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Pharmacogenomics-Guided Multi-Gene Therapy Yields Superior Motor Symptom Improvement Over Standard Treatment in Parkinson's Disease: Insights from a Small Real-World Prospective Cohort Study

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ABSTRACT

Dopamine replacement therapy forms the cornerstone of Parkinson's disease (PD) management; however, patient responses, drug tolerability, and safety outcomes vary widely, largely due to genetic variations affecting drug metabolism and action. Despite this, the potential of multigenetic pharmacogenomics-guided therapy (MPGT) to optimize treatment in PD has been insufficiently explored. This prospective cohort study aimed to investigate whether MPGT could improve motor function in PD patients. We followed 28 PD patients over four weeks. Among them, 22 underwent comprehensive pharmacogenomic testing, with 13 receiving treatment tailored according to their genetic profiles (MPGT group), while 15 received conventional therapy (TAU group). Baseline characteristics, changes in the Unified Parkinson's Disease Rating Scale (UPDRS) III total and sub-scores, and associations between specific single nucleotide polymorphisms (SNPs) and treatment outcomes were assessed using generalized linear models. At the end of the 4-week period, patients in the MPGT group showed significantly greater improvements in UPDRS III total scores ($p < 0.05$) and limb sub-scores ($p < 0.01$) than those in the TAU group. These differences remained significant after accounting for increases in levodopa equivalent daily dose ($p = 0.011$ and $p = 0.002$, respectively) and piribedil use ($p = 0.006$ and $p = 0.004$, respectively). Additionally, carriers of major homozygous alleles for rs4984241 (AA vs. AG+GG, $p = 0.003$), rs4680 (GG vs. GA+AA, $p = 0.013$), rs1076560/rs2283265 (CC vs. AC+AA, $p = 0.039$), and rs622342 (AA vs. AC, $p = 0.043$) experienced greater improvements in total UPDRS III, postural instability and gait difficulty (PIGD), rigidity, and tremor scores, respectively, compared to individuals carrying at least one minor allele. MPGT demonstrates considerable potential for personalizing PD treatment and enhancing motor outcomes, with certain SNPs appearing to influence response to long-term anti-parkinsonian therapy. Larger, well-designed studies are warranted to confirm these results and support broader clinical application.

Keywords: Personalized medicine, Parkinson's disease, Pharmacogenomics, Drug efficacy, Single nucleotide polymorphisms

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Introduction

Parkinson's disease (PD) ranks as the second most prevalent neurodegenerative disorder worldwide, following Alzheimer's disease (AD), and currently affects an estimated 6.1 million individuals, with risk increasing sharply with advancing age [1, 2]. The disease imposes profound physical, emotional, and socioeconomic burdens on patients, caregivers, and healthcare systems [2]. Central to PD management is dopamine replacement therapy (DRT), which aims to restore dopaminergic signaling in the nigrostriatal pathway. DRT strategies include levodopa-based therapies, dopamine receptor agonists (e.g., pramipexole, rotigotine, ropinirole), monoamine oxidase-B inhibitors (selegiline, rasagiline, zonisamide), and catechol-O-methyltransferase inhibitors (entacapone, tolcapone, opicapone). Additional options such as anticholinergics (trihexyphenidyl, benztropine) and amantadine are often used to complement dopaminergic therapies [3].

In practice, PD patients frequently receive combination regimens to achieve maximal symptom control while minimizing adverse effects from high-dose monotherapy. However, clinical responses to these drugs are heterogeneous, partly due to individual genetic differences. Pharmacogenomic studies indicate that single nucleotide polymorphisms (SNPs) within dopamine-related genes can influence PD susceptibility [4], the risk of adverse drug reactions [5-10], and therapeutic efficacy [11-16]. Despite these associations, the extent to which genetic profiling can guide individualized PD therapy remains uncertain.

Recent advances in commercial multigenic pharmacogenomic testing allow simultaneous assessment of multiple variants to inform drug selection, often outperforming single-gene approaches in predicting clinical outcomes [17]. While MPGT has shown benefits in psychiatric conditions [18- 20], its role in PD has not been fully explored. This study aimed to prospectively evaluate the impact of MPGT on motor outcomes in PD patients compared with standard treatment (TAU) and to examine how specific SNPs influence responses to chronic anti-parkinsonian medications.

Materials and Methods

Participants

A total of 35 PD patients admitted to the Geriatric Neurological Department of the Chinese PLA General Hospital between July and December 2023 were consecutively recruited. Diagnosis followed the 2015 Movement Disorder Society clinical criteria. Patients with atypical parkinsonian syndromes (e.g., multiple system atrophy, progressive supranuclear palsy, secondary parkinsonism), those with predominantly non-motor complaints despite controlled motor symptoms, or patients harboring pathogenic mutations in monogenic PD genes were excluded. Twenty-eight patients completed the 4-week follow-up after medication adjustments. Among them, 22 underwent multigenic pharmacogenomic testing, with 13 receiving MPGT-directed therapy (MPGT group). The remaining 15 patients, including those who were either untested or tested post-adjustment, received standard care (TAU group). All medication changes were conducted by the same experienced movement disorder specialist. The study received ethical approval from the Chinese PLA General Hospital Ethics Committee, and written informed consent was obtained from all participants.

