Genomic Analysis Identifies New Loci Associated With Motor Complications in Parkinson’s Disease

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Background: Parkinson’s disease (PD) is a common neurodegenerative disorder, characterized by a clinical symptomatology involving both motor and non-motor symptoms. Motor complications associated with long-term dopaminergic treatment include motor fluctuations and levodopa-induced dyskinesia (LID), which may have a major impact on the quality of life. The clinical features and onset time of motor complications in the disease course are heterogeneous, and the etiology remains unknown.

Objective: We aimed to identify genomic variants associated with the development of motor fluctuations and LID at 5 years after the onset of PD.

Methods: Genomic data were obtained using Affymetrix Axiom KORV1.1 array, including an imputation genome-wide association study (GWAS) grid and other GWAS loci; functional variants of the non-synonymous exome; pharmacogenetic variants; variants in genes involved in absorption, distribution, metabolism, and excretion of drugs; and expression quantitative trait loci in 741 patients with PD.

Results: FAM129B single-nucleotide polymorphism (SNP) rs10760490 was nominally associated with the occurrence of motor fluctuations at 5 years after the onset of PD [odds ratio (OR) = 2.9, 95% confidence interval (CI) = 1.8–4.8, P = 6.5 × 10⁻⁶]. GALNT14 SNP rs144125291 was significantly associated with the occurrence of LID (OR = 5.5, 95% CI = 2.9–10.3, P = 7.88 × 10⁻⁹) and was still significant after Bonferroni correction. Several other genetic variants were associated with the occurrence of motor fluctuations or LID, but the associations were not significant after Bonferroni correction.

Conclusion: This study identified new loci associated with the occurrence of motor fluctuations and LID at 5 years after the onset of PD. However, further studies are needed to confirm our findings.

Keywords: genome-wide association study, genomic variants, Parkinson’s disease, motor fluctuations, levodopa-induced dyskinesia
INTRODUCTION

Parkinson’s disease (PD) is a chronic, progressive neurodegenerative disorder characterized by a heterogeneous clinical symptomatology involving both motor and nonmotor symptoms (1–3). The pathological hallmarks of PD are abnormal accumulation of alpha-synuclein (α-syn) aggregates, Lewy bodies, and Lewy neurites (4, 5). The α-synucleinopathy in PD involves not only dopaminergic neurons in the substantia nigra pars compacta of the midbrain but also other vulnerable neurotransmitter systems in the central nervous system (6, 7).

Levodopa is the most effective and potent medication for the treatment of motor symptoms of PD (8), and early treatment with levodopa increases life expectancy (9). However, long-term treatment of patients with PD with levodopa can result in the occurrence of motor fluctuations and dyskinesias. These late motor complications can become major causes of disability and reduce the quality of life of patients (10). To date, the pathophysiologic mechanisms underlying motor fluctuations and levodopa-induced dyskinesia (LID) in patients with PD remain unclear.

Over the last two decades, rare variants of more than 20 genes have been reported to cause genetic PD (11). The common genetic risk factors for sporadic PD have been identified by genome-wide association studies (GWAS). To date, 90 independent genetic variants have been identified as risk factors for sporadic PD (12). Although previous GWAS and other genetic studies have indicated the importance of genetic contribution to the development of PD, the contribution of genetic factors to specific phenotypes of PD has not been well-studied. Identification of genetic risk factors for the major clinical phenotypes of PD may provide important insights into the underlying molecular mechanisms and valuable information for potential adjustments to overcome genetic heterogeneity in clinical trials. This GWAS aimed to identify the genetic variants associated with the occurrence of motor fluctuations and LID in patients with sporadic PD.

MATERIALS AND METHODS

Patients

We included 741 patients who were diagnosed with PD (Supplementary Figure 1). Experienced movement disorder specialists (SJC, HSR, MJK, JK, and YJK) made the diagnosis of PD using the clinical diagnostic criteria of the United Kingdom Parkinson’s Disease Society Brain Bank (13). All patients were enrolled from the clinical practice of the Department of Neurology of the Asan Medical Center, Seoul, South Korea, between January 1, 2011 and April 30, 2016. All patients were born and resided in South Korea. All patients were unrelated and ethnic Koreans without any foreign ancestry. The Institutional Review Board (IRB) of Asan Medical Center approved the study, and all patients provided an informed consent in accordance with the IRB regulations.

Clinical Assessment

Motor fluctuations were defined as alternating between periods of good motor symptom control (on-time) and periods of reduced motor symptom control (off-time), which were dependent on the scheduled intake time of levodopa and other dopaminergic medications (14). The time between the onset of PD motor symptoms and the occurrence of motor fluctuations was assessed in each patient.

LID was defined as involuntary choreiform or dystonic body movements, which occur most frequently when levodopa concentrations are at its highest (peak-dose dyskinesia) or, less commonly, at the beginning or end of levodopa administration, or both (diphasic dyskinesia) (14). The time between the onset of PD motor symptoms and the occurrence of LID was assessed in each patient. PD onset was defined as the onset of first motor symptoms in patients with PD.

The presence of motor fluctuations or LID was determined using the clinical history and Unified Parkinson’s Disease Rating Scale (UPDRS) part IV. Dystonia that occurred in the morning before taking a medication was not considered as LID (15).

