Rapid motor progression of Parkinson’s disease associates with clinical and genetic variants

Ling-Xiao Cao¹,², Yong Jiang¹, Ying-Shan Piao², Yue Huang¹,²,³,*

¹China National Clinical Research Centre for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, 100070 Beijing, China, ²Neurology Department, Beijing Tiantan Hospital, Capital Medical University, 100070 Beijing, China, ³Department of Pharmacology, School of Medical Sciences, Faculty of Medicine & Health, UNSW Sydney, 2033 Sydney, Australia

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Material and methods
   3.1 Participants
   3.2 Baseline evaluations
   3.3 Five-year follow-up evaluation
   3.4 Genotyping and selection of SNPs
   3.5 Statistical analysis
   3.6 Bioinformatics analysis
4. Results
   4.1 Clinical observations
   4.2 Genetic associations with longitudinal motor progression
   4.3 ROC curve analysis
   4.4 Analysis of molecular pathways related to rapid motor decline
5. Discussion
6. Conclusions
7. Author contributions
8. Ethics approval and consent to participate
9. Acknowledgment
10. Funding
11. Conflict of interest
12. References

1. Abstract

Introduction: 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 associations with PD, but whether they associate with the clinical features of PD have not been fully addressed yet. Methods: Clinical data of 365 patients with PD who enrolled in Parkinson’s Progression Markers Initiative (PPMI) study were obtained. Patients with rapid motor progression were determined through clinical assessments over five years follow-up. In addition, genetic information of 44 targeted SNPs was extracted from the genetic database of NeuroX for the same cohort. Logistic regression was used to analyze the genetic associations with rapid motor progression of PD. Results: Among 365 patients with PD, there are more male (66%) than female (34%). Seven SNPs (rs6808178, rs115185635, rs12497850, rs34311866, rs3793947, rs11060180, rs9568188) were associated with faster motor progression (p < 0.05), and only rs6808178 passed multiple comparison correction (p < 0.0011). In addition, the extended 44 SNPs with autonomic dysfunction reach a fair prediction of AUC at 0.821. Conclusion: Genetics and autonomic function factors contribute to the motor progression at the clinical initiation of PD.
2. Introduction

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 autonomic dysfunction, hyposmia, rapid eye movement sleep behavior disorder (RBD), cognitive impairment and other clinical features [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], although almost every patient with PD has non-motor symptoms ranging from 8 to 12 different symptoms, which is now considered as another crucial factor for driving quality of life of patients in PD [6]. Identifying factors influencing the progression of motor deterioration of PD is particularly important for the predicting the prognosis of patients with PD and discovery of novel therapies for PD. Genetic contributions to PD have been well acknowledged [2, 7–9]. 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, respectively [10, 11]. These 90 variants explained 16–36% of the heritable risk of PD depending on prevalence [11]. Recent studies showed that patients carrying a certain gene mutation have distinct clinical presentations and disease progression from sporadic PD [12, 13]. PD susceptibility genes have been associated with PD clinical features, such as onset age, subtype, and progression of PD [14–23]. However, these studies were either based on cross-sectional PD cohorts or with limited genetic variants involved. Although recent genome-wide association study (GWAS) revealed genetic contributions to PD motor and cognitive progression in longitudinal PD cohorts [24], the input of multiple clinical quantitative measures and the algorithm to reflect the clinical progression of PD are also challenges to truly reveal genetic factors association with the progression of PD. This study aims based on recent GWAS identified PD risk SNPs to investigate genetic and clinical associations with rapid motor progression in a longitudinal PD cohort with five-year follow up [10, 11].

3. Material and methods

3.1 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) [25]. 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). Data was downloaded from PPMI in September 2020. Participants with prodromal status, scan without dopaminergic deficit (SWEDD), incomplete clinical baseline data, incomplete longitudinal movement assessment, non-Caucasian and outliers are excluded. Thus, a total 365 patients with explicit clinical diagnosis of PD and dopamine transporter deficit on 123I ioflupane imaging (DaTscan) were selected in this study (please see Supplementary Fig. 1 for case selection flow diagram). All patients had been clinically assessed by Unified Parkinson’s Disease Rating Scale (UPDRS), including UPDRS-III for motor function (post dose) at baseline and annual examination up to five years, Montreal Cognitive Assessment (MoCA) for cognitive function, and Rapid Eye Movement Behavior Disorder Questionnaire (RBDQ), the University of Pennsylvania Smell Identification test (UPSTT), 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.

