

## **Appendix e-1. Supplemental Methods**

We classified PD as manifesting the tremor dominant (TD) or postural instability-gait disturbance (PIGD) phenotypes based on method previously described.<sup>1,2</sup> The following 11 MDS-UPDRS tremor items and 5 MDS-UPDRS PIGD items were used for the categorization.

### 11 MDS-UPDRS tremor items:

2.10. Tremor, 3.15a. Postural Tremor RUE, 3.15b. Postural Tremor LUE, 3.16a. Kinetic Tremor RUE, 3.16b. Kinetic Tremor LUE, 3.17a. Rest Tremor RUE, 3.17b. Rest Tremor LUE, 3.17c. Rest Tremor RLE, 3.17d. Rest Tremor LLE. 3.17e. Rest Tremor Lip/jaw, 3.18. Rest Constancy,

### 5 MDS-UPDRS PIGD items:

2.12. Walking Balance, 2.13. Freezing, 3.10. Gait, 3.11. Freezing of Gait, 3.12 Postural Stability were used for the categorization.

We first calculated the tremor and PIGD scores as the mean of the “11 tremor items” and of “5 PIGD items”, respectively. Then, we derived a tremor/PIGD ratio score and classified PD patients as TD if the ratio scores were  $\geq 1.15$ , as PIGD if the ratio scores was  $\leq 0.9$ , or as IND if the ratio score was between 0.9–1.15, or if both tremor and PIGD scores were zero. We assigned patients with a PIGD score of zero but TD score greater than zero to the TD phenotype. This classification method arises from the previous study<sup>1</sup> and discussion with PD specialists.

## Appendix e-2. Non-motor Assessment Questionnaires

<b>Sleep Disorder Tests</b>
Epworth Sleepiness Scale (ESS) REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)
<b>Olfactory Test</b>
University of Pennsylvania Smell Identification Test (UPSIT)
<b>Neurobehavioral Tests</b>
State-Trait Anxiety Inventory for Adults (STAI) <sup>a</sup> Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-Short) Geriatric Depression Scale (Short Version) (GDS-15)
<b>Autonomic Tests</b>
Scales for Outcomes in Parkinson's Disease-Autonomic Questionnaire (SCOPA-AUT)
<b>Neuropsychological Tests and Cognitive Domains</b>
<i>Global</i> Montreal Cognitive Assessment (MoCA)
<i>Memory</i> Hopkins Verbal Learning Test – Revised (HVLT-R) <sup>a</sup>
<i>Visuospatial</i> Benton Judgment of Line Orientation (JOLO) (15-item version)
<i>Working memory-executive</i> Letter Number Sequencing (LNS) Semantic Fluency (Animal, Vegetable, Fruit) <sup>c</sup>

Attention-processing speed

Symbol Digit Modalities Test (SDMT)

<sup>a</sup> Subcategories of STAI (trait vs. state anxiety) and HVLT-R (immediate vs. delayed recall vs. delayed recognition) were included to allow a more holistic examination of these possible symptoms.

<sup>c</sup> Since established normalized scores exist only for animal fluency, we therefore did not include results on vegetable and fruit fluency in our analyses.

**Table e-1.** Sex-specific differences among neuropsychological assessments in patients with PD and in healthy controls.

Neuropsychological Tests	PD				Healthy Controls				P <sub>interaction</sub>
	Total (n=414)	Male (n=269)	Female (n=145)	P Value <sup>a</sup>	Total (n=188)	Male (n=121)	Female (n=67)	P Value <sup>a</sup>	
Semantic fluency	51 (44-57)	51 (43-57)	51 (45-57)	0.96	52 (46-58)	51 (45-56)	53 (47-59)	0.22	0.34
Symbol digit modalities	46 (40-51)	45 (39-49.2)	47 (41.3-52)	0.29	50 (43.2-57)	48.8 (42.5-55)	52 (45-58.3)	<b>0.04</b>	0.27
MoCA	28 (26-29)	27 (26-29)	28 (26-29)	<b>0.0008</b>	28 (27-29)	28 (27-29)	28 (27-29)	0.52	0.06
Letter number sequencing	56.7(50-60)	53.3 (50-60)	56.7 (50-60)	0.38	56.7 (50-60)	56.7 (50-60)	56.7 (50-60)	0.71	0.47
Hopkins verbal learning									
Immediately recall	46 (39-54)	44 (37-52)	49.5 (43-57)	< <b>.0001</b>	51.0 (44-56)	49 (42-55)	52 (47-60)	<b>0.002</b>	0.85
Delayed recall	47 (38-55)	44 (37-53)	50 (41-56)	< <b>.0001</b>	53 (44-58)	51 (39-59)	55 (47-58)	<b>0.02</b>	0.16
Delayed recognition	49 (42-57)	47 (39-53)	52 (44-58)	<b>0.0001</b>	52 (45-58)	51 (44-58)	56 (51-59)	<b>0.01</b>	0.76
Benton judgment of line orientation	58.7 (52-64.7)	60.3 (55.1-66.7)	55.7 (46.6-60.6)	< <b>.0001</b>	59.5 (53.8-65.2)	60.9 (56.3-66.7)	55.8 (50-62.4)	<b>0.002</b>	0.80