Clinical assessments

Baseline demographic and clinical data—including age, sex, and disease duration—were collected. Motor and non-motor symptoms were evaluated in the "ON" state. Baseline assessments included MDS-UPDRS I–IV, Hoehn and Yahr stage, and levodopa equivalent daily dose (LEDD). Cognitive function was assessed using MMSE and MoCA (Beijing Version), and quality of life using PDQ-39. Disease duration was defined as the interval from onset of first motor symptoms to study enrollment. UPDRS III was reassessed at week 4, and sub-scores for rigidity (items 3.3a–e), tremor (items 3.15–3.18), postural instability and gait difficulty (PIGD, items 3.9–3.13), and limb function (items 3.4–3.8) were computed. Treatment effectiveness was measured as reductions in UPDRS III total and sub-scores at follow-up. Changes in LEDD and in doses of levodopa/benserazide, carbidopa-levodopa, entacapone, pramipexole, piribedil, amantadine, selegiline, and rasagiline were also documented.

Multigenetic pharmacogenomic testing

Eighteen alleles across 12 genes known to influence metabolism, efficacy, or adverse effects of anti-parkinsonian drugs were genotyped. Genomic DNA was extracted from buccal samples and analyzed using the MassArray (MALDI-TOF MS) platform by Conlight Medical Inc. (Shanghai, China). Medications were categorized per patient into: (1) "use as directed," indicating minimal gene-drug interaction; (2) "moderate gene-drug interaction," warranting monitoring or dose adjustment; and (3) "significant gene-drug interaction," requiring blood level monitoring or alternative therapy. Thirteen commonly used anti-parkinsonian drugs were included: levodopa, pramipexole, piribedil, ropinirole, selegiline, rasagiline, entacapone, tolcapone, amantadine, rotigotine, benzhexol, istradefylline, and zonisamide.

Statistical analysis

Continuous variables were summarized as either mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for skewed distributions. Comparisons between groups used two-tailed

ANOVA for normally distributed variables and Mann-Whitney U tests for non-normal data. Categorical variables were examined with χ^2 or Fisher's exact tests, and genotype distributions were checked for Hardy-Weinberg equilibrium using χ^2 tests. To explore the influence of genetic variants on short-term treatment response, dominant (aa + Aa vs. AA), recessive (aa vs. Aa + AA), and additive (AA vs. Aa vs. aa) genetic models were applied. Potential confounders, including changes in levodopa equivalent daily dose (LEDD) or piribedil, were controlled using generalized linear modeling. Statistical significance was defined as $p < 0.05$ (two-tailed). Analyses were performed in SPSS v26.0 (IBM), and graphical representations were created in R v4.3.1.

Results and Discussion

Baseline demographics and clinical profile

The baseline characteristics of the 28 patients completing the study are presented in **Table 1**. The MPGT cohort (n = 13) had a mean age of 69.7 ± 7.7 years (range 55–81), with a median disease duration of 4.87 ± 3.44 years (range 1–13). In the TAU cohort (n = 15), mean age was 67.4 ± 6.1 years (range 54–76), and median disease duration was 3.72 ± 2.16 years (range 0.5–8). No statistically significant differences were observed between the groups in age, sex distribution, or disease duration. Medication adjustments during the study period revealed a significant increase in piribedil dose in the MPGT group compared with the TAU group ($z = -2.082$, $p < 0.05$), whereas changes in other anti-parkinsonian drugs did not differ significantly between groups **(Table 1).**

Table 1. Comparing of baseline demographics and clinical characteristics, as well as changes in medication doses between the two groups.

Characteristics	MPGT (n = 13)	TAU (n = 15)	χ^2/t/z	p-value
Gender (Male/Female)	9/4	6/9	2.392	0.122
Age (years)	69.69 ± 7.65	67.40 ± 6.14	−0.879	0.387
Disease duration (years)	4.87 ± 3.44	3.72 ± 2.16	−1.074	0.293
Duration of medication (years)	0.5 (0, 4.4)	1.6 (0.1, 3.3)	−0.465	0.642
MDS-UPDRS I	8.92 ± 4.84	8.87 ± 6.09	−0.027	0.979
MDS-UPDRS II	15.85 ± 8.26	11.40 ± 6.62	−1.581	0.126
MDS-UPDRS III	38.54 ± 8.80	31.87 ± 18.44	−1.247	0.226
MDS-UPDRS IV	0 (0, 0)	0 (0, 1.0)	−0.546	0.717
H&Y stage	2.0 (2.0, 2.5)	2.0 (1.0, 3.0)	−1.015	0.310
MMSE	26.00 ± 3.79	27.07 ± 2.58	0.882	0.386
MoCA	21.62 ± 5.55	22.13 ± 3.57	0.284	0.779
PDQ-39	38.69 ± 27.20	33.00 ± 21.31	−0.621	0.540
Baseline LEDD (mg)	319.23 ± 311.49	310.32 ± 311.48	−0.604	0.551
Medication (mg)				
Δlevodopa and benserazide	125.0 (0.281.3)	62.5 (0.187.5)	−0.314	0.753
Δcarbidopa-levodopa	0 (0.0)	0 (0.62.5)	−1.727	0.084
Δentacapone	0 (0.250.0)	0 (0.100.0)	−0.485	0.628
Δpramipexole	0 (0.0.750)	0 (0.0.375)	−0.528	0.597
Δpiribedil	0 (0.50.0)	0 (0.0)	−2.082	0.037*
Δamantadine	0 (0.0)	0 (0.0)	−0.345	0.730
Δselegiline	0 (0.0)	0 (0.0)	−0.414	0.679
Δrasagiline	0 (0.0)	0 (0.0)	−1.074	0.283
Δtrihexyphenidyl	0 (0.0)	0 (0.0)	−1.074	0.283
ΔLEDD (mg)	240.02 ± 214.93	185.68 ± 165.72	−0.760	0.454