3.2 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 [26–28].

3.3 Five-year follow-up evaluation

Determine PD subgroup with rapid motor progression: The motor part of MDS-UPDRS (UPDRS-III) is currently the most authoritative scale for evaluating PD motor symptoms [29]. A number of studies have shown that the progression of motor deterioration of PD is a non-linear pattern in the disease course, although it does not reach the plateau phase during the initial five years after clinical motor symptoms become present [30]. While PD cases selected in this study were within their initial five years of the disease course. Thus, we identified rapid motor progressors if they had more than 22-point increase (15% of the cohort) in the UPDRS-III score from baseline to the follow-up at year 5 [18, 29, 31]. In comparison, a 16-point change (25% of the cohort) was also used to define the rapid motor progressors.

3.4 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 popula-
Fig. 1. ROC curve analysis showing genetic and autonomic dysfunction factors for predicting rapid motor progression in PD. The area under curve (AUC) of rs6808178 is 0.614, which is higher than autonomic dysfunction alone (AUC = 0.550). Seven related SNPs reach a higher AUC at 0.728, but less than 44 SNPs together (AUC = 0.813) for predicting rapid motor progression. The optimal AUC is combining 44 SNPs information with autonomic dysfunction together (AUC = 0.821). Abbreviations: ROC, receiver operating characteristic curve; AUC, area under curve; SNP, single nucleotide polymorphism.

...tion studies of risk factors and investigations of familial disease with known mutations [32, 33]. All samples and genotypes underwent stringent quality controls (QC). Genetic data were cleaned using PLINK (version 1.9 beta, Christopher Chang, USA). The threshold call rate for sample inclusion was 95%. QC of sample handling was determined by comparing the subject’s sex reported by Coriell Institute for Medical Research with the genotypic sex estimated from X chromosome heterogeneity. X chromosome heterogeneity calculations were based on common SNPs from the International HapMap Project that had genotypes with missingness <5% and hardy-Weinberg equilibrium (HWE) p values > $1 \times 10^{-6}$. Samples containing discrepancies between reported sex and genotypic estimated sex were excluded. Eventually the genotype information of 44 SNPs was extracted and no further GWAS PD significant SNPs ($p \leq 5 \times 10^{-8}$) were found in NeuroX or excluded by filtering (Supplementary Table 1).

3.5 Statistical analysis

SPSS Statistics (version 26, IBM, USA), MedCalc (version 20.0.3, MedCalc Software Ltd, Belgium), and CGTA (version 1.93, Yang Lab, China) were used for this study. Principal component analysis (PCA) was performed to exclude outliers. Chi-Square test was used for comparative analysis between groups. To assess genetic associations with rapid motor progression, logistic regression and Cox proportional hazards regression models were used to estimate odds ratios (OR) and hazard ratios (HR) with 95% CI based on every-year visit for 5 years, p-values of each genetic variable, and the predictive values of total 44 SNPs with each phenotype were calculated. 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, gender, family history, and age at onset as covariates. Receiver operating curve (ROC) analysis was performed to evaluate the predcitive values of the significant and total 44 SNPs for the rapid motor deterioration, and area under curves (AUC) were used to evaluate the predictive models. Youden index was used to find the best cut-off point and its sensitivity and specificity. Bonferroni’s method was applied for multiple correction ($p < 0.0011$).
Table 1. Demographic and clinical characteristics of the PD cohort.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Median (IQR)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of people, No./total No. (%)</td>
<td>241/365 (66%)</td>
<td>124/365 (34%)</td>
</tr>
<tr>
<td>Age at diagnosis, median (IQR)</td>
<td>62 (55 to 69)</td>
<td>60 (53 to 67)</td>
</tr>
<tr>
<td>Age at baseline examination, median (IQR)</td>
<td>63 (56 to 69)</td>
<td>60 (53 to 68)</td>
</tr>
<tr>
<td>Years of education, median (IQR)</td>
<td>16 (14 to 18)</td>
<td>16 (13 to 18)</td>
</tr>
<tr>
<td>UPDRS-III motor score at baseline, median (IQR)</td>
<td>20 (14 to 26)</td>
<td>20 (14 to 26)</td>
</tr>
<tr>
<td>UPDRS-III motor score change per 5 years, median (IQR)</td>
<td>9 (2 to 18)</td>
<td>8 (1 to 17)</td>
</tr>
<tr>
<td>Rapid motor progression (increasing scores ≥ 22 points), No./total No. (%)</td>
<td>44/241 (18%)</td>
<td>24/128 (18%)</td>
</tr>
<tr>
<td>UPDRS-III motor score change per 5 years among fast motor progression patients, median (IQR)</td>
<td>26 (23 to 33)</td>
<td>27 (23 to 33)</td>
</tr>
<tr>
<td>MoCA cognition score at baseline, median (IQR)</td>
<td>27 (24 to 29)</td>
<td>28 (26 to 29)</td>
</tr>
<tr>
<td>Scales for SCOPA-AUT, median (IQR)</td>
<td>12 (7 to 18)</td>
<td>11 (7 to 15)</td>
</tr>
<tr>
<td>Geriatric Depression Scale (Short version), median (IQR)</td>
<td>5 (5 to 6)</td>
<td>5 (5 to 6)</td>
</tr>
<tr>
<td>Rapid Eye Movement Behavior Disorder Questionnaire, median (IQR)</td>
<td>4 (2 to 8)</td>
<td>4 (3 to 7)</td>
</tr>
<tr>
<td>UPSIT, Hyposmia No./total No. (%)</td>
<td>227 (94%)</td>
<td>112 (90%)</td>
</tr>
</tbody>
</table>