Genomic Analysis

Genotype data were obtained using the Korean Chip (K-CHIP), obtained from the K-CHIP consortium. K-CHIP was designed by the Center for Genome Science, Korea National Institute

### TABLE 1 | Demographic and clinical characteristics of patients.

| Characteristic                                                                 | Patients |
|-------------------------------------------------------------------------------|----------|
| Total sample, n                                                               | 741      |
| Men, n (%)                                                                    | 325 (43.9)|
| Women, n (%)                                                                  | 416 (56.1)|
| Age at onset of PD, years, mean ± SD (range)                                  | 57.1 ± 0.1 (28–87)|
| Disease duration, years, mean ± SD (range)                                   | 10.8 ± 4.5 (5–31)|
| Patients with motor fluctuations, n (%)                                        | 554 (74.8)|
| Duration between PD onset and development of motor fluctuations, years, mean ± SD (range) | 6.9 ± 3.4 (1–24)|
| Patients with levodopa-induced dyskinesia, n (%)                             | 496 (66.8)|
| Duration between PD onset and development of levodopa-induced dyskinesia, years, mean ± SD (range) | 7.2 ± 3.4 (1–21)|
| Patients with motor fluctuations at 5 years after PD onset, n (%)            | 219 (29.6)|
| Duration between PD onset and development of motor fluctuations, years, mean ± SD (range) | 3.9 ± 1.1 (1–5)|
| Patients with levodopa-induced dyskinesia at 5 years after PD onset, n (%)   | 172 (23.2)|
| Duration between PD onset and development of levodopa-induced dyskinesia, years, mean ± SD (range) | 3.9 ± 1.1 (1–5)|
| MMSE score (range)                                                            | 26.1 ± 3.2 (10–30)|
| MoCA score (range)                                                            | 22.6 ± 5.6 (3–30)|

PD, Parkinson’s disease; SD, standard deviation; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.
of Health, Korea (4845-301, 3000-3031) (www.cdc.go.kr). K-CHIP uses Affymetrix Axiom Customized Biobank Genotyping Arrays (Affymetrix, Santa Clara, CA, USA) and contains 827,783 variants. K-CHIP consists of an imputation GWAS grid [505,000 Asian-based grid with minor allele frequency (MAF) >5% in Asians]; exome contents [84,000 Korean-based grid with MAF >5%, in Koreans; 149,000 coding single-nucleotide polymorphisms (cSNPs); and insertions and deletions on the basis of data from 2000 whole exome sequences and 400 whole genome sequences with MAF > 0.1%]; new exome/loss of function contents (44,000 variants); expression quantitative trait loci (17,000 variants); absorption, distribution, metabolism, and excretion genes; and other miscellaneous variants.

Sample Quality Controls
The primary sample quality control was as follows: samples with low call rate (<0.95%) were excluded from the analysis because of the possibility of low DNA quality or experimental error; high heterozygosity was excluded from the analysis because of low DNA quality or possible contamination of samples. The entire sample distribution was checked, and low-quality samples were excluded if they deviated significantly from the entire sample distribution. SNP pruning was also performed. Because cryptic first-degree relative and multidimensional scaling (MDS) analyses are very time consuming when using whole data, only representative SNP information based on linkage disequilibrium were selected from the data. Due to the possibility of population stratification, samples that deviated from the whole sample were excluded from the analysis by assessing the MDS. If there were more than a certain number of SNPs with only one sample, the possibility of errors due to DNA quality and technical artifacts was excluded.

Secondary sample quality control consisted of genotype calling, excluding samples deemed to be of low quality based on the primary sample quality control criteria and sex-inconsistent samples. Samples that did not satisfy the quality control criteria after a repeat sample quality control were excluded. SNP data were excluded from the cryptic first-degree relative analysis.
because statistical analysis assumes the independence for each sample in most cases.

**SNP Quality Controls**

An SNPPolisher analysis was performed to exclude low-quality SNPs. SNPs with low call rates were excluded when the call rate was <95% because errors in the calling process can occur due to probe design and clustering analysis problems. If the Hardy–Weinberg equilibrium (HWE) test P-value of a specific SNP is low, it indicates a probable error in the genotype clustering process; therefore, the HWE P < 10^-6. If the frequency of a genetic variation is extremely different from that in Korean and Asian populations, there may be a genotype clustering error. Therefore, we excluded cases where the difference in MAF was >0.2. Both cases and controls were excluded if the MAF was <1%.

**Statistical Analysis**

The associations of each genetic variant with the occurrence of motor fluctuations and LID were investigated using multiple logistic regression models. We used the Cochran–Armitage trend test and the Jonckheere–Terpstra test, and adjusted all analyses by sex and age at onset of PD. For each genetic variant, we calculated the odds ratio (OR), 95% confidence interval (CI), and two-tailed P-value. For sensitivity analyses, similar analyses were performed for patients aged ≥50 years at onset of PD to further adjust for the effects of age at onset of PD on the occurrence of motor fluctuations and LID. The P-values from the primary analyses were assessed for significance using the Bonferroni correction for multiple comparisons. Clustering quality control was performed by visual inspection of analytic data of SNPs with a P < 0.0001. Markers that did not clearly separate between different genotypes and were not closely located in the same genotype were excluded (Supplementary Figure 2). Manhattan plots and quantile–quantile plots were constructed for P-values for all genotyped variants that passed quality controls.