Note: Values are presented as mean ± standard deviation for normally distributed variables and as median (lower quartile, upper quartile) for variables with non-normal distribution. Abbreviations: MDS-UPDRS, Movement Disorder Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale; H-Y stage, Hoehn and Yahr stage; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PDQ-39, 39-item Parkinson's Disease Questionnaire; LEDD, levodopa equivalent daily dose.

*Indicates $p < 0.05$.

Treatment outcome comparison between the two groups

Patients in the MPGT group experienced a notably larger decrease in UPDRS III scores (9.46 ± 5.47 vs. 2.69 ± 7.95; t = −2.586, p < 0.05) and limb sub-scores (4.08 ± 2.66 vs. 1.00 ± 2.75; t = −2.996, p < 0.01) from baseline to follow-up than those in the TAU group **(Figure 1)**. These improvements remained statistically significant even after adjusting for increases in LEDD (OR = −6.22, 95% CI: −11.03–1.42, p = 0.011, and OR = −3.08, 95% CI: −5.04–1.12, p = 0.002, respectively) or piribedil use (OR = −7.50, 95% CI: −12.83–2.16, p = 0.006, and OR = −3.06, 95% CI: −5.17–0.96, p = 0.004, respectively).

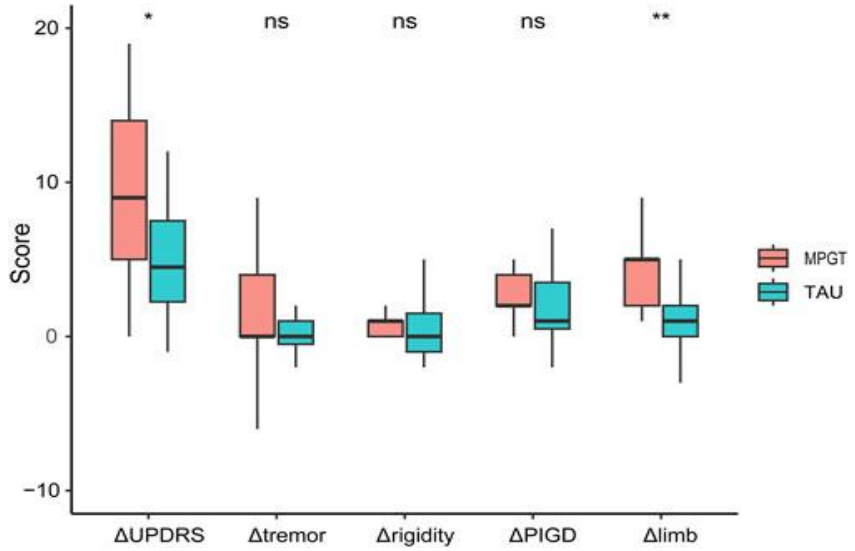

Figure 1. Four-week comparison of reductions in UPDRS III total and sub-scores between the two treatment groups. *p < 0.05; **p < 0.01; ns, not significant. Abbreviations: UPDRS III, Part III of the Movement Disorder Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale; PIGD, postural instability and gait difficulty.

Influence of genetic variants on treatment outcomes

To investigate how specific genetic polymorphisms affected therapeutic response, all 22 patients who underwent comprehensive pharmacogenomic testing were analyzed. The allele frequencies of the examined variants were in agreement with Hardy-Weinberg equilibrium. Among these, the DRD2 polymorphisms rs2283265 and rs1076560 were found to be closely linked, consistent with previous findings [21] **(Table 2).**

Table 2. Target genotype distribution (n = 22).

