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ORIGINAL ARTICLE

Longitudinal Implications of the *BDNF* rs6265 Polymorphism for Motor and Nonmotor Features of Parkinson's Disease in the Korean Population

Sang-Won Yoo,[1] Yun Joong Kim,[2]✉ Dong-Woo Ryu,[1] Yoonsang Oh,[1] Seunggyun Ha,[3] Joong-Seok Kim[1]✉

[1]Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Department of Neurology, Yonsei University College of Medicine, Seoul, Korea
[3]Division of Nuclear Medicine, Department of Radiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

ABSTRACT

Objective Brain-derived neurotrophic factor (BDNF) has been suggested to support the endurance and dopamine release of dopaminergic neurons. Its Val66Met polymorphism might modify Parkinson's disease (PD) evolution, although evidence in Asian populations remains limited. This study aimed to explore how the *BDNF* rs6265 genotype is associated with the clinical characteristics and longitudinal progression patterns of PD patients in a Korean population.

Methods A total of 247 patients were enrolled and followed for a mean duration of 50.9±23.9 months. Baseline and/or periodic assessments captured motor severity, nonmotor burden, cognition, orthostatic stress, cardiac denervation, and presynaptic dopamine transporter availability. The repeated measures were manipulated to infer any genotypic differences in the trajectories of each clinical domain.

Results The genotype frequencies were 31.2% (77/247) for Val/Val carriers and 68.8% (170/247) for Met-allele carriers. Baseline clinical characteristics and presynaptic dopamine transporter availability were comparable between genotypes. Initially, Val homozygotes showed more preserved myocardial innervation and poorer nonfrontal cognitive performance. Longitudinal analyses demonstrated genotype-specific increases in motor and cognitive severity. Compared with Met-allele carriers, the homozygous Val group exhibited accelerated motor progression and a more rapid decline in the frontal domain after 3 years of follow-up.

Conclusion The differences in myocardial denervation at diagnosis, cognitive profiles, and motor progression might suggest a potential modulatory role of *BDNF* polymorphisms in PD progression in the Korean population.

Keywords Parkinson's disease; Brain-derived neurotrophic factor; *BDNF* rs6265 polymorphism; Genotypic difference; Disease progression.

INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and is essential for neuronal survival.[1,2] Its role has been implicated in regulating the endurance and dopamine release of dopaminergic neurons in the substantia nigra, which is tied to the pathogenesis of Parkinson's disease (PD).[3-6]

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✉ **Corresponding author:** Joong-Seok Kim, MD, PhD
Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea / **Tel:** +82-2-2258-6078 / **E-mail:** neuronet@catholic.ac.kr
✉ **Corresponding author:** Yun Joong Kim, MD, PhD
Department of Neurology, Yongin Severance Hospital, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin 16995, Korea / **Tel:** +82-31-5189-8140 / **E-mail:** yunjkim@yuhs.ac

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The *BDNF* rs6265 polymorphism (Val66Met polymorphism) is associated with PD.[1,2] Its allele frequency varies by ethnicity and geographic region.[1] Approximately 30%−50% of Caucasian individuals are Met carriers, whereas approximately 60%−70% of Asian individuals are Met carriers.[1] These ethnic disparities may contribute to the heterogeneity of PD phenotypes.

The influence of the *BDNF* rs6265 polymorphism has been investigated primarily in Caucasian PD cohorts but rarely in Asian populations, and the existing results are inconsistent between Western and Asian studies.[6-11] In a Japanese population, Val homozygotes were more prevalent among PD patients than among controls,[6] whereas the opposite finding was reported in a Swedish population, and there was no difference in genotype frequency between PD patients and controls among Whites.[7] In addition to its association with PD risk, its influence on cognition is also controversial. In an Italian PD cohort, Met homozygotes were associated with worse cognition, whereas other studies reported a higher incidence of cognitive impairment or better verbal fluency among Met carriers; in a Greek population, no association between the polymorphism and cognition was observed.[8-11] These studies differed not only in genotype distributions but were also limited by a narrow focus on a single domain—primarily cognition—and by their predominantly cross-sectional design.

The present study aimed to explore how the *BDNF* rs6265 genotype could shape motor and nonmotor characteristics and longitudinal progression patterns in PD patients in a Korean population.

MATERIALS & METHODS

Patients

The study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, The Catholic University of Korea (Approval number: KC21OIDI0362). All the subjects provided written informed consent to participate. Research was conducted in accordance with the relevant guidelines and regulations.

This study utilized data from the Korean nationwide hospital-based PD (K-PD) cohort, an observational, prospective, longitudinal cohort study of the Korea National Institute of Health.[12] A total of 247 de novo PD patients diagnosed between July 2015 and May 2023 at a single participating hospital in the K-PD cohort were included. Diagnosis was established on the basis of the Movement Disorder Society (MDS)-PD diagnostic criteria, which was supported by positron emission tomography (PET) imaging studies using ^{18}F-N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (^{18}F-FP-CIT).[13] Patients exhibited decreased ^{18}F-FP-CIT uptake in the striatum, primarily in the posterior putamen.

Baseline characteristics, including age at diagnosis, sex, body mass index, disease duration at diagnosis, follow-up duration, and history of hypertension, diabetes mellitus, dyslipidemia, and smoking status, were investigated.

To avoid PD mimics and to minimize the inclusion of patients with cardiovascular dysautonomia or related complications, individuals meeting any of the following criteria were excluded: 1) any symptoms or signs of atypical and/or secondary parkinsonism during follow-up visits; 2) a history of diabetic neuropathy at initial evaluation; 3) a history of symptomatic stroke that could affect general cognition and performance; and 4) a history of heart failure.

Patients were monitored every 3−6 months for a mean follow-up duration of 50.9±23.9 months. PD diagnosis was independently confirmed by two neurologists (S.-W.Y. and J.-S.K.).

