Mitochondrial haplogroups and cognitive progression in Parkinson's disease

Supplementary material

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Supplementary Methods

Study participants

4,491 patients with PD (with available genotyping data and quality control) were longitudinally assessed with 3,3406 study visits in 15 cohorts from North America and Europe between 1986 and 2017: Harvard Biomarkers Study (HBS)[1], Neuroprotection Exploratory Trials in PD- Long term Study-1 (NET-PD LS1)[2], Drug Interaction with Genes in PD (DIGPD)[3] , PROfiling PARKinson's disease (PROPARK) study[4], PROPARK-Cross sectional cohort; Cambridgeshire Parkinson's Incidence from GP to Neurologist (CamPaIGN)[5-7]; Parkinsonism: Incidence, Cognition and Non-motor heterogeneity in Cambridgeshire (PICNICS)[8]; Parkinson's Disease Biomarkers Program (PDBP)[9]; Banner Health study(Arizona Study of Aging/Brain and Body Donation Program)[10]; ParkWest[11] and PIB[12]; Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP)[13]; Parkinson Research Examination of CEP-1347 Trial/A Longitudinal Follow-up of the PRECEPT Study Cohort (PreCEPT/PostCEPT)[14] and Tartu[15], Parkinson's Progression Markers Initiative (PPMI)[16] . For PPMI, approval was obtained to download and analyze the publicly accessible WGS and clinical data. 13 cohorts enrolled patients with a diagnosis of PD established according to modified UK PD Society Brain Bank diagnostic criteria as previously reported[1-5,8,9,11,12,14-18]. In DATATOP, the eligibility criteria required a clinical diagnosis of early, idiopathic PD (HY stages 1 or 2) with patients not on anti-parkinsonian medications[17]. Banner Health study: all subjects have come to autopsy and have had full neuropathological examinations with diagnosis[10]. Diagnostic certainty was increased by confirming the clinical diagnosis of PD during longitudinal follow-up visits[19] in all cohorts.

Serial Mini Mental State Exam (MMSE) scores[20] were longitudinally collected in 10 cohorts. Montreal Cognitive Assessment (MoCA)[21] scores were collected in the PDBP, PPMI study and converted to MMSE scores according to a published formula[22]. SCOPA-COG were collected in PROPARK, PROPARK-C and NET-PD LS1 cohort and converted to MMSE scores.

Polymorphism identification and haplogroup classification

The genotyping data of the 4,491 subjects with Parkinson's disease were reported in Ref.[23]. Briefly, the samples (excluded PPMI with WGS) were genotyped with Illumina Multi-Ethnic Genotyping Array (MEGA, Illumina), which includes 810 SNP markers in mtDNA after quality control as described in Ref.[23] 810 mtDNA variants were converted from "plink" format to "vcf" format according to the rCRS reference alleles. We removed 25 mismatched SNPs and InDel SNPs, 11 duplicated SNP probes on the array, and 11 variants with highly discordant MAF (> 5%) compared to Phase 1 and 3 of the 1000 Genomes Project[24] mitochondrial variants (n = 503 European) as called by the MToolBox pipeline[25]. The remained 763 SNPs were used to predict mitochondrial haplogroups using Haplogrep2.0[26] with default parameter using rCRS reference. Haplotype quality-control was performed according to the Haplogrep2 instruction and 44 subjects with quality score < 0.8 were excluded (**Supplementary Fig. 1**). We next simplified the sub-haplogroups (455 sub-haplogroups) to the 34 haplogroups (**Supplementary Table 1**) according to the mtDNA tree http://www.phylotree.org/tree/index.htm. 4,447 subjects were successfully assigned haplogroup, and 24 of these patients had no clinical records of note so were removed from the analysis. We further removed the haplogroups with less than 100 subjects (**Supplementary Table 1**, total 359 subjects), and the remaining 4,064 subjects with 30,515 study visits were used for haplogroup analysis (including H, HV* (excluding H, V), I, J, K, T, U#

(excluding K) haplogroups). It should be note that in our work, U# denotes all U haplogroups (U1, U2, U3, U4, U5, U6, U7…) but not haplogroup K as in Ref[27]. Out of 763 SNPs, 102 SNPs with allele frequency > 1% were used for single SNP Cox regression analysis. Notably, common mtDNA haplogroup or mtDNA variants are often ancient and are usually homoplasmic[28]. We did not analyze heteroplasmic mtDNA mutations in this study.