The statistical analysis was performed using the PLINK program (version 1.90, NIH-NIDDK Laboratory of Biological Modeling, Bethesda, MD, USA), Haploview (version 4.2, Daly Lab at the Broad Institute, Cambridge, MA, USA), LocusZoom (version 1.4, University of Michigan, Department of Biostatistics, Center for Statistical Genetics, Ann Arbor, MI, USA), and R (version 3.1.2, Free Software Foundation, Inc., Boston, MA, USA).

**RESULTS**

**Patients**

Clinical and genotyping data were obtained from 741 patients with PD who were followed for at least 5 years after the onset of PD. The demographic and clinical features of study patients are summarized in Table 1. The study group consisted of 325 men

| Gene   | SNP     | Chr | Position | Region relative to gene | Allele (minor/major) | Minor allele frequency (case/control) | OR (95% CI) | P-value |
|--------|---------|-----|----------|-------------------------|----------------------|--------------------------------------|-------------|---------|
| FAM129B| rs10760490 | 9   | 130335418 | Intron A/G | 0.08/0.03 | 2.93 (1.80, 4.77) | 6.50E−06 |
| SNX29  | rs150380018 | 16  | 12569788 | Intron G/T | 0.04/0.01 | 6.53 (2.54, 16.79) | 8.35E−06 |
| C5orf52 | rs10051838 | 5   | 157102159 | Missense A/G | 0.17/0.09 | 2.09 (1.50, 2.91) | 9.07E−06 |
| STK10  | rs77462941 | 5   | 17953147 | Intron C/T | 0.13/0.23 | 0.50 (0.36, 0.68) | 9.41E−06 |
| FAM163A| rs6680679 | 5   | 19065339 | Intron C/G | 0.33/0.20 | 1.71 (1.33, 2.19) | 2.05E−05 |
| NAV2   | rs7949975 | 11  | 45540415 | Upstream, downstream A/T | 0.20/0.10 | 2.39 (1.58, 3.62) | 2.48E−05 |
| GALNT13| rs6710932 | 2   | 154872606 | Intron A/G | 0.08/0.16 | 0.45 (0.31, 0.66) | 2.81E−05 |
| NPYB   | rs75845252 | 12  | 104539534 | Upstream T/C | 0.09/0.04 | 2.62 (1.64, 4.19) | 2.97E−05 |
| RBMS3-A53| rs13068014 | 3   | 291070975 | Downstream A/C | 0.30/0.20 | 1.71 (1.33, 2.20) | 3.31E−05 |
| AKR1C4 | rs191812506 | 10  | 5272947 | Downstream, upstream C/T | 0.05/0.01 | 4.14 (2.01, 8.55) | 3.31E−05 |
| GALNT16| rs77688865 | 4   | 172563203 | Intron G/T | 0.05/0.01 | 3.69 (1.90, 7.19) | 4.17E−05 |
| GALNT14| rs14412592 | 2   | 3110655 | Intron T/C | 0.05/0.02 | 3.47 (1.84, 6.52) | 4.35E−05 |
| DPP6   | rs59309371 | 7   | 159398863 | Intron T/C | 0.25/0.38 | 0.59 (0.46, 0.76) | 4.51E−05 |
| CTU1   | rs117770234 | 19  | 51614232 | Intron A/G | 0.04/0.01 | 4.43 (2.03, 9.68) | 4.78E−05 |
| CDH8   | rs138852987 | 16  | 61482087 | Intron C/T | 0.06/0.02 | 3.29 (1.79, 6.05) | 5.01E−05 |
| OX3    | rs11624718 | 14  | 100969522 | Downstream, upstream G/A | 0.39/0.50 | 0.63 (0.50, 0.79) | 5.20E−05 |
| SLCA2A1| rs8010937 | 14  | 37324893 | Intron A/C | 0.13/0.07 | 2.12 (1.46, 3.07) | 5.32E−05 |
| PPP6R3 | rs61186841 | 11  | 68336714 | Intron G/A | 0.04/0.01 | 4.63 (2.05, 10.47) | 5.58E−05 |
| LOCS9593| rs6040792 | 20  | 11597971 | Intron, downstream G/T | 0.25/0.16 | 1.74 (1.33, 2.28) | 5.83E−05 |

SNP: single-nucleotide polymorphism; Chr, chromosome; OR, odds ratio; CI, confidence interval.
### TABLE 3
Top 20 genomic variants associated with the occurrence of levodopa-induced dyskinesia, in decreasing order of statistical significance.