DNA analysis: *BDNF* and *APOE* genes

DNA was extracted using a NanoDrop® ND-2000 UV−Vis Spectrophotometer. Samples were genotyped for *BDNF* rs6265 and apolipoprotein E (APOE) using TaqMan SNP Genotyping Assays obtained from Applied Biosystems. Genomic DNA was diluted to a concentration of 5 ng/μL on PCR plates. PCR was performed in 5 μL of a mixture containing 2 μL of a DNA sample, 0.125 μL of each TaqMan™ SNP Genotyping Assay (Thermo Fisher Scientific), 2.5 μL of TaqMan™ Genotyping Master Mix (Thermo Fisher Scientific), and 0.375 μL of distilled water. After the PCR amplification, allelic discrimination was performed on the same machines (QuantStudio 12K Flex Real-Time PCR System). The allelic discrimination was an endpoint plate read.

Imaging acquisition and processing of ^{18}F-FP-CIT PET

Brain computed tomography (CT) and ^{18}F-FP-CIT PET images were obtained using a Discovery STE PET/CT scanner (Discovery PET/CT 710, General Electric Healthcare). After 3 hours of intravenous injection of 3.7 MBq/kg ^{18}F-FP-CIT, brain CT scans were obtained for attenuation correction, followed by a 10-min PET scan.

Image processing was conducted using Statistical Parametric Mapping 8 software (SPM8; Wellcome Trust Centre for Neuroimaging) and an in-house automated pipeline program implemented in MATLAB 2015a (MathWorks). A detailed description of the imaging process is provided in Supplementary Material 1. Every patient was evaluated with ^{18}F-FP-CIT PET images (Figure 1).

UPDRS and MDS-UPDRS

Disease severity was evaluated using the original Unified Par-

kinson's Disease Rating Scale (UPDRS) and the MDS-UPDRS. Baseline motor severity was assessed in the OFF medication state, whereas subsequent examinations were conducted in the ON state, when patients exhibited a full response to dopaminergic therapy. A total of 137 (56.8%) patients were initially evaluated using the UPDRS, and 104 (43.2%) patients were assessed using the MDS-UPDRS. Patients were subsequently re-evaluated using the same tool, as appropriate. Motor scores from the original UPDRS (Parts II and III) were converted to MDS-UPDRS scores using a previously published conversion method.[14] Total motor scores were calculated by summing the scaled Part II and III scores. Patients were reassessed 2−3 times during follow-up after the baseline investigation (Figure 1).

Head-up tilt test

Every patient was tested in the full resting state. Continuous electrocardiographic and noninvasive blood pressure (BP) monitoring equipment (YM6000, Mediana Tech) was applied to the patients. A supine position was maintained for 20 minutes during the recording of BP and heart rate every 5 minutes before tilting to 60 degrees. At the tilted position, measurements were taken at 0, 3, 5, 10, 15, and 20 minutes. The definitions of supine hypertension, orthostatic hypotension (OH), neurogenic OH (nOH), and supine/orthostatic mean arterial pressure (MAP) are specified in Supplementary Material 2.

Two hundred and forty-one patients were assessed at the time of diagnosis (Figure 1).

^{123}I-MIBG myocardial scintigraphy

^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy was conducted using a dual-head camera equipped with a low-energy, high-resolution collimator, and data were collected at