Statistical analysis

The Cox proportional hazards statistic was used to estimate the influence of different mitochondrial haplogroups on time (years from onset of PD) to reaching the endpoint of motor disability with postural instability (Hoehn and Yahr stage HY 3) or global cognitive impairment (GCI) as indicated by a MMSE ≤ 25 according to the recommendation the International Parkinson and Movement Disorder Society (MDS) Task Force[29] as in Ref.[30]. For HY analysis, age at onset of PD, sex and *GBA* carrier status were included as covariates. In the GCI analysis, age at onset of PD, sex, years of education, and polygenic hazard score (PHS including *GBA* carrier status, *APOE* ε4 allele haplotype and three novel progression variants rs182987047, rs138073281 and rs8050111 from Ref.[23]) were included as covariates in the Cox analyses. A "cohort" term was included as a random effect (a random effects Cox model is often termed a "frailty" model). 29,115 (95.4 %) of the visits from 4,088 patients with PD occurred within 12 years of longitudinal follow-up from disease onset with a median follow-up time of 6.7 years (inter-quartile range, 4.2 years), thus we focused our survival analyses on the 12-year time frame from disease onset. Patients were left-censored and those with missing or non-quality clinical data were excluded. Cox proportional hazards analyses were performed using the coxph function in the Survival package (v2.38-1)[31] and the "breslow" method was used for handling observations that have tied

survival times in the analysis and *P* values less than or equal to 0.05 were considered as indicative of haplogroup significance.

For single polymorphism variants analysis, we used a similar Cox proportional hazards regression model (same co-variants as mentioned above) to investigate each SNP effect on motor and cognitive impairment. Bonferroni correction was performed using p.adjust function with "bonferroni" in R.

Generalized longitudinal mixed fixed and random effects analysis (LMM)[32] of cognitive decline was performed with serial Mini Mental State Exam (MMSE) scores longitudinally assessed at varying times (enrollment visit and multiple longitudinal follow-up visits) in the combined data set. Two cohorts (PROPARK-C and Tartu) were excluded from the LMM because no longitudinal MMSE scores were available. The MMSE score was the dependent variable and the primary predictors were mitochondrial haplogroup status, time in the study (years), and their interaction. An intercept term and linear rate of change across time per subject were the random terms (permitted to be correlated). Subject level fixed covariates were age at baseline, sex, years of education, duration of PD illness at baseline, as well as PHS score. A study term was included as a random effect. This analysis was performed using the lme4 package (v1.1-23). All analyses were conducted in the R statistical environment version 4.0.2.

Comparison of models

The original multivariable Cox model from a previous study[33] included age at Parkinson's disease onset, years of education, sex, MMSE at enrolment, MDS-UPDRS III score at enrolment, depression at enrolment and *GBA* carrier status, and a cohort term was included as a random effect (using a frailty Cox model). 2,629 patients in the original nine longitudinal cohorts with available

mitochondrial variants, and 2,376 patients (253 left censored patients were removed) with 22,617 visits within 12 years of longitudinal follow-up from disease onset were used for comparison of different Cox regression genetic models (*GBA* carrier, *APOE* ε4, m.2706A>G, m.14766C>T), adjusting by age at Parkinson's disease onset, years of education, sex, MMSE at enrolment, MDS-UPDRS III score at enrolment, depression at enrolment, and a cohort term was included as a random effect.

Combination analysis of two genetic risk (*GBA* carrier and m.2706A>G variant/*APOE* ε4 and m.2706A>G variant) was performed using 2,376 patients from the Cox regression model, adjusting by the same six clinical predictors as mentioned bove, and a cohort term was included as a random effect.

Supplementary Table 1 Classification of mitochondrial haplogroups in patients with PD across the 15 cohorts

Haplogroups	Number	Sub-haplogroups of H	Number
H	1,829		
U#	666	H1	599
T	440	H2	599
J	427	H3	155
K	393	H5	146
HV*	218	H6	94
I	115	H4	75
W	93	H13	47
X	75	H46	20
N1	65	H15	11
V	42	H26	11
R0[&]	17	H7	10
L2	11	H41	8
M1	9	H14	6
D	7	H79	6
A	5	H85	6
C	5	H28	5
L1	4	H44	5
R1	4	H24	4
L3e	3	H100	3
B	2	H22	3
L3b	2	H81	3
M9	2	H56	2
N2	2	H94	2
N3	2	H17	1
G	1	H30	1
L0	1	H33	1
M7	1	H34	1
M30	1	H42	1
M33	1	H49	1
M49	1	H50	1
N9	1	H73	1
Y	1	H77	1
Z	1		

Haplogroups according to the mtDNA tree http://www.phylotree.org/tree/index.htm. 4,447 subjects were successfully assigned haplogroup. HV*: not including H, HV; U[#]: including all U haplogroups (U1, U2, U3, U4, U5, U6, U7…) but not haplogroup K as in Ref[27]; R0[&]: not including HV, H, V.