| Gene     | SNP      | Chr | Position | Region relative to gene | Allele (minor/major) | Minor allele frequency (case/control) | OR (95% CI) | P-value  |
|----------|----------|-----|----------|-------------------------|----------------------|---------------------------------------|-------------|----------|
| GALNT14  | rs144125291 | 2   | 31106055 | Downstream, upstream    | T/C                  | 0.07/0.01                             | 5.45 (2.87, 10.33) | 7.88E−09 |
| C17orf51 | rs139221627 | 17  | 21715669 | Upstream               | T/C                  | 0.07/0.02                             | 4.68 (2.51, 8.73)  | 1.20E−07 |
| C21orf7  | rs208882   | 21  | 18813490 | Intron                 | A/G                  | 0.40/0.26                             | 1.90 (1.47, 2.45)  | 5.74E−07 |
| LRPPRC   | rs10495912 | 2   | 44305461 | Upstream, downstream   | A/G                  | 0.07/0.02                             | 4.03 (2.24, 7.24)  | 5.81E−07 |
| CBFA2T3  | rs150854091| 16  | 89028784 | Intron                 | A/G                  | 0.08/0.02                             | 3.64 (2.10, 6.33)  | 1.12E−06 |
| TMEM132C | rs1531246  | 12  | 128999121| Intron                 | G/C                  | 0.18/0.09                             | 2.28 (1.62, 3.21)  | 1.60E−06 |
| SCL11A1  | rs953169   | 11  | 2083542  | Upstream               | G/A                  | 0.45/0.31                             | 1.80 (1.41, 2.31)  | 2.57E−06 |
| TMEM158  | rs118109628| 3   | 45279523 | Downstream, upstream   | T/G                  | 0.10/0.03                             | 3.12 (1.89, 5.55)  | 9.66E−06 |
| ZNF138   | rs117999072| 7   | 64228326 | Downstream, upstream   | A/G                  | 0.08/0.03                             | 3.24 (2.10, 5.52)  | 9.66E−06 |
| ADAM10   | rs118049686| 15  | 58895720 | Upstream               | A/G                  | 0.06/0.02                             | 4.07 (2.11, 7.86)  | 6.93E−06 |
| LRPPRC   | rs17031893 | 12  | 44283172 | Downstream, upstream   | G/A                  | 0.08/0.03                             | 3.24 (2.10, 5.52)  | 9.66E−06 |
| TMEM132C | rs1531246  | 12  | 128999121| Intron                 | T/C                  | 0.08/0.03                             | 3.12 (1.89, 5.55)  | 9.66E−06 |
| SCL11A1  | rs953169   | 11  | 2083542  | Upstream               | G/A                  | 0.45/0.31                             | 1.80 (1.41, 2.31)  | 2.57E−06 |
| TMEM158  | rs118109628| 3   | 45279523 | Downstream, upstream   | T/G                  | 0.10/0.03                             | 3.12 (1.89, 5.55)  | 9.66E−06 |
| ZNF138   | rs117999072| 7   | 64228326 | Downstream, upstream   | A/G                  | 0.08/0.03                             | 3.24 (2.10, 5.52)  | 9.66E−06 |
| ADAM10   | rs118049686| 15  | 58895720 | Upstream               | A/G                  | 0.06/0.02                             | 4.07 (2.11, 7.86)  | 6.93E−06 |
| LRPPRC   | rs17031893 | 12  | 44283172 | Downstream, upstream   | G/A                  | 0.08/0.03                             | 3.24 (2.10, 5.52)  | 9.66E−06 |
| TMEM132C | rs1531246  | 12  | 128999121| Intron                 | T/C                  | 0.08/0.03                             | 3.12 (1.89, 5.55)  | 9.66E−06 |

**SNP**, single-nucleotide polymorphism; **Chr**, chromosome; **OR**, odds ratio; **CI**, confidence interval.

**FIGURE 2** | Representative regional plots for genetic variants that showed associations with the occurrence of levodopa-induced dyskinesia 5 years after the onset of Parkinson's disease. (A) rs144125291, (B) rs10495912, (C) rs11799072, (D) rs6737342, and (E) rs6795866.
TABLE 4 | Demographic and clinical characteristics of patients aged \( \geq 50 \) years at onset of Parkinson’s disease.

| Characteristic | Patients |
|---------------|----------|
| Total sample, \( n \) | 578 |
| Men, \( n \) (%) | 247 (42.7) |
| Women, \( n \) (%) | 331 (57.3) |
| Age at onset of PD, years, mean ± SD (range) | 61.1 ± 7.1 (50–87) |
| Disease duration, years, mean ± SD (range) | 10.3 ± 3.9 (5–27) |
| Patients with motor fluctuations, \( n \) (%) | 403 (69.7) |
| Duration between PD onset and development of motor fluctuations, years, mean ± SD (range) | 7.1 ± 3.2 (1–20) |
| Patients with levodopa-induced dyskinesia, \( n \) (%) | 354 (61.1) |
| Duration between PD onset and development of levodopa-induced dyskinesia, years, mean ± SD (range) | 7.3 ± 3.2 (1–19) |
| Patients with motor fluctuations 5 years after PD onset, \( n \) (%) | 141 (24.4) |
| Duration between PD onset and development of motor fluctuations, years, mean ± SD (range) | 3.9 ± 1.2 (1–5) |
| Patients with levodopa-induced dyskinesia 5 years after PD onset, \( n \) (%) | 115 (19.9) |
| Duration between PD onset and development of levodopa-induced dyskinesia, years, mean ± SD (range) | 4.0 ± 1.1 (1–6) |
| MMSE score (range) | 25.8 ± 3.2 (10–30) |
| MoCA score (range) | 21.8 ± 5.7 (3–30) |

PD, Parkinson’s disease; SD, standard deviation; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

(43.9%) and 416 women (56.1%). The mean age at onset of PD was 57.1 years, while the mean disease duration from the onset of PD to the last follow-up was 10.8 ± 4.5 years.