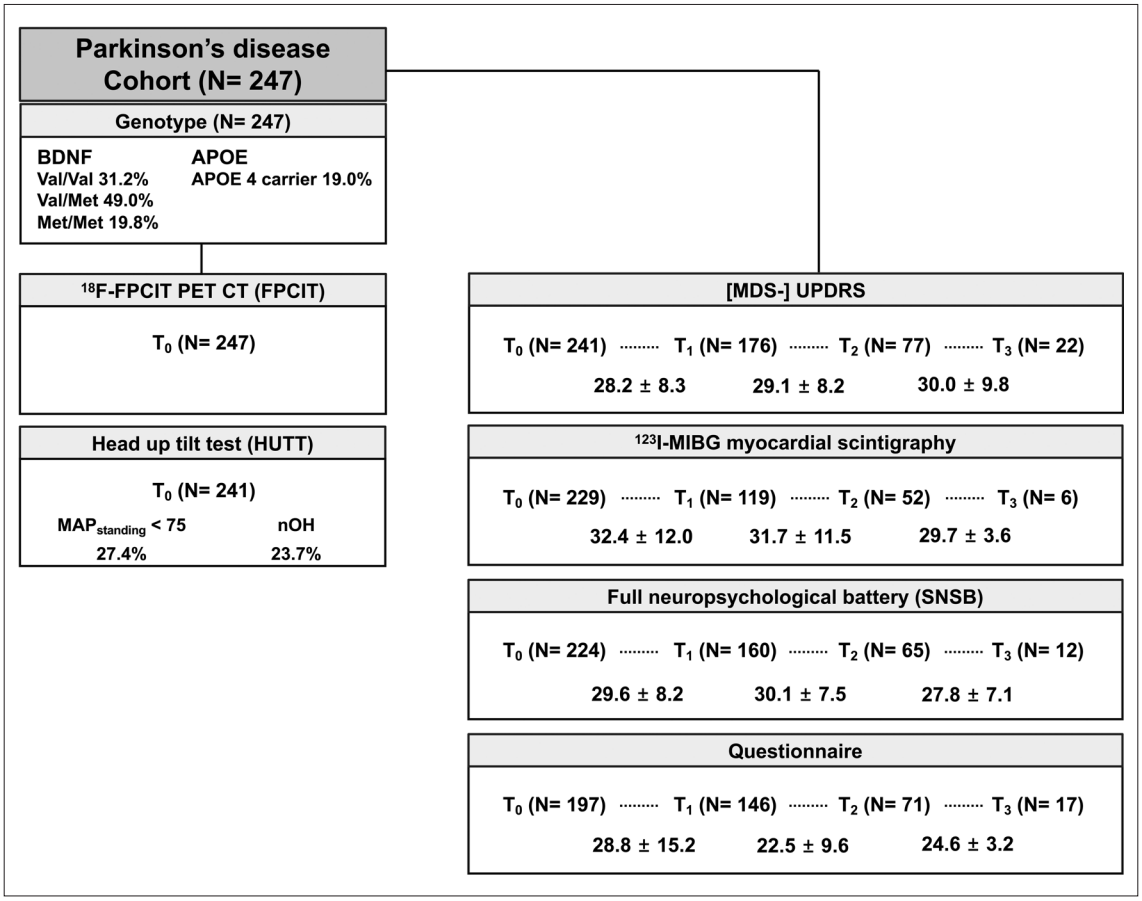

Figure 1. A flowchart of overall evaluations in this longitudinal study. For each investigation, the baseline evaluation was defined as T_0, and subsequent follow-up time points were numbered sequentially (T_1, T_2, T_3). The average intervals with standard deviations between successive assessments were illustrated in the figure and expressed in months. The questionnaire included the Non-Motor Symptoms Scale (NMSS), Montgomery-Asberg Depression Rating Scale, Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale-2, REM Sleep Behavior Disorder Screening Questionnaire, and 39-Item Parkinson's Disease Questionnaire (PDQ39) at baseline. The NMSS and PDQ39 summay index were repeatedly assessed. Val, valine; Met, methionine; ^{18}F-FP-CIT, ^{18}F-N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane; PET, positron emission tomography; CT, computed tomography; $MAP_{standing}$, orthostatic mean arterial pressure; nOH, neurogenic orthostatic hypotension; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; ^{123}I-MIBG, ^{123}I-meta-iodobenzylguanidine; SNSB, Seoul Neuropsychological Screening Battery.

30 min (early) and 120 min (late) time points after the injection of 111 MBq of ^{123}I-MIBG. A static image was obtained with a 128×128 matrix. Regions of interest were manually drawn around the heart and mediastinum. Tracer uptake was measured within each region of interest to calculate the heart-to-mediastinum (H/M) ratio for the early and late phases. ^{123}I-MIBG scintigraphy was reassessed 2–3 times (Figure 1).

Neuropsychological evaluation

The results of the neuropsychological evaluations were evaluated by experienced psychologists who were blinded to the clinical data. Five cognitive domains were assessed by a comprehensive neuropsychological battery, the Seoul Neuropsychological Screening Battery 2nd edition (SNSB-II), and subtests of each domain were selected.[15-18] The constructs of each domain (attention/working memory domain, frontal/executive domain, memory domain, language domain, and visuospatial domain) are detailed in Supplementary Material 3.

The frontal cognitive profile was defined as the average z scores of attention/working memory and frontal/executive domains, and the average of delayed recall, language, and visuospatial domains comprised the nonfrontal summary.[17] Global efficiency was calculated as the mean frontal and nonfrontal scores. Cognition was reassessed 2–3 times (Figure 1).

Clinical instruments

The patients completed the following evaluations: 1) Non-Motor Symptoms Scale (NMSS), 2) Montgomery-Asberg Depression Rating Scale (MADRS), 3) Epworth Sleepiness Scale (ESS), 4) Parkinson's Disease Sleep Scale-2 (PDSS-2), 5) REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), and 6) 39-Item Parkinson's Disease Questionnaire (PDQ39). Brief descriptions of each instrument are provided in Supplementary Material 4.

NMSS and PDQ39 summary index (PDQ39SI) were separately investigated in the longitudinal analyses because each signified different aspects of the disease. The patients were re-interviewed 2–3 times with the same questionnaires (Figure 1). All the questionnaires were evaluated in a blinded manner to the clinical information of the patients.

Composite scores

The NMSS, MADRS, ESS, PDSS-2, and RBDSQ were selected to represent the composite of the nonmotor quality of PD. Each tool was standardized by median absolute deviation to adjust for the different scales. The average standardized score was estimated to indicate the overall nonmotor burden. With the available resources in this study, the composite score was preplanned to incorporate the affection and sleep domains with the NMSS because its construct of those domains lacked specificity. The composite scores were calculated for each time point.

Statistical analyses

Statistical analyses were conducted with jamovi software (version 2.6.44; The jamovi project, https://www.jamovi.org/) and R (version 4.4.3; R Foundation for Statistical Computing) for Mac. Independent *t*-tests or Mann–Whitney U tests were performed for continuous variables when appropriate, and Fisher's exact tests were used for categorical variables. Analysis of covariance, partialized by age, sex, and disease duration at onset, was performed for between-group marginal mean comparisons.

Random slope and intercept mixed modeling, controlled by disease duration at onset, was applied to the repeated measures of the longitudinal data with a constrained residual covariance structure (nlme package; version 3.1). Statistical significance was defined as a two-tailed p-value <0.05. The exact method of model estimation is further described in Supplementary Material 5.

Data sharing

Anonymized data generated during the current study are available from the corresponding author upon reasonable request from individuals affiliated with research or health care institutions.

RESULTS

Baseline characteristics across *BDNF* genotypes

Patients with early PD (n=247) were enrolled and followed (Table 1 and Figure 1). The mean age at diagnosis was 67.0±9.3 years, and 131 patients (53.0%) were male. The median disease duration at diagnosis was 1.0 year (interquartile range [IQR], 0.5–1.5 years), and the patients were followed for an average of 50.9± 23.9 months. Forty-seven patients (19.0%) were *APOE* ε4 allele carriers. These baseline characteristics did not differ between the *BDNF* genotypes. The prevalence of the homozygous valine (Val/Val) and methionine (Met/Met) genotypes were 31.2% and 19.8%, respectively. The percentage of heterozygotes (Val/Met) was 49.0%. Overall, approximately 69% of the study population were Met carriers. The proportions of *BDNF* genotypes did not differ significantly across the evaluation tools, and no dose-dependent effects of alleles were observed across clinical characteristics (Supplementary Tables 1 and 2).