*Chi-Square test was used. Abbreviations: UPDRS-III, Unified Parkinson’s Disease Rating Scale part III; MoCA, Montreal Cognitive Assessment; SCOPA-AUT, Scales for Outcomes in Parkinson’s disease - Autonomic; UPSIT, the University of Pennsylvania Smell Identification test; IQR, interquartile range; N.S., not significant.

Table 2. Non-motor symptoms at baseline associations with rapid motor progression of PD.

<table>
<thead>
<tr>
<th>Non-motor symptoms</th>
<th>Beta</th>
<th>p value</th>
<th>OR (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic dysfunction</td>
<td>0.041</td>
<td>0.039</td>
<td>1.042 (1.002–1.084)</td>
<td>1.024 (0.936–1.120)</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>–0.057</td>
<td>0.255</td>
<td>0.945 (0.857–1.042)</td>
<td>0.687 (0.417–1.132)</td>
</tr>
<tr>
<td>RBD</td>
<td>–0.094</td>
<td>0.089</td>
<td>0.910 (0.816–1.014)</td>
<td>0.939 (0.574–1.536)</td>
</tr>
<tr>
<td>Hyposmia</td>
<td>–0.447</td>
<td>0.402</td>
<td>0.639 (0.224–1.822)</td>
<td>0.944 (0.779–1.145)</td>
</tr>
<tr>
<td>Depressive</td>
<td>0.009</td>
<td>0.919</td>
<td>1.009 (0.843–1.209)</td>
<td>1.042 (0.945–1.148)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; RR, relative risk.

3.6 Bioinformatics analysis

STRING (version 11, https://cn.string-db.org/) 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 [34].

4. Results

4.1 Clinical observations

**Baseline data observation:** Of the 365 patients from PPMI database, 241 were men (66.0%) and the ratio of male vs female was 1.95. The median age at diagnosis was 61 years, 339 patients (92.8%) had hyposmia, detected by UPSIT test. As for other non-motor tests, median scores of MoCA, SCOPA-AUT, GDS (Short version), RBDQ were 27, 12, 5, and 4, respectively (Table 1). There were no significant gender differences in age of onset, cognitive impairment, RBD symptoms, hyposmia symptoms, autonomic dysfunction, and depressive symptoms of this PD cohort (p > 0.05).

**Longitudinal observation:** The median UPDRS-III score change was 8 by the fifth year follow up in this cohort. 68 patients had rapid motor progression with median UPDRS-III score change of 26 by the 12th visit at the 5th year. Only baseline autonomic dysfunction was associated with rapid motor progression (OR = 1.042, p = 0.039), while other non-motor symptoms at baseline were not (Table 2).