Supplementary Table 2 Clinical characteristics of patients with PD at enrollment with different macro-haplogroups across the 15 cohorts

***n* = 4,423**	**Marco-haplogroup**								***P*[&]**
	H	**HV***	**I**	**J**	**K**	**T**	**U[#]**	**Others**	
Number of men (*n*, %)	1,819 (63.2)	217 (65.4)	115 (57.4)	427 (61.8)	391 (65.7)	435 (62.1)	660 (63.8)	359 (62.1)	0.76
Age at onset, mean (SD), years	60.6 (10.6)	61.4 (10.1)	61.0 (10.8)	61.6 (10.9)	61.1 (9.6)	60.9 (10.5)	60.7 (11.0)	61.3 (10.1)	0.45
Age at enrollment, mean (SD), years	64.2 (10.2)	64.8 (9.8)	64.5 (10.5)	65.1 (10.4)	64.2 (9.3)	64.4 (10.1)	64.3 (10.5)	64.8 (10.3)	0.62
Years of education, mean (SD), years	14.2 (3.8)	14.6 (3.7)	14.1 (4.1)	14.4 (3.9)	14.6 (3.8)	14.1 (3.9)	14.2 (3.6)	14.7 (3.6)	0.08
Study years, mean (range), years	3.8 (0-19.9)	3.7 (0-9.3)	3.9 (0-8.3)	3.6 (0-13.1)	3.8 (0-14.5)	3.6 (0-13.5)	3.6 (0-12.6)	3.5 (0-12.3)	0.26
Hoehn and Yahr, mean (SD)	1.9 (0.8)	1.9 (0.7)	1.8 (0.6)	1.9 (0.8)	1.9 (0.7)	2.0 (0.7)	2.0 (0.7)	1.9 (0.7)	0.28
MDS-UPDRS III, mean (SD)	28.4 (14.2)	27.2 (13.5)	27.4 (13.7)	27.9 (14.5)	26.9 (13.0)	28.4 (13.7)	28.4 (14.0)	27.9 (14.9)	0.72
MMSE, mean(SD)	28.2 (2.2)	28.2 (1.9)	28.5 (1.5)	28.1 (2.3)	28.3 (2.0)	28.2 (2.1)	28.2 (2.2)	28.3 (2.4)	0.47
LED, mean(SD)	436.6 (439.9)	402.3 (470.0)	428.6 (458.2)	415.2 (428.0)	373.6 (398.2)	399.9 (416.8)	433.2 (446.0)	418.7 (447.7)	0.34

24 subjects have no available clinic data, the table showed clinical characteristics of 4,423 patients with PD.

[&] Fisher exact test was used for the number of men in each group. Group comparisons were performed using Kruskal-Wallis test for age at onset, age at enrollment, years of education, study years, HY, MDS-UPDRS III, MMSE, LED.

HV*: The sub-haplogroups of haplogroup HV, not including haplogroup H, V.

U[#]: The sub-haplogroups of haplogroup U, not including haplogroup K.

Supplementary Table 3 The percentage (%) of different mitochondrial haplogroups in European population from literatures

Haplogroup	Latvia[34] n=299	Spain[35] n=312	Portugal[36] n=241	France[37] n=210	Norway[34] n=397	Czech[38] n=300	Germany[34] n=333	Iceland[27] n=467	Italy[39] n=124
H	44.5	42.3	40.7	41.9	45.1	40.7	47.7	47.6	41.1
HV*	2.3	NA	NA	NA	0.3	2.7	0.6	NA	1.6
I	4.3	1.6	0.8	2.9	2.3	2.0	1.8	4.7	NA
J	6.4	6.7	6.6	5.2	12.6	8.3	8.4	14.1	4.8
K	2.3	4.8	5.4	11.4	5.0	4.0	7.5	7.7	1.6
T	9.4	8.3	10.8	11.9	9.8	8.0	9.0	10.1	8.1
U[#]	23.1	16.0	17.4	17.6	16.9	21.3	13.5	11.8	30.6

HV*: The sub-haplogroups of haplogroup HV, not including haplogroup H, V;
H: sum of available sub-haplogroups of H;
J: sum of available sub-haplogroups of J;
K: sum of available sub-haplogroups of K;
T: sum of available sub-haplogroups of T;
U[#]: sum of available sub-haplogroups of haplogroup U, but not including haplogroup K.