Motor scores indicated mild parkinsonism at enrollment (n=241/247, 97.6%). Converted MDS-UPDSR Parts II and III, and their totals were 5.7 (IQR, 3.0–10.0), 19.7±11.3, and 26.5 ±15.3, respectively. No between-group differences were ob-

Table 1. Baseline characteristics of the population

PD Population	Overall	Val/Val	Met carrier	*p*-value
Number of patients	247	77 (31.2)	170 (68.8)	
Age at diagnosis (yr)	67.0±9.3	65.5±9.9	67.7±9.0	0.081
Sex, male	131 (53.0)	42 (54.5)	89 (52.4)	0.784
Disease duration at diagnosis (yr)	1.00 [0.50, 1.50]	1.00 [0.42, 1.50]	0.83 [0.50, 1.29]	0.887
Total follow-up period (month)	50.9±23.9	51.1±24.1	50.9±23.9	0.933
Diabetes mellitus	44 (17.8)	9 (11.7)	35 (20.6)	0.107
Dyslipidemia	89 (36.0)	23 (29.9)	66 (38.8)	0.199
Hypertension	118 (47.8)	36 (46.8)	82 (48.2)	0.891
Non-smoker	241 (97.6)	77 (100.0)	164 (96.5)	0.181
APOE ε4 allele carrier	47 (19.0)	15 (19.5)	32 (18.8)	0.786
(MDS-)UPDRS	**Overall**	**Val/Val**	**Met carrier**	***p*-value**
Number of patients	241	76 (31.5)	165 (68.5)	
Converted MDS-UPDRS Part II	5.7 [3.0, 10.0]	6.0 [3.0, 10.3]	5.7 [3.0, 9.0]	0.183
Converted MDS-UPDRS Part III	19.7±11.3	20.1±11.3	19.5±11.4	0.674
Motor score, total (Part II + Part III)	26.5±15.3	27.6±15.7	26.0±15.2	0.435
Head-up tilt test	**Overall**	**Val/Val**	**Met carrier**	***p*-value**
Number of patients	241	76 (31.5)	165 (68.5)	
Supine SBP (mm Hg)	123.5±15.6	120.7±15.3	124.8±15.6	0.060
Supine DBP (mm Hg)	71.0±9.0	70.1±9.1	71.4±8.82	0.313
Supine MAP (mm Hg)	88.5±10.5	87.0±10.6	89.2±10.4	0.133
$MAP_{standing}$ (mm Hg)	83.3±13.3	82.5±14.0	83.6±12.9	0.533
ΔSBP_{min} (mm Hg)	10.3±14.6	9.2±14.2	10.8±14.8	0.438
ΔDBP_{min} (mm Hg)	2.7±8.3	2.1±8.5	2.9±8.2	0.495
ΔMAP (mm Hg)	5.2±9.9	4.5±9.8	5.5±9.9	0.446
MAP75	66 (27.4)	26 (34.2)	40 (24.2)	0.121
Supine hypertension (SH)	29 (12.0)	6 (7.9)	23 (13.9)	0.207
Neurogenic orthostatic hypotension (nOH)	57 (23.7)	15 (19.7)	42 (25.5)	0.415
SH + nOH	8 (3.3)	1 (1.3)	7 (4.2)	0.441
MAP75 + nOH	35 (14.5)	10 (13.2)	25 (15.2)	0.844
MAP75 or nOH	88 (36.5)	31 (40.8)	57 (34.5)	0.389
^{123}I-MIBG myocardial scintigraphy	**Overall**	**Val/Val**	**Met carrier**	***p*-value**
Number of patients	229	74 (32.3)	155 (67.7)	
HME	1.57±0.31	1.64±0.34	1.54±0.29	0.034*
HML	1.56±0.36	1.65±0.38	1.51±0.35	0.005**
Neuropsychological tool (SNSB)	**Overall**	**Val/Val**	**Met carrier**	***p*-value**
Number of patients	224	71 (31.7)	153 (68.3)	
Education, years	12.0 [9.0, 16.0]	12.0 [9.0, 16.0]	12.0 [9.0, 16.0]	0.802
Global cognition†	-0.28±0.78	-0.39±0.91	-0.23±0.70	0.161
Frontal profile‡	-0.17±0.75	-0.14±0.81	-0.18±0.72	0.733
Nonfrontal profile§	-0.36±0.98	-0.56±1.11	-0.27±0.89	0.041*
Attention/Working memory domain‖	-0.09±0.83	-0.05±0.87	-0.10±0.81	0.661
Digit Span Forward	-0.04±0.95	0.17±0.89	-0.14±0.97	0.025*
K-CWST	-0.14±1.16	-0.27±1.25	-0.07±1.11	0.228
Frontal/executive domain¶	-0.25±0.87	-0.24±0.90	-0.26±0.86	0.866
Digit Span Backward	-0.23±1.00	-0.11±1.08	-0.28±0.96	0.262
COWAT: Phonemic	-0.28±1.10	-0.36±1.14	-0.24±1.09	0.452
Memory domain: immediate††	-0.38±0.82	-0.44±0.88	-0.35±0.79	0.466
SVLT-E: Immediate recall	-0.49±1.13	-0.50±1.20	-0.48±1.10	0.914

Table 1. Baseline characteristics of the population (continued)

