to those gene products (BST1, RIMS1, FGF20 and tau) with significant implication for rapid cognitive decline, indicating they are independent risk factors. However, MAPT and FGF20 encode hub proteins with more than 5 molecular interactions (Figure 2)\cite{34}.

Regarding to the genes related to rapid motor progression, NUCKS1, SIPA1L2 and RIT2, NUCKS1 is an independent risk factor, and SIPA1L2 and RIT2 may jointly activate the RAS type GTPase. In addition, NUCKS1 and RIT2 are hub nodes in the network (Figure 2).

Discussion

Our study revealed up to 50 SNPs located in different genetic loci associated with the rapid cognitive and motor deterioration in PD (Table 2). Furthermore, we confirmed the predictive effect of susceptibility genes on rapid disease progression phenotypes through AUC analysis (Figure 1). In addition, we verified the correlations between susceptibility genes and clinical quantitative traits in previous studies\cite{35, 36} from genetic associations with clinical baseline data (Supplementary table and figure).

In this study, we found there was more male with PD than female (Table 1). Gender was significantly related to rapid motor progression, but not related to other clinical features (Table 1). Previous study showed that female patients were more likely to have slower disease progression, due to higher dopaminergic activity at baseline and protective effect of estrogens\cite{37}. Our results showed multi genetic network provide better predicative values for the measures of clinical features in PD (table 2, figures 2, supplementary figures 1 & 2). This partially explained why almost every patient with PD has non-motor symptoms ranging from 8 to 12 different symptoms, which is now considered as a crucial factor for driving quality of life of patients in PD\cite{38}. FGF20 is the common gene showing significant association with multiple PD clinical features, early onset, depression and rapid cognitive decline (Table 2 & Supplementary Table 2). FGF20 rs591323 was associated with late onset age and rapid cognitive decline (see below), while older age at onset has been associated with a higher risk of dementia \cite{39}. FGF20 is a hub protein interaction with SNCA, LRRK2, ACMSD, GAK, MCCC1 and GPNMB (Figure 2). Our study revealed the underlying molecular mechanisms and the molecular network as a whole contributing to the concurrent clinical features of PD.
In this study, we found three variants **NUCKS1 rs823118**, **SIPA1L2 rs10797576**, **RIT2 rs12456492** were associated with rapid motor deterioration in PD (Table 2). NUCKS1 is a hub protein with connection of TMEM175, MCCC1, ACMSD, LRRK2, GAK and FAM47E, and RIT2 is another hub node connecting with GAK, ACMSD, MCCC1, LRRK2, SNCA, MAPT and SIPA1L2 (Figure 2), while **GBA** and **SNCA** genes have been shown associated with rapid motor progression\(^\text{[21,40-42]}\). Motor deterioration has been related to dopaminergic neuronal loss in the substantia nigra\(^\text{[43]}\). Microglial activation and neuroinflammation has been attributed to the neuronal cell death after the disease onset\(^\text{[44]}\), while RIT2 enables to induce inflammatory response\(^\text{[45]}\). In addition, impaired lysosomes, autophagosomes and mitochondria function in dopaminergic neurons facilitate α-synuclein deposits and subsequent neuronal death \(^\text{[46,47]}\), while TMEM175 and Lrrk2 have been attributed to this mechanism of PD. As 50 SNPs and gender together gave rise to a fair predication of rapid motor progression (Figure 1A), additional genetic factors are required to be identified to achieve the most optimized predictive value for rapid motor progression.

Furthermore, our study identified excellent genetic predicative markers for fast cognitive decline in PD (AUC=0.961, Figure 1B) under the foundation of rs11724635**(BST1 loci)**, rs12528068 **(RIMS1 loci)**, rs591323 **(FGF20 loci)**, and rs17649553 **(MAPT loci)**. Although all variants examined in this study are PD susceptible, both **RIMS1 rs12528068** and **MAPT rs17649553** demonstrated cognition protective effects (Table 2). Our findings are consistent with the genetics - neuropathology association study\(^\text{[48]}\), indicating the same genetic products may play different directions at the disease onset and during the disease progression. Indeed, based on the clinical data at the initial visit, when motor symptoms occur and onset of PD is often made, cognitive performance is associated with **IP6K2 rs12497850** and **LRRK2 rs76904798** in this cohort (Supplementary table 2), possibly through joint effects via their direct interaction (Figure 2). In this study, the most significant genetic impact on rapid cognitive decline is **RIMS1 rs12528068** (p=0.008) (Table 2). Research showed that the T allele of rs12528068 increased the **RIMS1** expression in the hippocampus\(^\text{[49]}\), while **RIMS1** is essential for maintaining normal probability of neurotransmitter release and has been shown involving in cognition processes in human\(^\text{[50]}\).

This study has the following limitations. First, we focus on the main concerns of rapidity of motor and cognitive decline, rather than the disease progression profile, which incorporate other non-motor symptoms, such as pain, anxiety, fatigue and so on, due to limitation of database. Second, the NeuroX genetic data did not include all 90 SNPs recently summarized\(^\text{[13]}\). Consequently, we could not assess the associations between missing SNPs and symptoms of PD, which might lead to not ideal AUC value for predication of rapid motor progression. Third, patients enrolled in this study were mostly at early stage of PD, and some genetic variants may affect the disease progression at later stages, which were unable to be discovered in this study. Fourth, to our knowledge, this is the second paper reporting genetic associations with the progression of PD. Compared to the first study from Tan MMX et al\(^\text{[22]}\), our genetic variants coverage is not whole genome wide.