4.2 Genetic associations with longitudinal motor progression

Seven SNPs (rs6808178, rs115185635, rs12497850, rs34311866, rs3793947, rs11060180, rs9568188) were associated with faster motor progression with p < 0.05, and only rs6808178 (located in LINCO00693, p = 0.0007) (Table 3) was significantly associated with faster motor progression after correction for multiple testing (p < 0.0011). Cox proportional hazards regression model also showed that LINCO00693 rs6808178 was associated with faster motor progression (p = 0.0004) after correction for multiple testing (p < 0.0011). When 25% percentile of the cohort were defined as fast motor progressors, there are four associated SNPs (rs6808178, rs12497850, rs11060180, rs9568188) (p < 0.05, Supplementary Table 2), but no SNP was associated with fast motor progression after multiple testing correction (p < 0.0011).
than 5 molecular interactions in the network (Fig. 4.3 ROC curve analysis

*LINC00693* rs6808178 gives rise to a model of 0.614 AUC for predicting rapid motor progressors, which is higher than the non-genetic factor of autonomic dysfunction (AUC = 0.550) (Fig. 1). Seven related SNPs reach a higher AUC at 0.728. All 44 SNPs together reach a fair prediction of rapid motor progressors (AUC = 0.813), while 44 PD risk SNPs with autonomic dysfunction together can slightly improve the discriminative value for rapid motor progression (AUC = 0.821). The optimal sensitivity and specificity of this predictive model is 83.82% and 71.38% respectively, and the positive predictive value (PPV) and negative predictive value (NPV) are 40.1% and 95.1% (Table 4).

4.4 Analysis of molecular pathways related to rapid motor decline

*LINC00693* is a non-coding RNA gene. Thus, we analyzed other 6 genes that had probable associations with motor progression. STRING analysis showed the number of edges was 71 vs the expected of 9, average node degree was 3.38, and there was significant more interactions in this protein network (p < 1 × 10−6). Regarding to the genes related to rapid motor progression, *OGFOD2* and *CAB39L* are independent risk factors, and *TMEM175*, *DLG2*, *IP6K2*, *CHMP2B* may jointly activate multiple molecular pathways. Importantly, *TMEM175* encodes a protein with more than 5 molecular interactions in the network (Fig. 2).

5. Discussion

In this study, we found there were more male than female affected with PD, but not related to other clinical features (Table 1). In contrast to other studies [35, 36], age at onset did not associate with PD motor progression via statistical analysis of either ANOVA taking onset age as continuous variables and binomial the motor progression as fast and slow, or using Chi Square after binomial onset age outcomes to early and late onset, which is possibly due to similar factors contributing to the fast motor progression in either early or late onset of PD.

We found that among the non-motor symptoms, early and severe autonomic dysfunction was associated with rapid motor progression, which is consistent with previous research [37]. AUC did not reach a higher level when considering all NMS in this study, which indicates that autonomic dysfunction is the major predictive factor of motor progression among non-motor symptoms in this study. Fast motor deterioration may reflect rapid neuronal loss within the substantia nigra of PD, while autonomic dysfunction is considered due to enervation of the cranial vagus nerve, which is composed of the largest part of the parasympathetic nervous system. The dorsal motor nucleus of the vagus nerve located in the medulla oblongata is the earliest affected site by α-synuclein related pathologies within the brain in idiopathic PD, and then the α-synuclein related pathologies take upwards advancement pattern affecting pontine tegmentum and the substantia nigra of midbrain [38]. The association between early autonomic dysfunction and rapid motor progression of PD is coherent with the anatomical and pathological connections of PD.

Our results showed that multigenetic network with autonomic dysfunction together provided the optimal predictive model for fast motor progression in PD (AUC = 0.821, Figs. 1, 2, Table 4). We identified seven genetic