RCFT: Immediate recall	-0.27±0.92	-0.38±0.90	-0.22±0.94	0.247
Memory domain: Delay††	-0.41±0.84	-0.44±0.85	-0.39±0.84	0.683
SVLT-E: Delayed recall	-0.51±1.09	-0.51±1.11	-0.51±1.08	0.998
RCFT: Delayed recall	-0.31±0.95	-0.38±0.88	-0.28±0.99	0.472
Memory domain: Recognition††	-0.36±0.88	-0.32±0.93	-0.38±0.86	0.672
SVLT-E: Recognition	-0.34±1.21	-0.34±1.28	-0.34±1.18	0.995
RCFT: Recognition	-0.37±1.02	-0.30±0.99	-0.41±1.04	0.460
Language domain‡‡	-0.22±1.86	-0.55±2.05	-0.07±1.75	0.071
Visuospatial domain§§	-0.45±1.38	-0.67±1.89	-0.35±1.06	0.101
Questionnaire	**Overall**	**Val/Val**	**Met carrier**	***p*-value**
Number of patients	197	61 (31.0)	136 (69.0)	
RBDSQ, total	2.0 [1.0, 5.0]	3.0 [1.0, 5.0]	2.0 [1.0, 4.0]	0.270
PDSS-2, total	6.0 [3.0, 11.0]	6.0 [2.0, 11.0]	6.5 [3.0, 11.3]	0.604
ESS, total	3.0 [1.0, 4.0]	3.0 [2.0, 5.0]	3.0 [1.0, 4.0]	0.629
MADRS, total	2.0 [0.0, 5.0]	2.0 [0.0, 8.0]	2.0 [0.0, 5.0]	0.678
NMSS, total	26.9±23.2	28.6±26.5	26.2±21.5	0.492
Composite score	0.45±0.94	0.57±1.04	0.39±0.89	0.222
PDQ39SI	11.0±9.3	12.0±10.3	10.6±8.8	0.323

Values are presented as mean±standard deviation, *n* (%), or median [interquartile range]. Independent *t*-test or Mann–Whitney U test was performed for continuous variables when appropriate, and Fisher's exact test for categorical variables. Multiple comparisons across the various scales were not adjusted.

*p<0.05; **p<0.01; †Average z-scores of frontal and non-frontal profiles; ‡Average z-scores of attention/working memory and frontal/executive domains; §Average z-scores of memory, language and visuospatial domains; ǁAverage z-scores of Digit Span Forward and K-CWST; ¶Average z-scores of Digit Span Backward and COWAT: Phonemic; ††Average z-scores of SVLT-E and RCFT with their respective immediate and delayed recall, and recognition; ‡‡Z-scores of K-BNT; §§Z-scores of RCFT.

PD, Parkinson's disease; Val, valine; Met, methionine; APOE, apolipoprotein E; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; MAP75, standing mean arterial pressure below 75 mm Hg; SNSB, Seoul Neuropsychological Screening Battery; K-CWST, Korean-Color Word Stroop Test; COWAT, Controlled Oral Word Association Test; SVLT-E, Seoul Verbal Learning Test-Elderly's version; K-BNT, Korean-Boston Naming Test; RCFT, Rey Complex Figure Test; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; RBDSQ, REM Sleep Behavior Disorder Screening Questionnaire; PDSS-2, Parkinson's Disease Sleep Scale-2; ESS, Epworth Sleepiness Scale; MADRS, Montgomery-Asberg Depression Rating Scale; NMSS, Non-Motor Symptoms; PDQ39SI, 39-Item Parkinson's Disease Questionnaire summary index; MIBG, metaiodobenzylguanidine; HME, early heart-to-mediastinum ratio; HML, late heart-to-mediastinum ratio; SBP_{min} and DBP_{min}, lowest SBP and DBP at 3 or 5 minutes during the tilted position; ΔSBP_{min}, ΔDBP_{min}, and ΔMAP, orthostatic blood pressure changes in systolic, diastolic, and mean arterial pressure.

served (Table 1).

Two hundred forty-one (241/247, 97.6%) and two hundred twenty-nine (229/247, 92.7%) patients underwent head-up tilt tests and ^{123}I-MIBG myocardial scintigraphy, respectively (Table 1). Sixty-six patients (66/241, 27.4%) had an orthostatic MAP below 75 mm Hg (MAP75). Supine hypertension was present in 12.0% (29/241) of patients, and 23.7% (57/241) exhibited hypotension during upright tilt. Thirty-five patients (35/241, 14.5%) had nOH with a standing MAP75. These frequencies did not differ between the *BDNF* genotypes. The Met carrier group demonstrated significantly lower H/M ratios (both early and late).

Two hundred twenty-four (224/247, 90.7%) and one hundred ninety-seven (197/247, 79.8%) patients completed the initial comprehensive neuropsychological examinations and questionnaires, respectively (Table 1). Their global and subdomains of cognition were relatively preserved. Genotypic comparisons revealed no significant differences, except in the nonfrontal cognitive profile, in which the Val/Val group demonstrated poorer performance. The Digit Span Forward test was more preserved in Val homozygotes; however, this did not translate to a significant difference in the overall frontal profile.

The nonmotor burden was moderate (NMSS, 26.9±23.2). The nonmotor symptoms, composite scores, and quality of life assessments did not differ across the *BNDF* subtypes (Table 1). Comparisons of subregional presynaptic dopamine transporter densities across the *BDNF* genotypes also revealed no significant differences (Table 2).

Longitudinal analyses

The initial evaluations were longitudinally reassessed (Figure 2 and Supplementary Table 3). Mixed-effects models were applied to discern genotypic differences in trajectory patterns. With respect to the average disease duration at diagnosis (2.8 years), Val homozygotes and Met carriers did not differ in motor severity; however, the Met carrier group had a significant linear progression of motor severity (effect of disease duration: Model 1A vs. Model 1B vs. Model 1C; 95% confidence interval

Table 2. Subregional SUVR differences across genotypes

Subregional SUVR	Val/Val	Met carrier	*p*-value
Both caudate	4.50±0.14	4.46±0.09	0.727
Anterior caudate	4.85±0.16	4.81±0.11	0.761
Posterior caudate	3.46±0.11	3.51±0.07	0.802
Both putamen	4.08±0.11	3.89±0.07	0.115
Anterior putamen	4.34±0.13	4.11±0.09	0.141
Posterior putamen	3.17±0.10	3.05±0.07	0.320
Both ventral striatum	5.02±0.13	4.78±0.09	0.099
Both ventral putamen	3.72±0.08	3.60±0.06	0.171
Both globus pallidus	3.49±0.08	3.41±0.05	0.384
Both thalamus	1.51±0.01	1.51±0.01	0.892

Data is shown as the estimated marginal mean±standard error. To observe between-group differences, an analysis of covariance with age, sex, and disease duration at onset as covariates was performed.
SUVR, standardized uptake value ratio; Val, valine; Met, methionine.