SNP	Gene	Major/Minor allele	MAF[a]	Genotype	Frequencies, n (%)	HWE, p-value
rs4984241	*CA12*	A/G	0.41	AA	8 (36.4)	0.071
				AG	5 (22.7)	
				GG	9 (40.9)	
rs4680	*COMT*	G/A	0.28	GG	11 (50.0)	0.794
				GA	10 (45.5)	
				AA	1 (4.5)	
rs1799732	*DRD2*	G/-	0.1	GG	17 (77.3)	0.856
				G/-	5 (22.7)	
				−/−	0 (0)	
rs1076560	*DRD2*	C/A	0.42	CC	4 (18.2)	0.441
				AC	14 (63.6)	
				AA	4 (18.2)	

rs2283265	*DRD2*	C/A	0.25	CC	4 (18.2)	0.441
				AC	14 (63.6)	
				AA	4 (18.2)	
rs6280	*DRD3*	T/C	0.31	TT	8 (36.4)	0.697
				CT	12 (54.5)	
				CC	2 (9.1)	
rs76126170	*DRD3*	C/T	0.13	CC	19 (86.4)	0.950
				CT	3 (13.6)	
rs9817063	*DRD3*	T/C	0.45	TT	7 (31.8)	0.998
				CT	11 (50.0)	
				CC	4 (18.2)	
rs9868039	*DRD3*	G/A	0.37	GG	7 (31.8)	0.441
				AG	8 (36.4)	
				AA	7 (31.8)	
rs622342	*SLC22A1*	A/C	0.14	AA	18 (81.8)	0.865
				AC	4 (18.2)	
rs4704559	*HOMER1*	A/G	0.09	AA	18 (81.8)	0.199
				AG	3 (13.6)	
				GG	1 (4.5)	
rs3832043	*UGT1A9*	(T)10/(T)9	0.03	2(T)10	6 (27.3)	0.224
				(T)10/(T)9	13 (59.1)	
				2(T)9	3 (13.6)	

[a] Based on allele frequencies reported for East Asian populations in the NCBI SNP database.
SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium.

Regarding CA12 rs4984241, patients with the AA genotype (n = 8) were significantly older than those with AG or GG genotypes (n = 14) ($p < 0.01$). No notable differences in baseline characteristics were found among genotype groups for COMT rs4680, DRD2 rs1076560/rs2283265, or SLC22A1 rs622342 **(Table 3)**. Because of the limited number of participants, DRD2 rs1799732 and DRD3 rs76126170 could not be evaluated in dominant models for their association with UPDRS motor scores. Additionally, COMT rs4680, DRD3 rs6280, DRD2 rs1799732, DRD3 rs76126170, HOMER1 rs4704559, and UGT1A9 rs3832043 were excluded from analyses employing recessive or additive models.

Table 3. Baseline characteristics of patients in each genotype group under the dominant model.

	rs4984241			**rs4680**			**rs1076560 and rs2283265**			**rs622342**		
Genotype	AA (n = 8)	AG + GG (n = 14)	p-value	GG (n = 11)	GA + AA (n = 11)	p-value	CC (n = 4)	AC + AA (n = 18)	p-value	AA (n = 18)	AC (n = 4)	p-value
Gender (Male/Female)	6/2	8/6	0.649	8/3	6/5	0.659	3/1	11/7	1.000	11/7	3/1	1.000

PDQ-39	MoCA	MMSE	H&Y stage	MDS-UPDRS IV	MDS-UPDRS III	MDS-UPDRS II	MDS-UPDRS I	Duration of medication (years)	Disease duration (years)	Age (years)
33.00 ± 25.69	23.57 ± 5.19	27.88 ± 2.10	2.0 (2.0, 2.5)	0 (0, 0)	34.25 ± 12.33	12.88 ± 7.22	6.50 ± 4.38	0.8 (0.2, 2.5)	4.91 ± 3.81	62.88 ± 6.27
37.71 ± 24.27	20.08 ± 4.92	25.71 ± 3.60	2.0 (1.9, 2.6)	0 (0, 5.0)	35.14 ± 15.54	14.86 ± 7.90	11.36 ± 5.83	2.2 (0, 5.3)	4.66 ± 2.35	71.07 ± 6.10
0.672	0.154	0.139	0.914	0.207	0.891	0.566	0.055	0.654	0.851	0.007**
37.18 ± 30.41	23.27 ± 4.65	27.00 ± 3.10	2.0 (2.0, 2.5)	0 (0, 1.0)	38.82 ± 8.73	16.55 ± 8.70	9.27 ± 4.84	1.0 (0, 6.5)	5.12 ± 3.49	68.91 ± 7.96
34.82 ± 17.63	18.89 ± 4.96	26.00 ± 3.49	2.0 (1.0, 3.0)	0 (0, 4.0)	30.82 ± 17.59	11.73 ± 5.59	9.91 ± 6.79	2.3 (0, 3.5)	4.39 ± 2.21	67.27 ± 6.72
0.826	0.057	0.486	0.238	1.000	0.192	0.138	0.803	0.842	0.566	0.608
28.75 ± 13.89	21.67 ± 7.10	27.50 ± 2.65	2.0 (1.3, 2.0)	0 (0, 3.0)	29.50 ± 17.14	9.75 ± 5.06	6.00 ± 3.65	1.7 (0.1, 3.4)	4.13 ± 2.43	63.75 ± 8.77
37.61 ± 26.07	21.24 ± 5.04	26.28 ± 3.41	2.0 (2.0, 2.6)	0 (0, 2.0)	36.00 ± 13.69	15.11 ± 7.77	10.39 ± 5.91	1.3 (0, 5.3)	4.89 ± 3.01	69.06 ± 6.76
0.523	0.898	0.511	0.163	0.786	0.419	0.206	0.174	0.830	0.640	0.191
31.67 ± 17.70	20.81 ± 5.50	26.330 ± 3.52	2.0 (1.9, 2.6)	0 (0, 1.8)	35.83 ± 15.43	13.11 ± 5.48	9.28 ± 5.93	1.3 (0, 3.7)	4.82 ± 2.88	67.28 ± 7.40
55.50 ± 41.64	23.25 ± 3.40	27.25 ± 1.89	2.0 (2.0, 2.4)	0 (0, 8.3)	30.25 ± 4.35	18.75 ± 12.79	11.00 ± 5.48	2.3 (0.3, 5.8)	4.45 ± 3.27	71.75 ± 5.85
0.338	0.414	0.623	0.928	0.871	0.489	0.183	0.601	0.667	0.821	0.274