Abbreviation: MoCA = Montreal Cognitive Assessment; PD = Parkinson disease.

Estimates are median (interquartile range) of normalized T-scores except for MoCA, which used the original scores.

<sup>a</sup> Based on quantile regression analysis adjusted for age and education.

**Table e-2.** Logistic regression models examining predictors of motor phenotypes among PD cases.

NMS <sup>a</sup>	TD	PIGD	IND
	(n=291)	(n=76)	(n=47)
<b>Sleep Disorder</b>			
Epworth sleepiness scale	<b>0.67 (0.52-0.87)</b>	<b>1.41 (1.06-1.88)</b>	1.30 (0.92-1.84)
RBDSQ	0.92 (0.71-1.19)	1.19 (0.88-1.59)	0.92 (0.65-1.32)
<b>Olfactory</b>			
UPSIT	0.95 (0.71-1.26)	0.97 (0.70-1.36)	1.17 (0.79-1.72)
<b>Neurobehavioral</b>			
State anxiety	1.00 (0.71-1.40)	0.81 (0.54-1.20)	1.33 (0.83-2.13)
Trait anxiety	0.86 (0.59-1.26)	1.54 (0.99-2.38)	0.74 (0.43-1.28)
Geriatric depression	0.80 (0.58-1.09)	1.28 (0.90-1.81)	1.06 (0.69-1.64)
<b>Cognitive Domains<sup>b</sup></b>			
Global	0.97 (0.77-1.23)	1.06 (0.81-1.39)	0.96 (0.69-1.34)
Memory	<b>1.40 (1.02-1.91)</b>	0.71 (0.49-1.03)	0.83 (0.54-1.28)
Visuospatial	0.84 (0.63-1.10)	1.07 (0.78-1.47)	1.35 (0.90-2.03)
Working Memory-Executive	0.75 (0.51-1.09)	1.33 (0.84-2.10)	1.25 (0.74-2.11)
Attention-Processing Speed	0.81 (0.59-1.10)	1.28 (0.89-1.84)	1.05 (0.69-1.61)
<b>Autonomic</b>			
SCOPA-AUT	1.07 (0.81-1.42)	<b>0.69 (0.49-0.98)</b>	<b>1.43 (1.00-2.06)</b>