Motor Fluctuations

Five years after the onset of PD, 219 (29.6%) patients exhibited motor fluctuations. No difference was observed between patients with PD with motor fluctuations (92 men, 42.0%) and those without motor fluctuations (233 men, 44.6%) \( (P = 0.480) \) in terms of sex. The mean age at onset of PD was lower in patients with motor fluctuations than in those without motor fluctuations \( (54.0 ± 10.3 \) years vs. \( 58.4 ± 9.7 \) years, \( P < 0.001) \). The mean disease duration between the onset of PD and the last follow-up was shorter in patients with motor fluctuations than in those without motor fluctuations \( (9.5 ± 4.0 \) years vs. \( 11.3 ± 4.6 \) years, \( P < 0.001; \) Supplementary Table 1). The 583,353 SNPs that passed quality controls were genotyped and analyzed. Quantile–quantile plots were made for the presence of PD at 5 years after onset of PD \( (\text{Supplementary Figure 3A}) \), and a Manhattan plot is described in Figure 1A. The top 20 SNPs associated with the occurrence of motor fluctuations are listed in Table 2. FAM129B SNP rs10760490 was nominally associated with the occurrence of motor fluctuations at 5 years after onset of PD \( (OR = 2.9, 95\% \ CI = 1.8–4.8, P = 6.5 \times 10^{-6}) \). However, FAM129B SNP rs10760490 and other SNPs were not significant after Bonferroni correction (Table 2).

Levodopa-Induced Dyskinesia

Five years after the onset of PD, 172 patients had LID (23.2%). No difference was observed between patients with LID (75 men, 43.6%) and those without LID (250 men, 43.9%) \( (P = 0.892) \) in terms of sex. The mean age at onset of PD was lower in patients with LID than in those without \( (55.2 ± 10.7 \) years vs. \( 57.7 ± 9.8 \) years, \( P = 0.007) \). The mean duration between disease onset and the last follow-up was shorter in patients with LID than in those without \( (9.1 ± 3.5 \) years vs. \( 11.3 ± 4.6 \) years, \( P < 0.001; \) Supplementary Table 2). After quality controls, 583,379 SNPs were genotyped and analyzed. Quantile–quantile plots were made for the occurrence of LID \( (\text{Supplementary Figure 3B}) \), and a Manhattan plot is described in Figure 1B. The top 20 SNPs associated with the occurrence of LID 5 years after the onset of PD are listed in Table 3. The GALNT14 SNP rs144125291 had the lowest \( P \)-value and was significantly associated with LID even after Bonferroni correction \( (OR = 5.5, 95\% \ CI = 2.9–10.3, P = 7.88 \times 10^{-5}; \) Table 3). The representative regional association plots of rs10495912, rs117999072, rs6737342, and rs6795866 showed other risk variants within 150 kb \( (\text{Figures 2A–E}) \).

Sensitivity Analysis for Patients With PD Aged \( \geq 50 \) Years at the Onset of PD

The clinical features of patients with PD are presented in Table 4 and Supplementary Tables 3, 4. Five years after the onset of PD, 141 (24.4%) of 578 patients with PD exhibited motor fluctuations. A Manhattan plot is described in Figure 3A. The top 20 SNPs associated with the occurrence of motor fluctuations are listed in Table 5. RAB6L SNP rs191519045 had the lowest \( P \)-value, but none of the SNPs were significant after Bonferroni correction. Representative regional association plots of rs72850586, rs76767606, and rs124085111 showed other risk variants within 150 kb \( (\text{Supplementary Figures 4A–C}) \).

Five years after the onset of PD, 115 (19.9%) of 578 patients with PD had LID. A Manhattan plot is described in Figure 3B. The 20 SNPs associated with the occurrence of LID are listed in Table 6. None of these SNPs were significant after Bonferroni correction. Regional association plots of rs117999072, rs149201992, and rs6907129 showed other risk variants within 150 kb \( (\text{Supplementary Figures 4D–F}) \).

DISCUSSION

We found several genetic variants that showed associations with motor fluctuations and LID in patients with PD. The occurrence of motor fluctuations was associated with genetic variants in FAM129B, SNX29, C5orf52, and STK10 with \( P < 1.0 \times 10^{-5} \), although the associations were not significant after Bonferroni correction. The occurrence of LID was most significantly associated with GALNT14 SNP rs144125291, and this association was significant after Bonferroni correction.

The pathophysiology of LID in PD is not well-understood. The functional state of the basal ganglia may be characterized by changes in the neuronal firing rate and oscillatory neuronal activity, which become excessive and possibly have a pathogenic role in the occurrence of abnormal corticostriatal
connectivity (16). These mechanisms have been implicated in the pathophysiology of LID in PD. A polymorphism in brain-derived neurotrophic factor, recognized as modulating human cortical plasticity, affects the time to onset of LID in PD in addition to the response to rTMS (17, 18). Further studies using non-invasive brain stimulation techniques may be warranted to clarify the role of those genetic variants in LID.