ΔLEDD (mg)	229.75 ± 251.77	154.82 ± 128.41	0.362	243.89 ± 223.06	120.25 ± 102.47	0.110	187.50 ± 145.06	180.86 ± 191.49	0.949	149.01 ± 112.80	330.81 ± 347.46	0.374

**$p < 0.01$.

In analyses using dominant genetic models, carriers of the CA12 AA genotype experienced a notably larger reduction in ΔUPDRS III compared with individuals carrying AG or GG genotypes, after accounting for age and ΔLEDD (AA vs. AG + GG, OR = 10.81, 95% CI: 3.65–17.97, p = 0.003). For COMT rs4680, significant improvement in the PIGD sub-score was observed for GG carriers relative to GA + AA carriers, both prior to (p = 0.028) and following adjustment for ΔLEDD (OR = 3.01, 95% CI: 0.63–5.39, p = 0.013). Patients with the CC genotype of DRD2 rs1076560/rs2283265 showed greater rigidity score reductions than those with AC or AA genotypes after ΔLEDD adjustment (CC vs. AC + AA, OR = 1.86, 95% CI: 0.09–3.62, p = 0.039). Similarly, tremor sub-scores decreased more in subjects carrying the SLC22A1 rs622342 AA genotype compared to AC carriers after accounting for ΔLEDD (OR = 3.90, 95% CI = 0.13–7.67, p = 0.043) **(Table 4)**. No significant links were detected between genotype and treatment response when evaluated under recessive or additive models (**Tables 5 and 6).**

Table 4. Effect of genotypes on the improvement of UPDRS motor scores after medication adjustment in dominant models (n = 22).

Gene	SNP	Genotype	Δ UPDRS III	Δ tremor	Δ rigidity	Δ PIGD	Δ limb
CA12	rs4984241	AA (n = 8)	8.25 ± 6.65	1.25 ± 4.95	1.13 ± 0.991	4.25 ± 3.77	3.88 ± 3.14
		AG+GG (n = 14)	3.88 ± 9.01	0.50 ± 2.85	0.07 ± 2.40	1.57 ± 2.28	2.07 ± 3.32
		t	1.194	0.455	1.175	2.092	1.250
		p-value	0.246	0.654	0.254	0.049*	0.226
		p^a-value	0.003**	0.776	0.708	0.085	0.003**
COMT	rs4680	GG (n = 11)	7.39 ± 5.33	1.27 ± 3.82	0.91 ± 1.45	4.00 ± 3.52	3.18 ± 2.44
		GA+AA (n = 11)	3.55 ± 10.47	0.27 ± 3.58	0.00 ± 2.49	1.09 ± 1.81	2.27 ± 4.05

DRD3	rs9817063		*DRD3*	rs6280			*DRD2*	rs1076560/rs2283265						
TT (n = 7)	p^b -value	*p*-value	*t*	CT + CC (n = 14)	TT (n = 8)	p^b -value	*p*-value	*t*	AC+AA (n = 18)	CC (n = 4)	p^b-value	*p*-value	*t/t'*	
8.00 ± 4.12	0.283	0.431	0.803	4.38 ± 9.52	7.38 ± 5.83	0.222	0.267	1.143	4.52 ± 8.32	9.75 ± 8.06	0.439	0.291	1.085	
0.00 ± 4.32	0.900	0.798	−0.259	0.93 ± 3.39	0.50 ± 4.31	0.850	0.873	−0.161	0.83 ± 3.35	0.50 ± 5.45	0.746	0.534	0.663	
0.14 ± 1.77	0.658	0.939	0.077	0.43 ± 2.38	0.50 ± 1.41	0.039*	0.094	1.756	0.11 ± 1.97	2.00 ± 1.83	0.694	0.308	1.047	
2.86 ± 2.80	0.184	0.547	−0.612	2.86 ± 3.23	2.00 ± 3.02	0.682	0.708	−0.379	2.67 ± 3.40	2.00 ± 1.41	0.013*	0.028*	2.436	
3.71 ± 2.36	0.573	0.500	0.688	2.36 ± 3.67	3.38 ± 2.62	0.208	0.244	1.201	2.33 ± 3.25	4.50 ± 3.32	0.537	0.531	0.637	