### Table 3. Genetic associations with rapid motor deterioration of PD.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Related Gene</th>
<th>Beta</th>
<th>p value</th>
<th>OR (95% CI)</th>
<th>RR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs6808178</td>
<td>LINC00693</td>
<td>−0.77</td>
<td>0.0007*</td>
<td>0.463 (0.296–0.724)</td>
<td>0.827 (0.739–0.926)</td>
<td>0.501 (0.341–0.736)</td>
</tr>
<tr>
<td>rs11518635</td>
<td>CHMP2B</td>
<td>−2.175</td>
<td>0.039</td>
<td>0.114 (0.014–0.899)</td>
<td>0.834 (0.760–0.916)</td>
<td>0.199 (0.025–1.576)</td>
</tr>
<tr>
<td>rs12407850</td>
<td>IP6K2</td>
<td>−0.454</td>
<td>0.045</td>
<td>0.635 (0.408–0.989)</td>
<td>0.898 (0.809–0.988)</td>
<td>0.823 (0.542–1.259)</td>
</tr>
<tr>
<td>rs34311866</td>
<td>TMEM175</td>
<td>−0.612</td>
<td>0.022</td>
<td>0.542 (0.321–0.917)</td>
<td>0.906 (0.824–0.997)</td>
<td>0.730 (0.423–1.261)</td>
</tr>
<tr>
<td>rs3793947</td>
<td>DLG2</td>
<td>0.492</td>
<td>0.016</td>
<td>1.635 (1.096–2.438)</td>
<td>1.069 (0.970–1.178)</td>
<td>1.392 (0.942–2.085)</td>
</tr>
<tr>
<td>rs11060180</td>
<td>OGFOD2</td>
<td>−0.476</td>
<td>0.022</td>
<td>0.621 (0.414–0.933)</td>
<td>0.901 (0.801–1.012)</td>
<td>0.685 (0.460–1.020)</td>
</tr>
<tr>
<td>rs968188</td>
<td>CAB39L</td>
<td>−0.551</td>
<td>0.030</td>
<td>0.576 (0.350–0.948)</td>
<td>0.909 (0.826–1.001)</td>
<td>0.484 (0.284–0.825)</td>
</tr>
</tbody>
</table>

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; RR, relative risk; HR, hazard ratios. * p < 0.0011.

### Table 4. Predictivities of genetic and autonomic dysfunction factors for rapid motor deterioration in PD.

<table>
<thead>
<tr>
<th>Predictive factors</th>
<th>AUC</th>
<th>Youden’s index</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PLR</th>
<th>NLR</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic dysfunction only</td>
<td>0.550</td>
<td>0.106</td>
<td>33.82</td>
<td>76.77</td>
<td>1.46</td>
<td>0.86</td>
<td>25.0</td>
<td>83.5</td>
</tr>
<tr>
<td>rs6808178</td>
<td>0.614</td>
<td>0.238</td>
<td>58.82</td>
<td>64.98</td>
<td>1.68</td>
<td>0.63</td>
<td>27.8</td>
<td>87.3</td>
</tr>
<tr>
<td>Related SNPs*</td>
<td>0.728</td>
<td>0.372</td>
<td>85.29</td>
<td>51.85</td>
<td>1.77</td>
<td>0.28</td>
<td>28.9</td>
<td>93.9</td>
</tr>
<tr>
<td>44 SNPs</td>
<td>0.813</td>
<td>0.551</td>
<td>82.35</td>
<td>72.73</td>
<td>3.02</td>
<td>0.24</td>
<td>40.9</td>
<td>94.7</td>
</tr>
<tr>
<td>All factors*</td>
<td>0.821</td>
<td>0.552</td>
<td>83.82</td>
<td>71.38</td>
<td>2.93</td>
<td>0.23</td>
<td>40.1</td>
<td>95.1</td>
</tr>
</tbody>
</table>

Abbreviations: SNP, single nucleotide polymorphism; AUC, area under curve; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

- *Related SNPs refer to seven SNPs associated with rapid motor progression (p < 0.05); b all factors include 44 SNPs and autonomic dysfunction. Abbreviations: SNP, single nucleotide polymorphism; AUC, area under curve; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.
variants (LINC00693 rs6808178, CHMP2B rs115185635, IP6K2 rs12497850, TMEM175 rs34311866, OGFOD2 rs11060180, CAB39L rs9568188, and DLG2 rs3793947 were associated with rapid motor deterioration in PD (Table 3), and only LINC00693 rs6808178 passed multiple testing correction. Long non-coding RNA (lncRNA) has been shown function in regulating gene expression and cellular homeostasis [39]. Alterations in lncRNAs expression levels have been shown in brain tissues affected by PD compared to controls [40, 41]. Unfortunately, previous studies did not examine LINC00693. A recent study using machine learning model found that rs6808178 was one of two key variants among 90 SNPs for developing PD using the same PPMI cohort [42], which suggest LINC00693 is important in the onset and progression of PD.