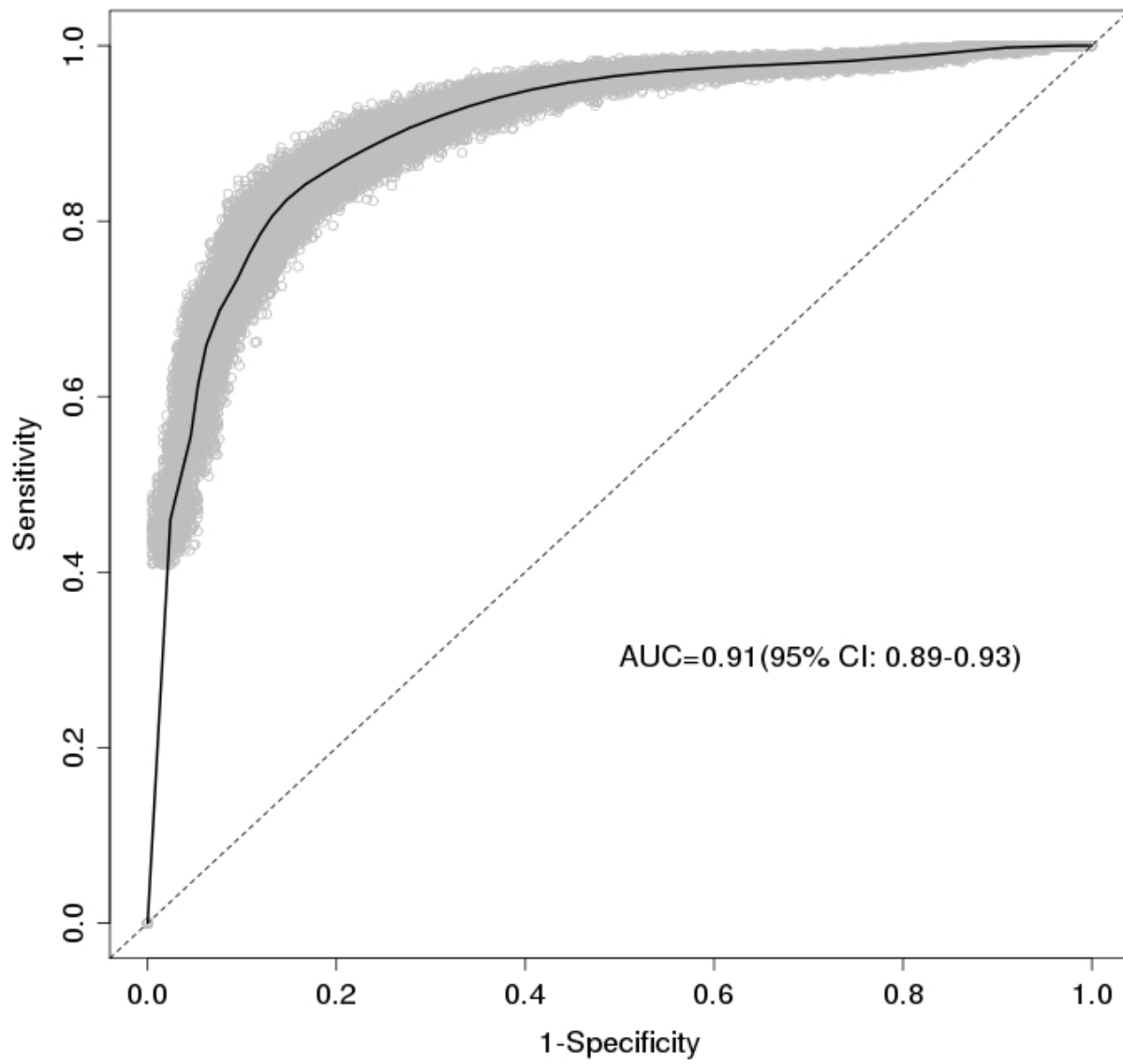
Abbreviations: IND = intermediate phenotype; NMS = non-motor symptoms; PIGD = postural instability-gait disturbance; SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; TD = tremor dominant; UPSIT = University of Pennsylvania Smell Identification Test.

Estimates are odds ratio (95% confidence interval) for each variable for all analyses.

<sup>a</sup> Standardized z-scores.

<sup>b</sup> The *global* domain included the Montreal Cognitive Assessment (MoCA) test. The *memory* domain included the immediate recall, delayed recall, and delayed recognition of the Hopkins Verbal Learning Test-Revised (HVLT-R). The *visuospatial* domain included the Benton Judgment of Line Orientation (JOLO). The *working memory-executive* domain included the Letter Number Sequencing (LNS) and the Semantic Fluency-Animal tests. The *attention-processing speed* included the Symbol Digit Modalities Test (SDMT).

**Figure e-1. The receiver operating characteristic curve (ROC) based on 1000 rounds of 3-fold cross-validation analyses.** In each round of analysis, we first randomly partitioned the full data set into 3 parts with the same case/control ratios in each part, then we used 2/3 of the data as the training set to select the top 5 NMS with best differentiation for building the predictor model (using a logistic regression model) and the other 1/3 as the test set to cross-validate the predictors. The black line is the averaged ROC across 1000 analyses, gray open circles denote 95% CI, and the dashed line is the reference line of area under the ROC curve (AUC) = 0.5. The most frequently selected variables across all analysis were: UPSIT, SCOPA-AUT, MoCA, State Anxiety, and RBDSQ. MoCA = Montreal Cognitive Assessment; RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; UPSIT = University of Pennsylvania Smell Identification Test.



## **e-References**

1. Jankovic J, McDermott M, Carter J, et al. Variable expression of Parkinson's disease: A base-line analysis of the DATATOP cohort. *Neurology* 1990;40:1529-34.
2. Kang JH, Irwin DJ, Chen-Plotkin AS, et al. Association of cerebrospinal fluid beta-amyloid 1-42, T-tau, P-tau181, and alpha-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. *JAMA Neurol* 2013;70:1277-1287.