[CI] 0.61−1.18 vs. 0.59−1.78 vs. 0.59−1.78) (Supplementary Table 3). The Val/Val genotype significantly contributed a positive quadratic effect to average motor progression, and as the disease advanced, motor worsening exceeded the trajectory of the Met carrier after approximately 3 years of follow-up (interaction effect on disease duration^2: Model 1A vs. Model 1B vs. Model 1C; 95% CI 0.05−0.40 vs. 0.11−0.83 vs. 0.11−1.83) (Supplementary Table 3). In summary, *BDNF* interacted with motor severity, resulting in faster motor progression in Val homozygotes than in Met carriers after 3 years of follow-up.

On average, the Met carriers showed a linear association with worsening NMSS, PDQ39SI, and nonmotor composite scores across disease spans (effect of disease duration: Model 2A vs. Model 2B vs. Model 2C; 95% CI 1.52−5.07 vs. 0.88−2.64 vs. 0.08−0.21) (Supplementary Table 3). The Met carrier genotype exerted a greater effect on the progression of nonmotor burden.

The mixed model failed to explain any significant effect of *BDNF* genotype on the progression of cognition (Model 3) (Supplementary Table 3). The overall trajectories of each genotype paralleled global cognition, with an accelerated decline after 3 years of follow-up. When cognition was stratified by frontal vs. nonfrontal profiles, the Val/Val genotype had a predominant effect on the augmented decline in frontal cognition.

Compared with the Met carrier, the Val/Val genotype resulted in a significantly higher late H/M ratio (*BDNF* estimate: Model 4; 95% CI 0.02−0.20) (Supplementary Table 3). The H/M ratios significantly decreased in an inverse linear fashion over time, with comparable slopes between the groups (Model 4) (Supplementary Table 3). Overall, *BDNF* genotypes did not affect the progression of myocardial denervation in a genotype-dependent manner, although Val homozygotes demonstrated more preserved myocardium at diagnosis.

DISCUSSION

Baseline characteristics were similar across *BDNF* genotypes, except that the Met carrier group exhibited more denervated myocardium but relatively more preserved nonfrontal cognition at diagnosis. Longitudinal analyses demonstrated genotype-specific increases in motor and cognitive severity. Compared with the Met carriers, the homozygous Val group showed accelerated motor progression and faster cognitive decline in the frontal domain after 3 years of follow-up. These findings suggest that the *BDNF* rs6265 polymorphism may influence distinctive clinical progression patterns in the Korean population.

The prevalence of the Met variant is higher in Asian populations than in Caucasian populations.[1,2] An ethnically homogeneous Korean population has been reported to harbor approximately twice the Met allele frequency of its Caucasian counterpart.[19] Our data support this ethnic difference, underscoring the need for population-specific research to determine how *BDNF* genotypes influence PD in Korea.

BDNF is involved in the survival and maintenance of several types of neurons (including dopaminergic neurons), the formation of synaptic connections and the regulation of synaptic plasticity. Its synthesis and maturation occur both in the intra- and extracellular environment; the immature pro-BDNF isoform forms into mature BDNF (m-BDNF). In adulthood, m-BDNF plays a dominant role by binding to the tropomyosin-related kinase B (TrkB) receptor, whereas pro-BDNF promotes apoptosis upon binding to the receptors of neurotrophin p75 (p75NTR) and sortilin.[1,2,20] Neurons exposed to elevated levels of pro-BDNF or reduced levels of m-BDNF may undergo long-term depression, synaptic retraction, and cell death, which may be exacerbated by aging through the depletion of extracellular proteases responsible for BDNF maturation.[1,2,20] The Met allele impairs m-BDNF production, which contributes to the loss of nigral dopaminergic neurons in PD.[1,2]

If experimental evidence demonstrated a dose-dependent detrimental effect of the Met allele on the survival of dopaminergic neurons, a stronger rationale for investigating genotype-specific effects on clinical outcomes would have been established. In the absence of such literature, the genotypes were dichotomized into the homozygous Val group and the Met allele carrier group for subsequent analyses.

Early-stage PD patients who exhibited mild parkinsonism at the time of cohort enrollment were included. This facilitated cross-sectional comparisons of baseline characteristics, as differing disease stages could distort interpretation. Initial workups did not reveal any significant genotypic differences, except for cardiac sympathetic denervation and the cognitive profile. Motor severity, orthostatic stress, nonmotor aspects, and quali-

ty-of-life measures were comparable across genotypes.