HOMER1	rs4704559	AA (n = 18)	AG + GG (n = 4)	*t*	*p*-value	p^b -value	*DRD3*	rs9868039	GG (n = 7)	AG+AA (n = 15)	*t/t'*	*p*-value	p^b -value	*t*	*p*-value	p^b -value	CT+CC (n = 15)
		5.13 ± 8.97	7.00 ± 5.23	−0.398	0.695	0.593			6.14 ± 7.67	5.15 ± 8.88	0.253	0.803	0.776	0.971	0.343	0.157	4.29 ± 9.62
		0.56 ± 3.88	1.75 ± 2.50	−0.583	0.567	0.473			−0.29 ± 0.95	1.27 ± 4.33	−1.321	0.204	0.091	−0.669	0.511	0.632	1.13 ± 3.40
		0.44 ± 2.26	0.50 ± 0.58	−0.048	0.962	0.802			1.43 ± 1.72	0.00 ± 2.07	1.583	0.129	0.415	−0.480	0.636	0.997	0.60 ± 2.20
		2.72 ± 3.43	1.75 ± 0.50	0.556	0.585	0.589			2.29 ± 1.89	2.67 ± 3.60	−0.261	0.796	0.549	0.314	0.757	0.626	2.40 ± 3.33
		2.78 ± 3.52	2.50 ± 2.38	0.149	0.883	0.892			2.57 ± 2.94	2.80 ± 3.55	−0.148	0.884	0.768	0.957	0.350	0.270	2.27 ± 3.63

SLC22A1	rs622342	AA (n = 18)	4.91 ± 8.96	1.22 ± 3.77	0.11 ± 1.78	2.44 ± 3.37	2.72 ± 3.61
		AC (n = 4)	8.00 ± 4.69	−1.25 ± 2.50	2.00 ± 2.71	3.00 ± 1.83	2.75 ± 1.50
		t	−0.662	1.241	−1.756	−0.316	−0.015
		p-value	0.516	0.229	0.094	0.755	0.988
		p^b -value	0.807	0.043*	0.274	0.917	0.926
UGT1A9	rs3832043	A(T)10AT (n = 6)	6.00 ± 2.19	0.67 ± 3.56	0.83 ± 1.94	2.00 ± 1.67	1.83 ± 0.75
		A(T)10AT/ A(T)9AT+A (T)9AT (n = 16)	5.27 ± 9.78	0.81 ± 3.80	0.31 ± 2.12	2.751 ± 3.53	3.06 ± 3.82
		t/t'	0.281	−0.081	0.524	−0.494	−0.771
		p-value	0.782	0.936	0.606	0.627	0.450
		p^b -value	0.872	0.683	0.945	0.466	0.354

[a] Adjusted for increased levodopa equivalent daily dose (ΔLEDD) and age.
[b] Adjusted for increased levodopa equivalent daily dose (ΔLEDD).
*p < 0.05; **p < 0.01.

Table 5. Effect of genotypes on the improvement of UPDRS motor scores after medication adjustment in recessive models (n = 22).

Gene	SNP	Genotype	Δ UPDRS III	Δ tremor	Δ rigidity	Δ PIGD	Δ limb
CA12	rs4984241	GG (n = 9)	4.56 ± 11.23	0.78 ± 2.77	−0.11 ± 2.47	1.33 ± 1.80	2.11 ± 4.14
		AG+AA (n = 13)	6.10 ± 6.07	0.77 ± 4.27	0.85 ± 1.68	3.38 ± 3.60	3.15 ± 2.67

												t	−0.418	0.005	−1.086	−1.572	−0.721
												p-value	0.680	0.996	0.290	0.132	0.479
												p^a-value	0.706	0.942	0.260	0.105	0.458
DRD2												AA (n = 4)	−1.17 ± 12.40	0.25 ± 2.87	−0.25 ± 3.40	1.75 ± 3.86	0.25 ± 4.57
												AC+CC (n = 18)	6.94 ± 6.80	0.89 ± 3.86	0.61 ± 1.72	2.72 ± 3.03	3.28 ± 2.82
												t	−1.861	−0.310	−0.756	−0.556	−1.739
												p-value	0.078	0.760	0.459	0.585	0.097
												p^a-value	0.067	0.852	0.580	0.612	0.071
												CC (n = 4)	6.50 ± 10.54	−0.75 ± 0.96	2.00 ± 2.16	2.50 ± 2.65	2.25 ± 3.78
												CT+TT (n = 18)	5.24 ± 8.13	1.11 ± 3.95	0.11 ± 1.91	2.56 ± 3.28	3.83 ± 3.29
												t	0.267	−0.919	1.756	−0.032	−0.313
												p-value	0.792	0.369	0.094	0.975	0.757
												p^a-value	0.671	0.051	0.429	0.678	0.582
DRD3												rs9868039	AA (n = 7)					
													8.00 ± 4.12	0.00 ± 4.32	0.14 ± 1.77	2.86 ± 2.80	3.71 ± 2.36
													rs9817063					
													DRD3					
													rs1076560/rs2283265					
													DRD2					

		AG+GG (n = 15)	4.29 ± 9.62	1.13 ± 3.40	0.60 ± 2.20	2.40 ± 3.33	2.27 ± 3.63
		t	0.971	−0.669	−0.480	0.314	0.957
		p-value	0.343	0.511	0.636	0.757	0.350
		p[a]-value	0.157	0.632	0.997	0.626	0.270

[a] Adjusted for increased levodopa equivalent daily dose (ΔLEDD) and age.
*$p < 0.05$; **$p < 0.01$.