GALNT14 SNP rs144125291 is located in the intergenic region 27,276 bases downstream of the gene variant for GALNT14. The GALNT14 gene encodes a Golgi protein that is a member of the polypeptide N-acetylgalactosaminyltransferase protein family (19). This enzyme catalyzes the transfer of N-acetyl-D-galactosamine to the hydroxyl group on serines and threonines in target peptides (19). Alterations in this gene may play a role in cancer progression and response to chemotherapy in several types of cancer (20–26). Some genes, such as LRRK2 and PRKN, may be associated with both cancer and PD (27–30). GALNT14 contributes to breast cancer invasion by altering cell proliferation and motility, by altering the expression levels of EMT genes, and by stimulating MMP-2 activity (31). MMP-2 is reported to play a role in the inflammatory response (32). GALNT14 may also cause abundant post-translational modifications, such as glycosylation, which is closely related to tumor growth and metastasis as well as resistance to chemotherapy (33). The development of LID in patients with PD is also related to altered post-synaptic transcription factors and maladaptive plasticity in the nigrostriatal neurons (34). Although the precise pathogenic mechanisms of LID remain unclear, chronic inflammation in the brain and altered post-synaptic plasticity may play key roles in the development of LID (34–36). GALNT14 SNP rs144125291 may affect the basal level of neuroinflammation in the brain or maladaptive post-synaptic plasticity. However, further functional studies are needed to elucidate the precise role of GALNT14 in LID.

Several other genes also showed possible association with the occurrence of LID, including LRPPRC. LRPPRC SNP
rs10495912 showed a possible association with LID and is an intergenic variant located 60,028 bases upstream of LRPPRC. LRPPRC encodes a leucine-rich pentatricopeptide motif-containing protein that predominantly localizes to the mitochondria. The pentatricopeptide repeat (PPR) protein family plays a major role in RNA stability, regulation, processing, splicing, translation, and editing (37). LRPPRC regulates energy metabolism, and the maturation and export of nuclear mRNA. LRPPRC mutations have been found to cause Leigh syndrome in a French–Canadian population and are associated with reduced levels of LRPPRC and lower steady-state levels of mitochondrial transcripts (38). Leigh syndrome is an inherited neurometabolic disorder characterized by the occurrence of severe and deathly acidotic crises due to a tissue-specific deficiency in cytochrome c oxidase (38). An LRPPRC intronic variant may affect the normal splicing of LRPPRC and has been associated with susceptibility to PD (39). Mitochondrial susceptibility in the putamen is reported to play a role in the development of dyskinesia in patients with PD (40), suggesting that abnormal energy metabolism caused by LRPPRC variants may be associated with the occurrence of LID. However, further genetic and functional studies are needed to elucidate the role of LRPPRC in the development of LID.

Of the genes associated with the occurrence of motor fluctuations, FAM129B showed the lowest P-value (OR = 2.93, 95% CI = 1.8–4.8, P = 6.5 × 10⁻⁴⁰). Knockdown of FAM129B in HeLa cells accelerates the onset of apoptosis induced by TNF-α (41). Activation of the inflammatory response is closely associated with the pathogenesis of PD, and the increased release of pro-inflammatory cytokines such as TNF-α, interleukin-1β, and interferon-γ has been observed in the post-mortem brain of a PD patient (42). In addition to susceptibility to PD, neuroinflammation in the striatum as well as in the substantia nigra pars compacta may play an important role in the development of motor fluctuations in PD via presynaptic and post-synaptic mechanisms. The storage hypothesis for motor fluctuations posits that the loss of presynaptic dopaminergic terminals reduces the capacity for storage of dopamine in the striatum, thereby inhibiting the ability to compensate for oscillations in plasma levodopa levels, and neuroinflammation may contribute to this effect (43). Neuroinflammation and chronic overproduction and abnormal release of TNF-α by microglia may also contribute to the post-synaptic mechanisms of motor fluctuations, which may be associated with complex striatal functional abnormalities in basal ganglia motor circuits (44). Further functional studies are necessary to investigate the precise role of FAM129B in neuroinflammation in PD.

**Table 5** | Top 20 genomic variants associated with the occurrence of motor fluctuations in patients aged ≥50 years at onset of Parkinson’s disease.