Cardiac denervation and nOH independently reflect disease burden and progression.[21-24] They result primarily from peripheral dysautonomia but also mirror the central pathology.[25-27] OH implies diffuse neuropathology.[23,27] While orthostatic dysregulation did not differ between the genotypes in this study, the

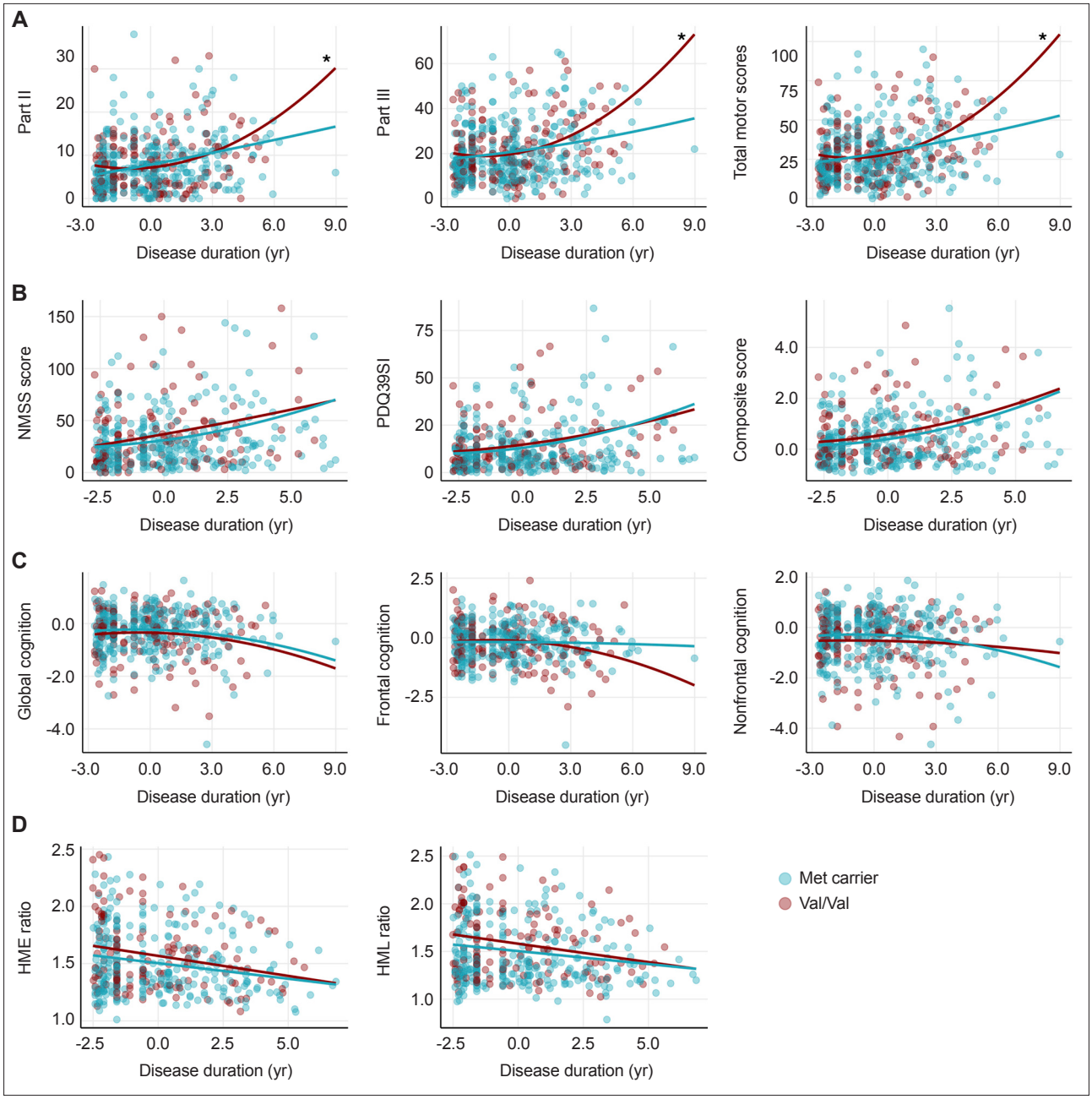

Figure 2. The trajectory of motor, non-motor, quality of life, and cognition across disease duration, stratified by *BDNF* genotypes. A: Motor function (Model 1). Part II and III represented the respective MDS-UPDRS subsets of motor scores. The total motor scores represented the sum of Part II and III motor scores. B: Nonmotor function and quality of life (Model 2). The composite score represented the average of standardized scores of NMSS, MADRS, ESS, PDSS-2, and RBDSQ to reflect the nonmotor overall burden. C: Cognitive function (Model 3). The frontal cognition was defined as the average z-scores of attention/working memory and frontal/executive cognitive domains, and the average of delayed recall, language, and visuospatial domains comprised the nonfrontal cognition. Global cognition was defined as the mean of the frontal and nonfrontal cognitive scores. D: Cardiac denervation (Model 4). *p<0.05. Statistical results for each model are presented in Supplementary Table 3. Val, valine; Met, methionine; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; NMSS, Non-Motor Symptoms Scale; PDQ39SI, 39-Item Parkinson's Disease Questionnaire summary index; MADRS, Montgomery-Asberg Depression Rating Scale; ESS, Epworth Sleepiness Scale; PDSS-2, Parkinson's Disease Sleep Scale-2; RBDSQ, REM Sleep Behavior Disorder Screening Questionnaire; HME, early heart-to-mediastinum ratio; HML, late heart-to-mediastinum ratio.

Met allele carriers had a higher incidence of nOH with MAP75 and more damaged myocardial denervation. This suggests that the *BNDF* polymorphism could correspond to a noradrenergic subtype, which is relevant to the body-first model.[26,28] This requires validation in future studies because our longitudinal analyses failed to confirm that Met allele carriers are fast progressors.[26,29]

In the longitudinal analyses, the Met carrier genotype was used as a reference because it contrasted with the Caucasian frequency and was associated with milder motor severity.[1,30] While the motor severity of the Met carrier group steadily increased over time, the Val/Val genotype exceeded that of the Met allele genotype after accelerating beyond 5–6 years of disease duration. Previous studies suggested that these findings were due to abrupt changes in vulnerability resulting from enhanced degeneration and the loss of compensatory mechanisms.[31,32] This finding was not anticipated considering its physiologic function[2] but could be partially explained by its age-dependent role.[20,33] In aged controls older than 65 years, the Val/Val genotype may promote pro-BDNF secretion, which has a detrimental effect on neuronal vulnerability.[20]

The effect of the *BDNF* polymorphism on quality of life and nonmotor burden over the follow-up period was not significant in this study. Although the Met allele genotype significantly worsened in a linear fashion, it did not differ from the Val genotype.