Supplementary Table 4 Test for residual heterogeneity for each haplogroup compared to haplogroups of H in GCI combined analysis

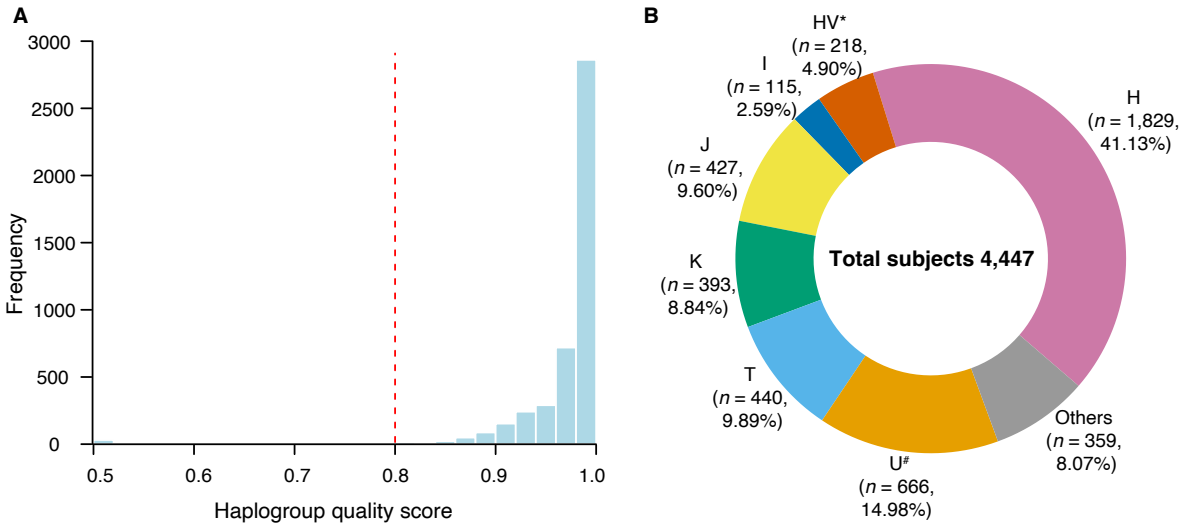
Haplogroups (H as reference)	Heterogeneity Q	*P* value[&]	I^2
HV*	5.32	0.87	0%
I	12.59	0.32	12.61%
J	4.88	0.96	0%
K	7.54	0.82	0%
T	5.05	0.96	0%
U[#]	15.90	0.20	24.54%

HV*: The sub-haplogroups of haplogroup HV, not including haplogroup H, V.
U[#]: The sub-haplogroups of haplogroup U, not including haplogroup K.
[&]The Cochran's Q-test was used to test for residual heterogeneity across studies via R metafor package (version 2.4-0). I^2 index (100%×(Q-df)/Q) was used to quantify the degree of heterogeneity.

Supplementary Table 5 The association of mitochondrial haplogroups in Alzheimer disease