| Gene     | SNP          | Chr | Position | Region relative to gene | Allele (minor/major) | Minor allele frequency (case/control) | OR (95% CI) | P-value  |
|----------|--------------|-----|----------|-------------------------|----------------------|----------------------------------------|-------------|----------|
| RABL6    | rs191519045  | 9   | 139707344| Intron, exon             | G/A                  | 0.04/0.002                             | 17.66       | 3.81E–07 |
| PPP6R3   | rs61188641   | 11  | 68336714 | Intron                  | G/A                  | 0.05/0.01                             | 8.40        | 1.91E–06 |
| SAYSD1   | rs72850586   | 6   | 39153495 | Upstream, downstream     | G/A                  | 0.05/0.01                             | 8.40/2.97   | 1.92E–06 |
| DIO3     | rs11624718   | 14  | 102095622| Downstream, upstream     | A/G                  | 0.35/0.49                             | 0.51 (0.39, 0.68) | 2.28E–06 |
| ANTXR1   | rs56216132   | 2   | 69377298 | Intron                  | A/C                  | 0.50/0.35                             | 1.87 (1.42, 2.46) | 6.07E–06 |
| MAP3K2   | rs147429309  | 2   | 128136163| Intron, upstream         | T/G                  | 0.05/0.01                             | 6.99 (2.63, 18.57) | 6.61E–06 |
| FAM129B  | rs10760490   | 9   | 130335418| Intron                  | A/G                  | 0.10/0.03                             | 3.24 (1.89, 5.55) | 7.10E–06 |
| ZNF92    | rs190170956  | 7   | 65066217 | Upstream, downstream     | C/T                  | 0.04/0.003                            | 10.62 (2.90, 38.88) | 9.74E–06 |
| SNX29    | rs150380018  | 16  | 12569786 | Intron                  | G/T                  | 0.04/0.004                            | 8.75 (2.76, 27.69) | 1.00E–05 |
| TBC1D5   | rs73817453   | 3   | 18117165 | Intron                  | A/G                  | 0.05/0.01                             | 5.38 (2.33, 12.42) | 1.20E–05 |
| LINC00460| rs117816291  | 13  | 106915837| Upstream, downstream     | A/G                  | 0.05/0.01                             | 5.38 (2.33, 12.42) | 1.20E–05 |
| GPPA     | rs12009947   | 23  | 16108832 | Intron                  | T/C                  | 0.22/0.41                             | 0.41 (0.27, 0.62) | 3.15E–05 |
| TBC1D5   | rs76767606   | 3   | 18064472 | Intron                  | A/G                  | 0.05/0.01                             | 5.63 (2.34, 13.56) | 1.61E–05 |
| CMAHP    | rs6456661    | 6   | 25214720 | Upstream, downstream     | A/G                  | 0.05/0.01                             | 6.04 (2.38, 15.29) | 1.79E–05 |
| NUPR1L   | rs146088024  | 7   | 56232344 | Downstream, upstream     | C/A                  | 0.06/0.01                             | 4.98 (2.21, 11.21) | 1.99E–05 |
| XPO6     | rs142186210  | 16  | 28138044 | Intron                  | A/G                  | 0.05/0.01                             | 5.96 (2.35, 15.09) | 2.12E–05 |
| GBE1     | rs6798680    | 3   | 81905441 | Intron, upstream, downstream | A/C                  | 0.38/0.48                             | 0.56 (0.42, 0.73) | 2.40E–05 |
| RYR2     | rs12408511   | 1   | 237842915| Intron                  | T/A                  | 0.10/0.04                             | 2.92 (1.74, 4.91) | 2.47E–05 |
| PFKP     | rs117516530  | 10  | 2966617  | Upstream, downstream     | G/A                  | 0.17/0.08                             | 2.31 (1.55, 3.43) | 2.58E–05 |

SNP, single-nucleotide polymorphism; Chr, chromosome; OR, odds ratio; CI, confidence interval.
TABLE 6 | Top 20 genomic variants associated with the occurrence of levodopa-induced dyskinesia in patients aged ≥50 years at the onset of Parkinson’s disease.

| Gene | SNP | Chr | Position | Region relative to gene | Allele (minor/major) | Minor allele frequency (case/control) | Minor allele OR (95% CI) | P-value |
|------|-----|-----|----------|-------------------------|---------------------|--------------------------------------|------------------------|---------|
| TMEM158 | rs118109628 | 3 | 45279523 | Downstream, upstream | A/G | 0.04/0.03 | 20.96 (5.46, 96.32) | 3.26E-08 |
| C21orf7 | rs208892 | 10 | 18813490 | Intron | A/G | 0.43/0.25 | 2.26 (1.67, 3.05) | 6.84E-08 |
| PCSK6 | rs12908851 | 15 | 102042815 | Intron, downstream | T/C | 0.07/0.01 | 6.82 (3.05, 15.24) | 8.15E-08 |
| DUSP26 | rs147270897 | 8 | 34132814 | Intron, upstream | C/T | 0.05/0.01 | 8.62 (3.20, 23.24) | 3.89E-07 |
| ZNF138 | rs117990072 | 7 | 64228326 | Downstream, upstream | A/G | 0.09/0.02 | 4.33 (2.32, 8.08) | 6.42E-07 |
| CHD9 | rs149201992 | 16 | 52837183 | Downstream, upstream | C/T | 0.07/0.01 | 5.81 (2.63, 12.82) | 1.04E-06 |
| HESX1 | rs191751991 | 3 | 57241967 | Intron, upstream | G/A | 0.04/0.003 | 12.65 (3.40, 47.12) | 1.35E-06 |
| EVA1C | rs141704048 | 21 | 31106055 | Downstream, upstream | T/C | 0.07/0.01 | 5.23 (2.48, 11.03) | 1.56E-06 |
| GALNT14 | rs7749491 | 6 | 46598263 | Intron, upstream | A/G | 0.04/0.003 | 12.45 (3.34, 43.68) | 1.68E-06 |
| CYP39A1 | rs6907129 | 6 | 46597608 | Intron | T/G | 0.04/0.01 | 8.36 (2.83, 24.69) | 5.10E-06 |
| CYP39A1 | rs6905960 | 6 | 46597262 | Intron | G/A | 0.04/0.02 | 8.34 (2.82, 24.64) | 5.25E-06 |
| CYP39A1 | rs7749491 | 6 | 46598263 | Intron | G/A | 0.04/0.01 | 8.32 (2.82, 24.58) | 5.41E-06 |
| CYP39A1 | rs16858681 | 6 | 46598637 | Intron | T/A | 0.04/0.01 | 8.30 (2.81, 24.53) | 5.57E-06 |
| RNU6-21P | rs141125291 | 2 | 31106055 | Downstream, upstream | T/C | 0.07/0.01 | 5.23 (2.48, 11.03) | 1.56E-06 |
| LOC284080 | rs191751991 | 3 | 57241967 | Intron, upstream | G/A | 0.04/0.003 | 12.65 (3.40, 47.12) | 1.35E-06 |
| CYP39A1 | rs58120268 | 20 | 8120394 | Intron | A/G | 0.08/0.02 | 4.30 (2.24, 8.26) | 2.28E-06 |