For the other six probable fast motor progression associated genes, allele-specific expression of TMEM175 is identified in human brain [43], and TMEM175 deficiency could lead to lysosomal and mitochondrial dysfunction, as well as α-synuclein deposition [44]. In the PD risk protein coding genetic interaction network (Fig. 2), TMEM175 is a hub protein with connection of SNCA, GBA, LRRK2, ACMSD, GAK, MCCC1 and FAM47E, while SNCA, GBA and LRRK2 have been shown associated with rapid motor progression [14, 18, 45, 46]. CHMP2B is located in the Lewy bodies of human brainstem [47, 48], and mutations of CHMP2B may contribute to endosomal and autophagic pathway in α-synuclein deposition of PD [48]. IP6K2 is related to cell apoptosis, and its protein is highly expressed in granule cells of the cerebellum and related to impairment of locomotor function [49]. Mutations in DLG2 lead to reductions in excitatory synaptic input of dorsal striatum in mice [50]. The molecular mechanisms contributing to PD of DLG2 need further investigation, so are the same for OGFOD2 and CAB39L.
Table 5. Summary of literatures demonstrating genetic factors predicting fast motor progression in PD.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Study cohort (N, Ethnicity)</th>
<th>Study design</th>
<th>Study findings</th>
<th>Genetic Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Study method</td>
<td>Genetic factors Fast motor progressors defined</td>
<td>Clinical phenotype findings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fast motor progressors (%)</td>
<td>Clinical predictors</td>
</tr>
<tr>
<td>Huang et al., 2011, Journal of Parkinson’s Disease [17]</td>
<td>NeuRA (123, Caucasian)</td>
<td>Cross-sectional</td>
<td>SNCA, MAPT If change in UPDRS-III points ≥10 per annum</td>
<td>15%–30% (if the duration less than 5 years)</td>
</tr>
<tr>
<td>Wang et al., 2016, Parkinsonism and Related Disorders [18]</td>
<td>Ruijin (296, Chinese)</td>
<td>Cross-sectional</td>
<td>SNCA, MAPT If change in UPDRS-III ≥36 points and/or H&amp;Y scale ≥3 over 4 years</td>
<td>15%</td>
</tr>
<tr>
<td>Paul et al., 2018, JAMA Neurology [31]</td>
<td>PEG (285, Caucasian)</td>
<td>Longitudinal</td>
<td>23 risk SNPs If change in UPDRS-III ≥20 points over 4 years</td>
<td>22.40%</td>
</tr>
<tr>
<td>This Study</td>
<td>PPMI (365, Caucasian)</td>
<td>Longitudinal</td>
<td>44 risk SNPs If change in UPDRS-III ≥22 points over 5 years</td>
<td>15%</td>
</tr>
</tbody>
</table>

Abbreviations: SNP, single nucleotide polymorphism; UPDRS, Unified Parkinson’s Disease Rating Scale; H&Y, Hoehn & Yahr; NeuRA, Neuroscience Research Australia; PEG, Parkinson Environment and Gene; PPMI, Parkinson’s Progression Markers Initiative.
We took the rapidity of motor progression of PD, which is the main concern of PD patients, as our study question, rather than the disease progression profile, which incorporates other non-motor symptoms, such as pain, anxiety, fatigue and so on, to ensure the stability of the predictive model. A variety of research approaches have been adapted in investigating genetic associations with motor progression of PD in the literature, such as dichotomizing the cohort into fast motor progressors or not (Table 5), or differences in actual motor UPDRS score over time, etc. (Supplementary Table 3). SNCA, MAPT, LRRK2, GBA, PARK16, ATP8B2, SLC44A1 and polygenic risk score have been shown associations with the progression of PD [14, 17, 18, 22–24, 31, 46, 51]. The definition of fast motor progression in different studies results in different proportion of fast motor progression ranging from 15% to 30% (Table 5) [17, 18, 31]. The rapid motor progression defined in this study has relatively smaller UPDRS-III score change, which is possibly because that the patients in PPMI are at the early stage of PD, and UPDRS-III is evaluated at post dose. Huang et al. [17] and Wang et al. [18] conducted cross-sectional studies and revealed motor progression associated with SNCA & MAPT and SNCA respectively. Besides, Paul et al. [31] elucidated that PRS is significantly associated with the progression of PD, and thus it is reasonable of taking all 44 SNPs as a whole to predict motor progression in this study. Oosterveld et al., Deng et al. and Davis et al. [46, 51] carried out linear mixed model to compare motor progression between carriers and non-carriers (Supplementary Table 3). Tan et al. [22] based on mixed-effects regression model using PCA and testified the relevance of PCA scores with 90 genetic factors. Iwaki et al. [22, 23] carried out two meta-analyses with large samples. However, they aimed at investigating genetic associations with motor severity rather than motor progression. Our study showed that genetic and clinical features together demonstrated more predictivity towards fast motor progression, while others only took genetic factors into account (Table 5 and Supplementary Table 3).