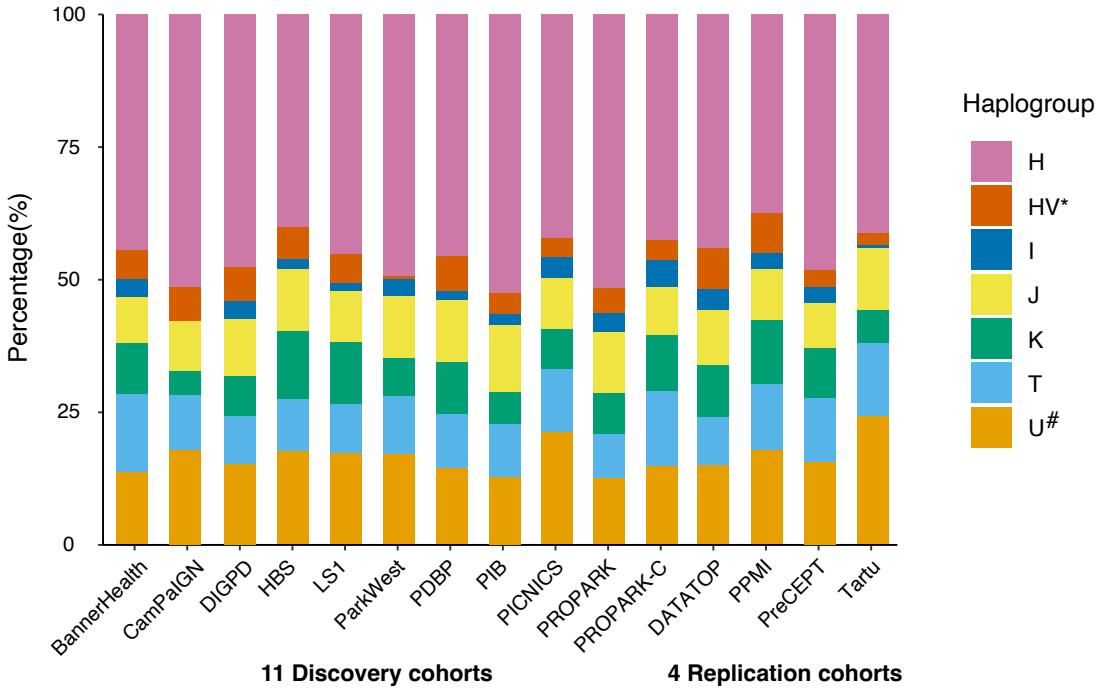
Haplogroup	Years	Effect	Ethnicity	Dataset size (case/control)	Dataset type
H	2009[40]	Risk	Poland	222/252	Whole mitochondrial genomics
	2011[41]	Risk	Caucasian	422/318	Control_region position (16624-576) + 9 coding SNPs
HV	2009[40]	Risk	Poland	222/252	Whole mitochondrial genomics
	2011[41]	Risk	Caucasian	422/318	Control_region position (16624-576) + 9 coding SNPs
K	2001[42]	Protective	Italian	213/389	10 restricted sites
	2011[41]	Protective	Caucasian	422/318	Control_region position (16624-576) + 9 coding SNPs
	2020[43]	Protective	American	309/507	Whole mitochondrial genomics
K1A1B	2013[44]	Risk	Caucasian	154/175	138SNPS
J	2009[40]	Protective in males	Poland	222/252	Whole mitochondrial genomics
	2020[43]	Risk	American	309/507	Whole mitochondrial genomics
T	2011[41]	Protective in females	Caucasian	422/318	Control_region position (16624-576) + 9 coding SNPs
JT	2011[41]	Protective in females	Caucasian	422/318	Control_region position (16624-576) + 9 coding SNPs
U	2001[42]	Protective	Italian	213/389	10 restricted sites
	2004[45]	Risk in males, protective in females	Caucasian	989/328	10 SNPs

Supplementary Figure 1 The classification of haplogroup in patients with PD across 15 cohorts.



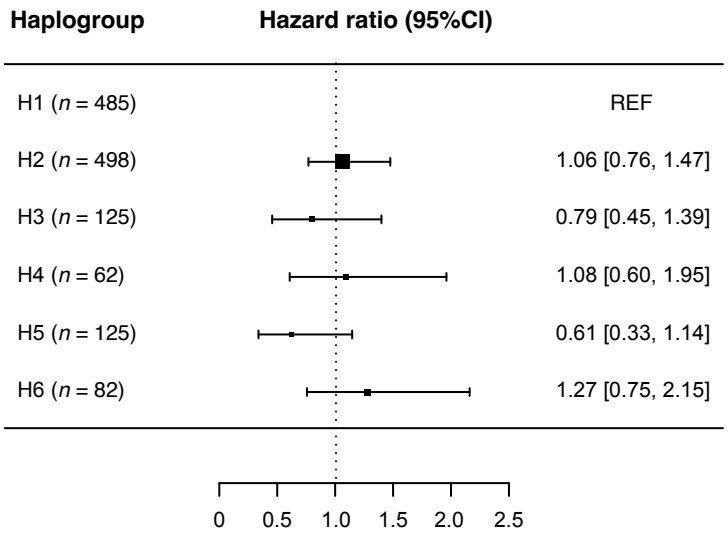
A The haplogroup quality score of 4,491 patients with PD was evaluated from HaploGrep2.0[26] based on Kulczynski measure: (HaplogroupWeight + SampleWeight) × 0.5. The HaploGrep2.0 applied this formula to all haplogroups in Phylotree and returned the overall best hit and the score represented its haplogroup quality. The quality of 0.8 as cutoff was recommended and 4,447 subjects were successfully assigned mitochondrial haplogroup. **B** The donut plot presents the proportion of patients with PD within diverse mitochondrial macro-haplogroups