SNP, single-nucleotide polymorphism; Chr, chromosome; OR, odds ratio; CI, confidence interval.

binding to RAB7a and SNX3 (46). This retromer function is closely linked to PD. VPS35 mutations are a rare cause of autosomal dominant late-onset PD. The clinical features of PD with VPS35 mutations were as follows: lower onset age, good response to levodopa, and motor complications (47). VPS13C mutations are a rare cause of autosomal recessive early-onset PD. The clinical features of PD with VPS13C mutations suggested that the progression is rapid and severe (48). Thus, VPS-related variants might be associated with motor complications in patients with PD. RYR2, which also associates with the occurrence of motor fluctuations in patients with PD aged over 50 years (P = 2.5 × 10⁻⁵), encodes a ryanodine receptor. Ryanodine receptors are intracellular calcium release channels found in the endoplasmic reticulum of all cells, with RYR2 predominating among the three isoforms (RYR1, RYR2, and RYR3) (49). When cellular Ca²⁺-regulating systems are compromised, synaptic dysfunction, impaired plasticity, and neuronal degeneration occur, such as in PD (50). Functional studies are needed to clarify the roles of TBC1D5 and RYR2 in the occurrence of motor fluctuations in PD.

The genetic association studies using a small number of pre-specified genetic region were able to determine the genetic risk variants for LID. A previous study reported that the Val158Met variant of catechol-O-methyltransferase was associated with LID (51). In another previous study, 229 (45.5%) of 503 Korean patients with PD experienced LID during the mean disease duration of 10.9 years (52). In their candidate gene association study, only the p.S9G variant of dopamine receptor D3 was associated with the occurrence of diphasic dyskinesia (52). However, these studies had limitations as only a limited number of candidate genes were selected due to their incomplete understanding of the pathophysiology of motor complications. Our GWAS investigated a genome-wide set of genetic variants, and this hypothesis-free GWAS may provide a comprehensive evaluation of genetic risk factors for motor complications.

This study has limitations. First, our study used retrospective clinical data. Motor fluctuations and LID are closely related to the pattern and dosage of dopaminergic medications, which were not randomized due to the inherent limitations of a retrospective study. The prevalence of motor fluctuations (29.6%) and LID (23.2%) was slightly lower in the present study than in the previous clinical studies (53, 54); however, this rate of motor complications may be dependent on the patterns of prescribing dopaminergic medications (55, 56). Recently, the prevalence of motor complications is now ∼20–28%, which is comparable to what we observed (57, 58). Motor fluctuations and LID are complex phenomena where several factors may contribute to their development and further studies are required to better understand their pathophysiology (59). Second, we assessed the UPDRS for the evaluation of LID, but we did not use more specific assessment tools, such as Unified Dyskinesia Rating Scale, due to practical issues. Hence, future studies should perform a more detailed clinical assessment of LID. Third, our
sample size was small compared with that of the traditional GWAS. Deep phenotyping in larger samples is challenging; thus, a well-designed GWAS on clinically important issues should be conducted.

In conclusion, this study provides new insights into the genetic contributions to motor fluctuations and LID in PD. Future collaborative longitudinal genomic studies are needed to further investigate the genetic risk factors associated with motor fluctuations and LID in patients with PD.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories: https://www.ncbi.nlm.nih.gov/SNP/snp_viewBatch.cgi?sbid=1063124. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board (IRB) of Asan Medical Center. The patients/participants provided their written informed consent to participate in this study.

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AUTHOR CONTRIBUTIONS

SC contributed to the conception, organization, execution of the research project, design, execution, review, critique of the statistical analysis, writing of the first draft, and review and critique of the manuscript. H-SR contributed to the execution of the research project, design, execution, review, critique of the statistical analysis, writing of the first draft, and review and critique of the manuscript. KP, NC, JiK, Y-MP, SJ, M-JK, YK, JuK, KK, and S-BK contributed to the execution of the research project, design, execution, review, critique of the statistical analysis, and review and critique of the manuscript.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.