This cohort did not demonstrate an effect of *BDNF* on global cognition, which is consistent with the findings of a previous study.[34] However, distinct genotypic patterns of cognitive deterioration were observed. A dynamic relationship was observed with the Val homozygote group. In the early stage, the attention/working memory domain was preserved by its physiologic maintenance of dopamine levels, but as the disease progressed, the Val/Val genotype showed accelerated worsening of frontal cognition because of its age-dependent detrimental effect.[1,2,20,33] This interpretation of an inverse relationship across disease spans was also supported by a previous longitudinal study with the *COMT* polymorphism.[34] The initial nonfrontal cognitive domain, which included delayed recall, was more preserved in the Met carriers.[35] The effect of *BDNF* was not affected by *APOE* genotype.

Cardiac denervation progressed linearly with disease duration, without the conditional influence of *BDNF* genotype.

This study encountered several limitations, including a substantial number of dropouts during the longitudinal follow-up, incomplete assessments conducted by certain individuals, and discrepancies in the timing of individual evaluations, which led to varying intervals. These shortcomings hindered the authors from disentangling the effect of dopaminergic supplementation across specific genotypes. It was paramount to adjust for the dopaminergic influence on motor severity, but owing to large dropouts, a mixed model with an additional time-varying predictor (levodopa-equivalent dose) at level 1 (within-person) was anticipated to fail in estimating the model. The study was thus predesigned to construct a parsimonious model with only one level-1 predictor, disease duration. As this study aimed to observe genotype-specific natural disease progression in real-world clinical practice, our model sufficiently aligned with this objective. Motor severity was not evaluated during the OFF state, except at baseline. This might have led to a biased estimate of the association between genotype and motor progression because of unstandardized medication effects on each individual patient. However, there is no standardized method to ensure a total washout OFF state because of the long-duration response to levodopa in treated PD patients.[36] The optimal medical response is also subjective for each patient; thus, the study investigated the optimal motor ON state for standardized measurements. It was also not feasible to withdraw medications long enough to obtain a full OFF state in clinical practice for chronic PD. This study did not rate Hoehn and Yahr staging to evaluate overall motor progression because it did not fully represent the clinical status, and its clinimetric properties were not well suited for the purpose of this study.[37] Finally, the effect of cognition-enhancing medications was not adjusted in the models, which could be the source of type II error in Model 3 (Supplementary Table 3).

The strength of this study is that the cohort comprises a relatively large population with extensive examinations and a lengthy follow-up period. A previous study used a longitudinal design to examine the influence of *BDNF* polymorphisms; however, the follow-up duration was too short, allowing assessment of changes in outcome measures from baseline at only a single time point. Limited domains of PD have also been investigated.[33] In contrast, our study's prolonged follow-up periods enabled the two neurologists to exclude atypical parkinsonian disorders that could mimic PD in their early diagnosis and maintain the validity of the cohort. The dataset also included both clinical metrics that fully captured the motor and nonmotor domains of the disease and objective surrogates of central and peripheral pathobiology. Extensive examinations conducted across the disease course allowed the prediction of protracted disease progression trajectories that would not have been possible with shorter follow-up periods. The mixed model adequately analyzed these unevenly spaced longitudinal data, which inevitably entailed missing data and autoregression. By providing cross-sectional and within-person longitudinal data, our study uniquely captured both early-stage PD at baseline and disease progression over time stratified by genotype. These findings were unprecedented compared with those of previous cross-sectional and

longitudinal studies.[10,11,35] The orthostatic challenge was specified by the MAP at the upright position (MAP75). Neurogenic OH with MAP75 further detailed cardiovascular dysautonomia to fully portray clinically significant OH. Our data also excluded the confounding effect of *APOE* polymorphism, as it occurred even across the *BDNF* genotypes.[38]

It has been widely reported that the frequencies of *BDNF* genotypes differ across ethnicities, and their effects on PD patients in a Korean cohort have rarely been investigated. The considerable differences in myocardial denervation at diagnosis and nonmotor burden and motor progression might suggest a differential ethnic role of *BDNF* polymorphism in disease evolution in PD among the Korean population.

Supplementary Materials

The Data Supplement is available with this article at https://doi.org/10.14802/jmd.25300.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Sang-Won Yoo, Yun Joong Kim, Joong-Seok Kim. Data curation: Sang-Won Yoo, Dong-Woo Ryu, Yoonsang Oh, Seunggyun Ha, Joong-Seok Kim. Formal analysis: Sang-Won Yoo, Yun Joong Kim, Joong-Seok Kim. Funding acquisition: Sang-Won Yoo, Joong-Seok Kim. Investigation: all authors. Methodology: Sang-Won Yoo, Yun Joong Kim, Joong-Seok Kim. Project administration: Joong-Seok Kim. Resources: all authors. Software: Sang-Won Yoo, Yun Joong Kim, Seunggyun Ha, Joong-Seok Kim. Supervision: Joong-Seok Kim. Validation: all authors. Visualization: Sang-Won Yoo, Yun Joong Kim, Seunggyun Ha, Joong-Seok Kim. Writing—original draft: Sang-Won Yoo. Writing—review & editing: all authors.

ORCID iDs

Sang-Won Yoo	https://orcid.org/0000-0002-7988-0228
Yun Joong Kim	https://orcid.org/0000-0002-2956-1552
Dong-Woo Ryu	https://orcid.org/0000-0003-3390-4607
Yoonsang Oh	https://orcid.org/0000-0002-1566-6265
Seunggyun Ha	https://orcid.org/0000-0003-2016-1373
Joong-Seok Kim	https://orcid.org/0000-0001-8087-7977

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