**Conclusions**
Our study showed genetic factors not only contribute to the initial clinical presentations of PD, but also contribute to the rapidity of motor and cognitive deterioration of PD. The molecular pathways & network for fast cognitive decline in PD identified in this study warrant validation in another cohort of PD.

**Abbreviations**

BST1, bone marrow stromal cell antigen 1;

FGF20, fibroblast growth factor 20;

GALC, galactosylceramidase;

GAK, cyclin G associated kinase;

IP6K2, inositol hexakisphosphate kinase 2;

ITPKB, inositol-trisphosphate 3-kinase B;

LRRK2, leucine rich repeat kinase 2;

MAPT, microtubule associated protein tau;

NDUFAF2, nicotinamide adenine dinucleotide ubiquinone oxidoreductase complex assembly factor 2;

NUCKS1, nuclear casein kinase and cyclin dependent kinase substrate 1;

RIMS1, regulating synaptic membrane exocytosis protein 1;

RIT2, ras like without CAAX motif 2;

SATB1, special AT-rich sequence-binding protein 1;

SCN2A, sodium voltage-gated channel alpha subunit 2;

SIPA1L2, signal induced proliferation associated 1 like 2;

USP25, ubiquitin specific peptidase 25

**Declarations**

**Ethics approval and consent to participate**

The PPMI study was approved by the Institutional Review Boards of each PPMI site. Informed written consent was obtained from all subjects at each site. Application to data usage was approved by the scientific committee of PPMI, and this study involved database usage was approved by the Ethics Board of the Beijing Tiantan Hospital, Capital Medical University of China (KY 2018-031-02).
Consent to publication

Not applicable.

Availability of data and material

The dataset information belongs to PPMI. The data analysis files for this study are available from the corresponding author upon reasonable request.

Competing Interests

All authors consent for publication and have no competing interests.

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Authors’ contributions

CLX did data extraction from the PPMI database, statistics analysis and drafted the manuscript. YSP revised the manuscript. YH designed the project and critically revised the manuscript.

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## Tables

### Table 1. Demographic and Clinical Characteristics of the PD Cohort

| Clinical Characteristics                                      | Median (IQR) | P value* |
|--------------------------------------------------------------|--------------|----------|
|                                                              | Male         | Female   | Total    |
| Number of people, No./total No. (%)                          | 249/377 (66%)| 128/377 (34%)| 377/377 (100%)| <0.01 |
| Age at diagnosis, median (IQR)                               | 62 (55 to 69)| 61 (54 to 68)| 61 (54 to 68)| N.S. |
| Age at baseline examination, median (IQR)                    | 63 (55 to 69)| 62 (55 to 68)| 62 (54 to 69)| N.S. |
| Years of education, median (IQR)                             | 16 (14 to 18)| 16 (13 to 17)| 16 (14 to 18)| N.S. |
| UPDRS-III motor score change per 5 years, median (IQR)       | 9 (1 to 16)  | 7 (0 to 13) | 8 (0 to 16) | N.S. |
| Rapid motor progression (increasing scores ≥ 16 points), No./total No. (%) | 77/249 (31%)| 22/128 (17%)| 99/377 (26%)| <0.01 |
| UPDRS-III motor score change per 5 years among fast motor progression patients, median (IQR) | 22 (17 to 28) | 22 (20 to 28) | 22 (18 to 28) | N.S. |
| MoCA cognition score at baseline, median (IQR)               | 27 (24 to 29)| 27 (25 to 29)| 27 (25 to 29)| N.S. |
| MoCA change per 5 years, median (IQR)                        | 0 (-1 to 1)  | 0 (0 to 0) | 0 (-1 to 1) | N.S. |
| Rapid cognitive decline (decrease in score ≥ 4 points), No./total No. (%) | 14/249 (5.6%)| 7/128 (5.5%)| 21/377 (5.6%)| N.S. |
| Scales for SCOPA-AUT, median (IQR)                           | 12 (7 to 17) | 11 (7 to 15) | 12 (7 to 16) | N.S. |
| Geriatric Depression Scale (Short version), median (IQR)     | 5 (5 to 6)   | 5 (5 to 6) | 5 (5 to 6) | N.S. |
| Rapid Eye Movement Behaviour Disorder Questionnaire, median (IQR) | 4 (2 to 8)   | 4 (3 to 7) | 4 (3 to 7) | N.S. |
| UPSIT, Hyposmia No./total No. (%)                            | 235 (94%)    | 116 (91%) | 351/377 (93%) | N.S. |
Table 2. Genetic Associations with Rapid Motor and Cognitive Deterioration in PD

| SNP            | Related Gene | OR (95%CI) | Beta | P Value | RR (95%CI) |
|----------------|--------------|------------|------|---------|------------|
| rs823118       | NUCKS1       | 1.46 (1.04-2.04) | 0.38 | 0.028   | 1.12 (0.94-2.56) |
| rs10797576     | SIPA1L2      | 0.59 (0.36-0.97) | -0.53 | 0.039   | 0.86 (0.76-0.98) |
| rs12456492     | RIT2         | 1.50 (1.07-2.10) | 0.41 | 0.018   | 1.11 (0.98-1.25) |
| rs11724635     | BST1         | 2.07 (1.10-3.90) | 0.73 | 0.025   | 1.04 (0.99-1.09) |
| rs12528068     | RIMS1        | 0.27 (0.10-0.70) | -1.33 | 0.008   | 0.70 (0.17-2.86) |
| rs591323       | FGF20        | 2.35 (1.15-4.80) | 0.85 | 0.019   | 1.03 (0.98-1.09) |
| rs17649553     | MAPT         | 0.24 (0.07-0.83) | -1.43 | 0.024   | 0.93 (0.89-0.97) |

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; RR, relative risk.