Supplementary Figure 2 The stacking diagram for distribution of seven macro-haplogroups in patients with PD across 15 cohorts



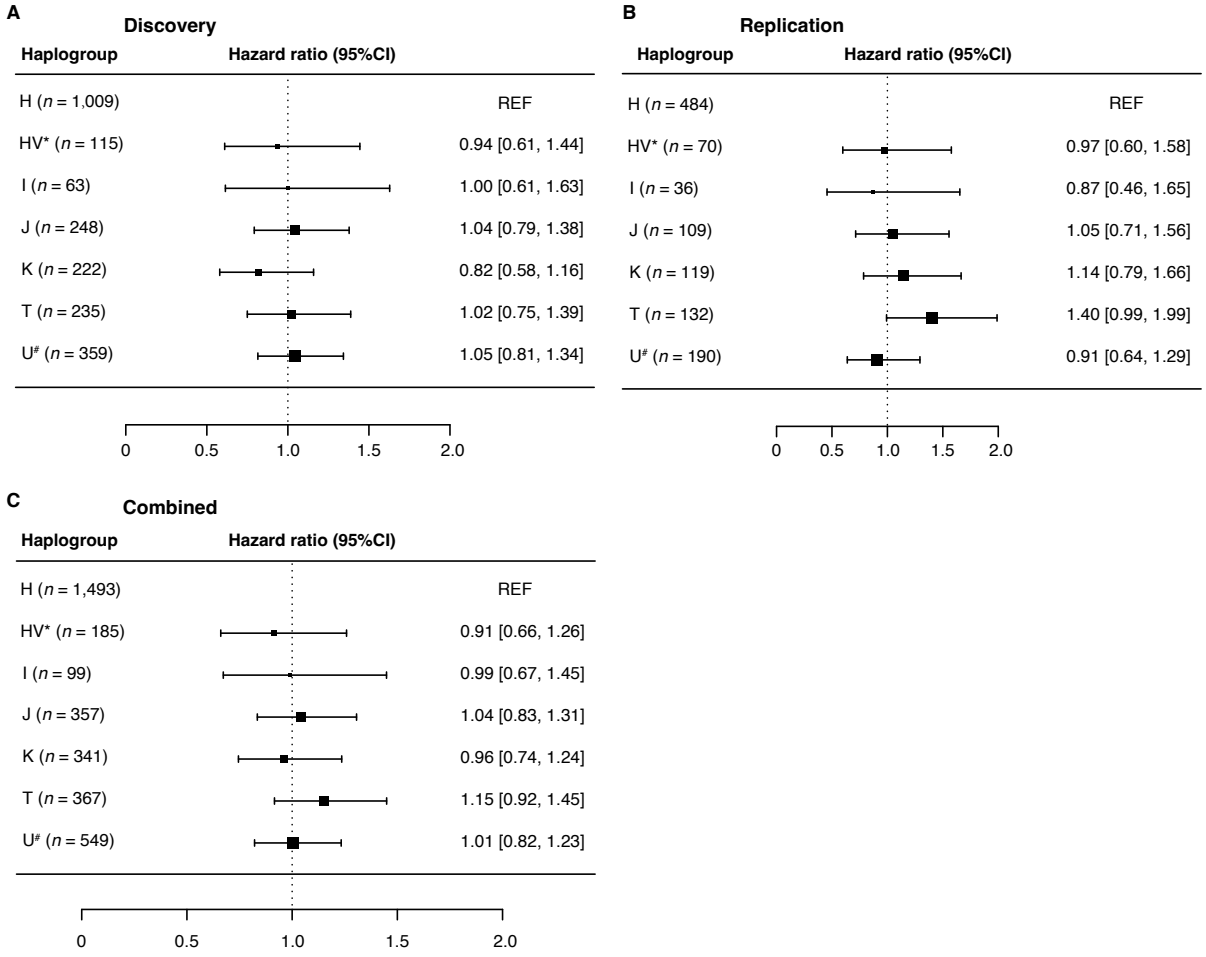
Each vertical bar corresponds to one cohort and consists of 7 sub-bars representing the proportions of the 7 macro-haplogroups H, HV*, I, J, K, T and U# in relevant cohort. There was no any difference in the proportion of seven macro-haplogroups in 15 cohorts ($P \approx 1$, Fisher exact test).