Table 6. Effect of genotypes on the improvement of UPDRS motor scores after medication adjustment in additive models (n = 22).

Gene	SNP	Genotype	Δ UPDRS III	Δ tremor	Δ rigidity	Δ PIGD	Δ limb
CA12	rs4984241	AA (n = 8)	8.25 ± 6.65	1.25 ± 4.95	1.13 ± 0.99	4.25 ± 3.77	3.88 ± 3.14
		AG (n = 5)	2.66 ± 2.99	0.00 ± 3.24	0.40 ± 2.51	2.00 ± 3.16	2.00 ± 1.23
		GG (n = 9)	4.56 ± 11.23	0.78 ± 2.77	−0.11 ± 2.47	1.33 ± 1.80	2.11 ± 4.14
		F	0.764	0.166	0.762	2.179	0.745
		p-value	0.480	0.848	0.481	0.141	0.488
		p[a]-value	0.541	0.915	0.515	0.096	0.437
DRD2	rs1076560/rs2283265	CC (n = 4)	9.75 ± 8.06	0.50 ± 5.45	2.00 ± 1.83	2.00 ± 1.41	4.50 ± 3.32
		AC (n = 14)	6.14 ± 6.50	1.00 ± 3.55	0.21 ± 1.53	2.93 ± 3.36	2.93 ± 2.70

DRD3	rs9868039	*F*	AA (n = 7)	AG (n = 8)	GG (n = 7)	p^a-value	*p*-value	*F*	CC (n = 4)	CT (n = 11)	TT (n = 7)	p^a-value	*p*-value	*F*	AA (n = 4)
		0.781	8.00 ± 4.12	2.66 ± 11.32	6.14 ± 7.67	0.366	0.537	0.642	6.50 ± 10.54	3.48 ± 9.67	8.00 ± 4.12	0.117	0.160	2.018	−1.17 ± 12.40
		1.251	0.00 ± 4.32	2.38 ± 4.31	−0.29 ± 0.95	0.079	0.404	0.951	−0.75 ± 0.96	1.82 ± 3.74	0.00 ± 4.32	0.956	0.931	0.072	0.25 ± 2.87
		1.228	0.14 ± 1.77	−0.12 ± 2.42	1.43 ± 1.72	0.718	0.256	1.466	2.00 ± 2.16	0.09 ± 2.07	0.14 ± 1.77	0.118	0.236	1.562	−0.25 ± 3.40
		0.055	2.86 ± 2.80	2.50 ± 4.38	2.29 ± 1.89	0.846	0.952	0.049	2.50 ± 2.65	2.36 ± 3.67	2.86 ± 2.80	0.758	0.761	0.278	1.75 ± 3.86
		0.491	3.71 ± 2.36	2.00 ± 4.34	2.57 ± 2.94	0.518	0.653	0.435	2.25 ± 3.78	2.27 ± 3.77	3.71 ± 2.36	0.118	0.180	1.878	0.25 ± 4.57

p-value	0.472	0.309	0.315	0.947	0.620
p^a-value	0.348	0.080	0.668	0.807	0.536

[a] Adjusted for increased levodopa equivalent daily dose (ΔLEDD) and age.
$^*p < 0.05$; $^{**}p < 0.01$.

To our knowledge, this study represents the first real-world, longitudinal, prospective cohort investigation assessing the effectiveness of MPGT in Chinese patients with Parkinson's disease (PD). Our findings indicate that individuals in the MPGT group experienced greater improvements in motor symptoms, particularly limb bradykinesia. Notably, patients carrying the CA12 AA genotype showed enhanced responsiveness to adjustments in anti-parkinsonian therapy. In addition, COMT GG homozygotes and DRD2 CC homozygotes demonstrated superior improvements in PIGD and rigidity, respectively, compared with other allele carriers, while the SLC22A1 A > C variant was associated with a diminished tremor response.

As genome-informed therapeutic strategies gain traction in personalizing drug dosing and selection, research has focused on understanding how specific gene variants influence both efficacy and side effects of dopaminergic medications. Despite this, pharmacogenomic guidance for PD remains limited, with no formal clinical recommendations established. In the PharmGKB database, data on PD are sparse, comprising only nine clinical annotations, most supported by low-level evidence. In our study, the multigenetic pharmacogenomic panel encompassed all variants listed in PharmGKB clinical annotations. Variants in drug-metabolizing enzymes, including CYP1A2 (linked to ropinirole and rasagiline responses) and CYP3A4 (linked to istradefylline response), were identified [22]. Additional detected variants were associated with therapeutic outcomes or adverse effects, such as DRD3 rs76126170, rs9817063, and rs9868039 for piribedil response [16]; CA12 rs2306719, rs4984241, and HLA-A for zonisamide-related adverse effects [23, 24]; APOE for adverse reactions to DRT [25] or trihexyphenidyl [26]; and UGT1A9*22 for entacapone or tolcapone toxicity [27]. In our cohort, piribedil dosage increased more frequently in the MPGT group, suggesting that pharmacogenomic insights influenced drug selection, although no significant differences in ΔLEDD were observed between groups. Overall, patients guided by MPGT achieved greater reductions in UPDRS III and limb sub-scores, likely reflecting synergistic effects of optimized medication combinations.

