

Table e-1: Demographic characteristics of each H&Y stage of PD patients.

	H&Y I	<i>p</i> -value ^a	H&Y II	<i>p</i> -value ^a	H&Y III	<i>p</i> -value ^a	H&Y IV	<i>p</i> -value ^a	H&Y V	<i>p</i> -value ^a	<i>p</i> -value ^b
Number	26	-	52	-	21	-	8	-	1	-	-
Sex (Male:Female)	12:14	0.635	29:23	0.222	8:13	0.749	5:3	0.465	0:1	-	-
Age [years], Mean ± SD	63.2 ± 10.4	1.000	67.4 ± 9.85	0.372	71.0 ± 8.56	0.080	69.0 ± 10.2	0.536	67.0	-	0.0492
Duration [years], Mean ± SD	3.68 ± 3.09	-	5.89 ± 0.69	-	7.76 ± 5.88	-	14.6 ± 10.3	-	10.0	-	<0.001
UPDRS part III, Mean ± SD	5.91 ± 4.00	-	13.0 ± 8.63	-	17.2 ± 7.95	-	27.7 ± 14.5	-	34.0	-	<0.001
LED, Mean ± SD	380 ± 219	-	590 ± 319	-	744 ± 281	-	891 ± 433	-	1650	-	<0.001
MMSE, Mean ± SD	28.9 ± 1.66	-	28.5 ± 1.82	-	28.6 ± 1.83	-	28.1 ± 1.54	-	29.0	-	0.579
Motor Fluctuation (%)	15	-	44	-	76	-	88	-	100	-	<0.001

Motor fluctuations include dyskinesia and wearing-off. The percentage of motor fluctuation positive rates are shown in parentheses.

Abbreviations: PD: Parkinson's Disease; H&Y stage: Hoehn and Yahr stage; SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale; LED: levodopa equivalent dose; MMSE: Mini Mental State Examination.

^a*p*-value obtained by the Steel's test comparing to the control.

^b*p*-value obtained by the analysis of covariance among the H&Y I-IV stages

Table e-2: Demographic characteristics of genomic analysis participants

	Control	PD	<i>p</i> -value ^a
Number	82	176	-
Sex (Male:Fmale)	38:44	91:85	0.422 ^b
Age [years], Mean \pm SD	66.0 \pm 13.6	67.3 \pm 10.4	0.156
Duration [years], Mean \pm SD	-	6.66 \pm 4.95	-
H&Y stage, Mean \pm SD	-	2.28 \pm 0.90	-
UPDRS part III, Mean \pm SD	-	14.89 \pm 10.12	-

Abbreviations: PD: Parkinson's Disease; SD: standard deviation; H&Y stage: Hoehn and Yahr stage; UPDRS: Unified Parkinson's Disease Rating Scale.

^a*p*-value obtained by the Wilcoxon test.

^b*p*-value obtained by the chi-square test.

Table e-3: Alterations in caffeine and metabolite levels in PD patients stratified by H&Y stage.

compounds	H&Y I Mean ± SD	<i>p</i> -value ^a	H&Y II Mean ± SD	<i>p</i> -value ^a	H&Y III Mean ± SD	<i>p</i> -value ^a	H&Y IV Mean ± SD	<i>p</i> -value ^a	H&Y V Mean	<i>p</i> -value ^a	<i>p</i> -value ^b
Caffeine	29.32 ± 27.2	0.0103	23.62 ± 22.8	0.0001	19.26 ± 16.6	0.0003	16.52 ± 13.7	0.0156	15.61	-	0.7516
Theophylline	6.61 ± 4.3	0.0038	6.41 ± 5.0	0.0002	5.93 ± 4.4	0.0017	3.82 ± 2.5	0.0043	3.52	-	0.5934
Theobromine	27.03 ± 34.2	0.0713	28.22 ± 37.9	0.0325	15.64 ± 7.2	0.0056	15.21 ± 22.5	0.0126	29.64	-	0.1979
Paraxanthine	31.72 ± 22.0	0.0036	33.94 ± 26.8	0.0009	26.68 ± 20.1	0.0008	19.72 ± 16.7	0.0079	10.47	-	0.4447
1,7-dimethyluric acid	0.47 ± 0.8	<0.0001	0.47 ± 0.6	<0.0001	0.52 ± 0.6	0.0003	0.43 ± 0.6	0.0088	0.01	-	0.9198
1,3,7-trimethyluric acid	0.51 ± 1.0	0.0065	0.59 ± 1.2	0.0081	1.30 ± 1.9	1.0000	0.26 ± 0.5	0.0604	1.44	-	0.1187
1-methylxanthine	0.60 ± 0.7	0.0003	0.80 ± 0.8	0.0005	0.75 ± 0.6	0.0057	0.35 ± 0.3	0.0030	0.49	-	0.4278
3-methylxanthine	1.41 ± 1.8	0.0206	1.58 ± 2.1	0.0076	1.40 ± 1.1	0.1492	0.92 ± 1.2	0.0912	3.54	-	0.4255
1-methyluric acid	1.74 ± 2.1	0.3837	2.01 ± 2.1	0.7441	2.10 ± 2.2	0.8435	2.33 ± 2.6	0.9988	0.22	-	0.6316
7-methylxanthine	1.52 ± 1.4	0.0140	1.85 ± 1.7	0.0259	1.50 ± 1.0	0.0524	1.19 ± 1.2	0.0483	1.98	-	0.6823
AFMU	0.64 ± 0.6	0.0003	0.62 ± 0.5	<0.0001	0.60 ± 0.5	0.0002	0.59 ± 0.6	0.0105	0.08	-	0.7588
AAMU	0.53 ± 0.6	0.0300	0.55 ± 0.5	0.0100	0.54 ± 0.4	0.0354	0.69 ± 0.8	0.6595	0.02	-	0.6490

Lower limits of detection (LLD) levels were calculated as half of the minimum value.

Abbreviations: PD: Parkinson' disease; H&Y stage: Hoehn and Yahr stage; SD: standard deviation; AFMU: 5-acethylamino-6-formylamino-3-methyluracil; AAMU: 5-acethylamino-6-amino-3-methyluracil.

^a*p*-value obtained by the Steel's test comparing to the control.

^b*p*-value obtained by the analysis of covariance among the H&Y I-IV stages.

Table e-4: Correlation analysis of caffeine metabolites with UPDRS-III scores and LED in PD patients.

compounds	UPDRS part III		LED	
	r^{2a}	p -value ^b	r^{2a}	p -value ^b
Caffeine	0.0084	0.346	<0.0001	0.976
Theophylline	0.0057	0.437	0.0011	0.736
Theobromine	<0.0001	0.949	<0.0001	0.937
Paraxanthine	0.0001	0.906	0.0035	0.541
1,7-dimethyluric acid	0.0003	0.855	0.0065	0.407
1,3,7-trimethyluric acid	0.0005	0.826	<0.0001	0.948
1-methylxanthine	0.0195	0.149	0.0017	0.668
3-methylxanthine	0.0109	0.911	0.0052	0.459
1-methyluric acid	0.0190	0.154	0.0115	0.269
7-methylxanthine	0.0073	0.378	0.0021	0.634
AFMU	0.0001	0.908	0.0001	0.913
AAMU	0.0082	0.350	0.0094	0.319

Abbreviations: PD: Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale; LED: levodopa equivalent dose AFMU: 5-acethylamino-6-formylamino-3-methyluracil; AAMU: 5-acethylamino-6-amino-3-methyluracil.

^{a, b}Correlation coefficient and *p*-value obtained by the analysis of covariance.