Supplementary Figure 3 Patients with PD with major sub-haplogroups of H have similar risk of progression to global cognitive impairment



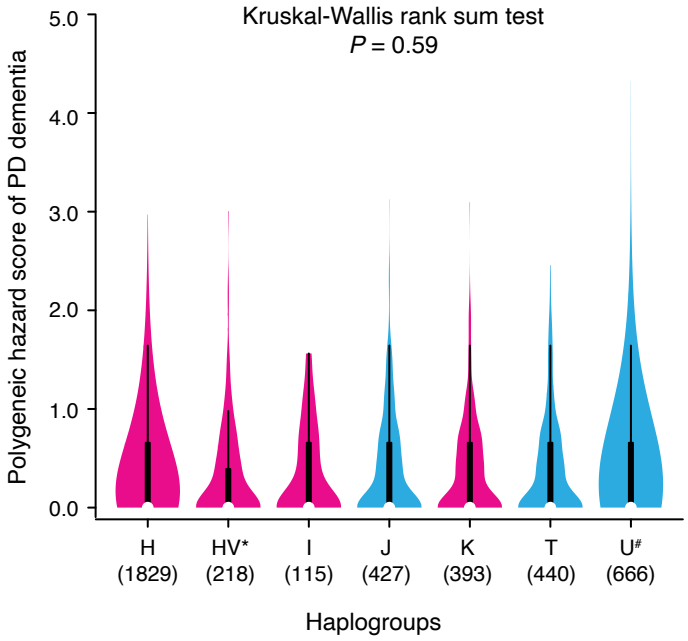
Cox regression analysis did not show any different hazard ratio (HR) to develop global cognitive impairment (MMSE $\leq$ 25) in combined population, according to the recommendation of the International Parkinson and Movement Disorder Society (MDS) Taks Force[29], among patients with PD in six major sub-haplogroups of H.

Supplementary Figure 4 Patients with PD in seven macro-haplogroups have similar risk of progression to HY3.



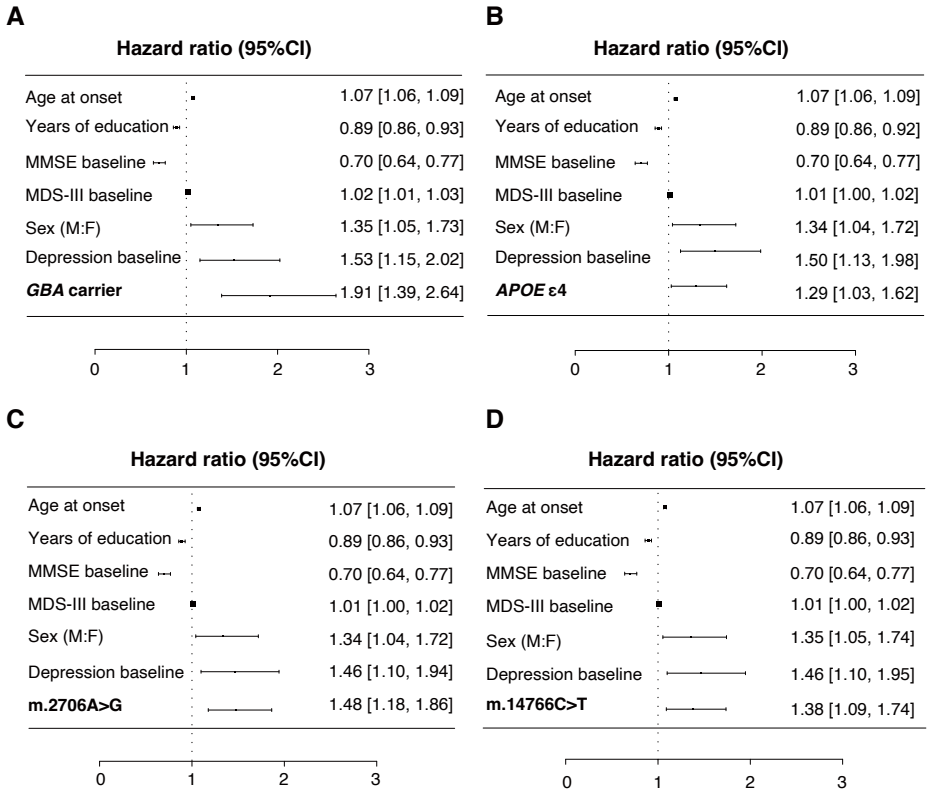
Cox regression analysis did not show any difference in hazard ratio (HR) for development of motor disability with postural instability (Hoehn & Yahr stage 3) during the progression of disease in seven macro-haplogroups from (**A**) discovery, (**B**) replication and (**C**) combined population.