Unlike conditions often managed with monotherapy, initial PD treatment commonly involves levodopa, sometimes combined with dopamine agonists or MAO-B inhibitors [3]. As PD progresses, COMT inhibitors are added to prolong levodopa's benefit, while amantadine and trihexyphenidyl are reserved for specific indications. Limited availability of other drug classes in our practice meant that individualized therapy primarily relied on selecting suitable dopamine agonists and deciding on the addition of entacapone. Piribedil was frequently recommended because three DRD3 SNPs (rs76126170, rs9817063, rs9868039) were linked to treatment response [16], with no prior associations to adverse effects. In our MPGT cohort, four patients received piribedil based on test guidance; one discontinued due to nausea and vomiting, emphasizing the need to integrate SNPs associated with both efficacy and tolerability into MPGT algorithms. Regarding levodopa, although robust pharmacogenomic evidence exists for its side effects, only SLC6A3 rs3836790 has been linked to motor response [28], and we did not replicate this association, consistent with findings from a Chinese cohort [29]. Consequently, levodopa was not selected as the optimal agent for any patient, highlighting the need to identify additional genes and loci that influence the effectiveness and safety of commonly used PD medications.

While all investigated SNPs have been previously reported, their impact under chronic, multi-drug therapy remains largely untested. To address this, we examined the influence of each genotype on treatment outcomes. Unexpectedly, CA12 variants were associated with motor response. CA XII, a major renal isoform, plays a crucial role in proximal tubule bicarbonate reabsorption and distal tubule acidification [30]. The rs4984241 AA genotype has been linked to lower serum bicarbonate in patients receiving topiramate or zonisamide [23], and prior studies show that amantadine uptake in proximal tubules is bicarbonate-dependent [31]. We hypothesize that the CA12 rs4984241 variant may enhance cellular uptake of certain anti-parkinsonian drugs such as amantadine. Nevertheless, its potential as a biomarker for treatment response requires further investigation.

Another variant, COMT rs4680 (G > A), which is associated with reduced COMT enzyme activity, has been linked to higher levodopa dosages, suggesting improved responsiveness to long-term levodopa therapy [32-34]. Conversely, individuals with the high-activity GG genotype have been shown to exhibit greater benefit from entacapone treatment [35]. In our cohort, patients carrying the GG genotype demonstrated more pronounced improvement in PIGD sub-scores following medication adjustment, an effect likely reflecting combined responses to multiple anti-parkinsonian agents rather than a single drug.

Our findings also corroborate the role of DRD2 rs1076560/rs2283265 in modulating motor response to treatment. Previous studies reported that CC homozygotes for these SNPs achieved earlier and more substantial symptomatic improvement with rasagiline therapy compared with A allele carriers [13]. Additionally, A allele carriers exhibited worse gait function relative to CC homozygotes under various anti-parkinsonian regimens [15]. Consistent with these observations, CC carriers in our study showed greater reduction in rigidity after adjusting therapy.

Regarding tremor, patients carrying the C allele of SLC22A1 rs622342 demonstrated a reduced response to medication adjustments. The SLC22A1 gene encodes the organic cation transporter 1 (OCT1), which facilitates cellular uptake of drugs including metformin, amantadine, pramipexole, and potentially levodopa [31, 36-39]. The minor C allele is thought to reduce OCT1 transporter function, which aligns with previous population-based findings where C allele carriers required higher doses of anti-parkinsonian medications, reflecting lower responsiveness [12].

Other variants, such as SLC6A3 rs3836790 and several DRD3 polymorphisms previously associated with responses to levodopa [28], pramipexole [11, 14], or piribedil [16], did not show significant associations with outcomes under repeated administration of multiple medications in our study.

A key strength of this work is its prospective, longitudinal design, which allowed us to demonstrate that integrating clinical expertise with MPGT can enhance therapeutic response in Chinese PD patients. All participants were carefully evaluated to exclude atypical Parkinson's syndromes through follow-up and dopaminergic imaging, and patients with prominent non-motor symptoms or monogenic forms of PD were excluded where possible to reduce heterogeneity.

However, several limitations must be acknowledged. The relatively small sample size limited our ability to evaluate adverse effects: only one advanced PD patient developed dyskinesia, and another experienced gastrointestinal issues following piribedil therapy, making meaningful comparisons between groups and genotype associations difficult. Additionally, the observational nature of the study meant that patients were not randomized and raters were not blinded; a double-blinded, randomized trial is required to validate these results. Finally, pharmacogenomic algorithms should consider ethnic differences and SNPs that influence responses to acute challenges versus chronic therapy. Broader implementation of personalized PD treatment will require identification and validation of additional gene variants affecting pharmacokinetics and pharmacodynamics.

Conclusion

In conclusion, our findings suggest that pharmacogenomics-guided therapy may enhance motor outcomes in PD patients, though large-scale randomized controlled trials are necessary to confirm these benefits.

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