This study also has its limitations: First, the NeuroX genetic data did not include all 90 SNPs recently summarized [11]. Consequently, we could not assess the associations of missing SNPs, leading to not ideal AUC value for prediction of rapid motor progression. Second, 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.

6. Conclusions

Our study indicated the rapidity of motor progression of PD could be attributed to clinical and genetical factors. Additional genetic information is required to enhance the value of genetic predicative model. Furthermore, the prediction of genetic associated molecular pathways & network for rapid motor progression in PD identified in this study warrant validation in other PD cohorts.

7. Author contributions

LC did data extraction from the PPMI database, statistics analysis and drafted the manuscript. YJ provided instructions of statistical and bioinformatic analysis of the study. YP interpreted clinical data and revised the manuscript. YH designed the project and critically revised the manuscript.

8. Ethics approval and consent to participate

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).

9. Acknowledgment

Data used in the preparation of this article were obtained from the Parkinson’s Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. PPMI — a public-private partnership — is funded by the Michael J. Fox Foundation for Parkinson’s Research and funding partners, including Abbvie, Allergan, Amathus Therapeutics, Avid Radiopharmaceuticals, Biogen, Biorelegend, Bristol-Myers Squibb, Celgene, Covance, GE Healthcare, Genentech, Golub Capital, Handl Therapeutics, Insitro, Janssen Neuroscience, Lilly, Lundbeck, Merck, Meso Scale Discovery, Neurocrine, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi Genzyme, Servier, Takeda, Teva, Ucb, Verily and Voyager Therapeutics.

10. Funding

The study was funded by National Natural Science Foundation of China (NSFC, 82071417, YH).

11. Conflict of interest

The authors declare no conflict of interest.

12. References

Movement Disorders. 2019; 34: 1839–1850.


Boros FA, Maszlag-Török R, Vécsesi L, Klivényi P. Increased level of NEAT1 long non-coding RNA is detectable in peripheral blood cells of patients with Parkinson’s disease. Brain Research. 2020; 1730: 146672.


Supplementary material: Supplementary material associated with this article can be found, in the online version, at https://www.imrpress.com/journal/FBL/26/12/10.52586/5044.

Abbreviations: ACMSD, aminocarboxymuconate semialdehyde decarboxylase; ATP8B2, ATPase phospholipid transporting 8B2; CAB39L, calcium binding protein 39 like; CHMP2B, charged multivesicular body protein 2B; DLG2, discs large MAGUK scaffold protein 2; FAM47E, family with sequence similarity 47 member E; GAK, cyclin G associated kinase; GBA, glucosylceramidase beta; IP6K2, inositol hexakisphosphate kinase 2; LINCO0693, long intergenic non-protein coding RNA 693; LRRK2, leucine rich repeat kinase 2; MAPT, microtubule associated protein tau; MCCC1, methylcrotonyl-coA carboxylase subunit 1; OGFOD2, 2-oxoglutarate and iron dependent oxygenase domain containing 2; SLC44A1, solute carrier family 44 member 1; SNCA, synuclein alpha.

Keywords: Parkinson’s disease; Rapid motor progression; Genes; Single nucleotide polymorphisms; Longitudinal study

Send correspondence to: Yue Huang, China National Clinical Research Centre for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, 100070 Beijing, China, Neurology Department, Beijing Tiantan Hospital, Capital Medical University, 100070 Beijing, China, Department of Pharmacology, School of Medical Sciences, Faculty of Medicine & Health, UNSW Sydney, 2033 Sydney, Australia, E-mail: yue.huang@ncrcnd.org.cn