Supplementary Figure 5 Patients with PD in seven mitochondrial macro-haplogroups have similar polygenic hazard scores



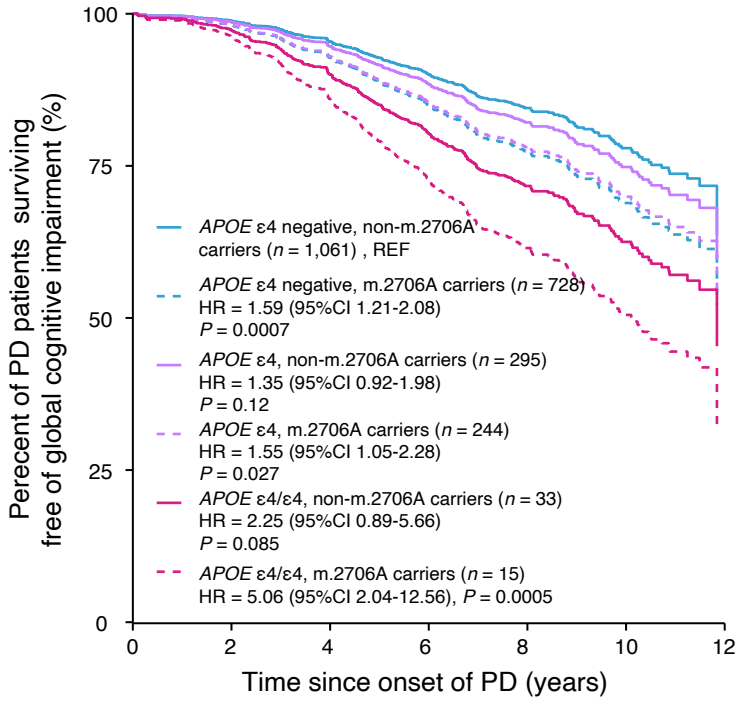
Violin-plot showed no significant difference between Polygenic hazard score to develop PD dementia among seven macro-haplogroups in combined population. Violin plot is a mixed of a box plot and a kernel density plot: the white dot represents the median, and black bar represents the interquartile range of score, the thin black line represents the rest of distribution and each side of the line is a kernel density estimation.

Supplementary Figure 6 The exploratory analysis for global cognitive impairment models with different genetic factors.



The forest plots show hazard ratios (Methods) for global cognitive impairment (GCI) in different genetic models (**A**) *GBA* carrier, (**B**) *APOE* ε4, (**C**) m.2706A>G and (**D**) m.14766C>T with the same six clinical risk factors. The squares represent point estimates, with the height of the square inversely proportional to the standard error of the estimates. The horizontal lines indicate 95% confidence intervals of the estimates.

Supplementary Figure 7 Exploratory analysis for global cognitive impairment models with *APOE* ε4 and m.2706A>G.



Covariate-adjusted survival curves for patients with PD stratified into six subgroups: *APOE* ε4 negative and non-m.2706A carriers (*n* = 1,061), *APOE* ε4 negative and m.2706A carriers (*n* = 728), *APOE* ε4 heterozygotes and non-m.2706A carriers (*n* = 295), *APOE* ε4 heterozygotes and m.2706A carriers (*n* = 244), *APOE* ε4/ε4 and non-m.2706A carriers (*n* = 33), *APOE* ε4/ε4 and m.2706A carriers (*n* = 15).

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