BRAIN
REPORT

Mitochondrial haplogroups and cognitive progression in Parkinson's disease

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Mitochondria are a culprit in the onset of Parkinson's disease, but their role during disease progression is unclear. Here we used Cox proportional hazards models to exam the effect of variation in the mitochondrial genome on longitudinal cognitive and motor progression over time in 4064 patients with Parkinson's disease. Mitochondrial macro-haplogroup was associated with reduced risk of cognitive disease progression in the discovery and replication population. In the combined analysis, patients with the super macro-haplogroup J, T, U# had a 41% lower risk of cognitive progression with $P = 2.42 \times 10^{-6}$ compared to those with macro-haplogroup H. Exploratory analysis indicated that the common mitochondrial DNA variant, m.2706A>G, was associated with slower cognitive decline with a hazard ratio of 0.68 (95% confidence interval 0.56–0.81) and $P = 2.46 \times 10^{-5}$. Mitochondrial haplogroups were not appreciably linked to motor progression. This initial genetic survival study of the mitochondrial genome suggests that mitochondrial haplogroups may be associated with the pace of cognitive progression in Parkinson's disease over time.

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Introduction

Disability and quality of life of patients with Parkinson's disease (PD) is affected by progressive cognitive impairment.[1] Increasing numbers of cognitively impaired patients with PD pose a medical and socio-economic challenge in many countries.[2] The pace of cognitive changes during the disease course, however, varies substantially from patient to patient[3] and the genetic architecture accounting for this heterogeneity in disease progression has not been well established.

Genome-wide association studies (GWAS) during the past decade have delineated the genetic architecture of disease susceptibility with 90 association signals in 78 common autosomal loci in PD patients of European ancestry.[4] Our recent genome-wide survival study identified associations with longitudinal progression from PD to Lewy body dementia in five loci, *RIMS2, GBA,* and *APOE*, *WWOX* and *TMEM108*.[5] This extends and confirms longitudinal studies implicating *GBA* variants[6,7] and *APOE* ε4[8] in cognitive decline in PD. These genome-wide and targeted sequencing efforts have paved the way for unravelling the genetic architecture of disease progression in PD, but have not yet investigated the second critical source of human DNA—the mitochondrial genome (mtDNA).

MtDNA mutations contribute to a spectrum of human diseases,[9] and in PD there is accumulating genetic and environmental evidence that mitochondrial dysfunction may play a key role in the pathogenesis of the disease.[10] There are high level of somatic mtDNA mutations in substantia nigra neurons in early PD[11] and dysregulation of mtDNA homeostasis in sporadic PD.[12] Mutations in the nuclear-encoded *PINK1* and *PRKN* cause autosomal recessive PD and disrupt mitophagy.[13] Moreover, there is a pervasive defect in *PGC-1alpha*-regulated mitochondrial bioenergetics gene expression in nigral dopamine neurons and substantia nigra even in prodromal, subclinical Lewy body neuropathology.[14]

The diversity of modern human mtDNA haplogroups (variants) has provided valuable information to trace the history of human evolution, and many studies in recent years have reported links between specific mtDNA haplogroups and susceptibility for PD,[15] however, the impact of mtDNA haplogroups or variants on progression in PD has not been defined. To characterize whether genetic variation in the mitochondrial genome influences the progression of PD, we performed a longitudinal, multi-cohort analysis, and identified specific mitochondrial haplogroups linked to cognitive decline in PD. Further exploratory analysis indicated two single

nucleotide polymorphisms (SNPs) in mtDNA specifically associated with cognitive progression.

Materials and methods

Study participants

The cohorts included in this study were described in previous work from the International Genetics of Parkinson Disease Progression Consortium.[5–7] In brief, 4491 patients with PD (with available geno-typing data and quality control) were longitudinally assessed with 33 406 study visits in 15 cohorts from North America and Europe between 1986 and 2017 (Supplementary material). Written informed consent for DNA collection and phenotypic data collection for secondary research use for each cohort was obtained from the participants with approval from the local ethics committees. The Institutional Review Board of Mass General Brigham and the Institutional Review Board of the School of Medicine, Sun Yat-sen University approved the current analyses. Patients whose longitudinal follow-up evaluations were not consistent with a diagnosis of PD were excluded. Fifteen cohorts were *a priori* assigned to discovery or replication cohorts as we previously described[5] (Supplementary Fig. 2). This achieves an approximately two-thirds to one-third split among the two stages and a balanced distribution of the distinct types of cohorts (for example, purpose-designed bio-markers studies, phase 3 clinical trials, population-based cohorts) across stages.

Polymorphism identification and haplogroup classification

We analysed 763 mitochondrial SNPs in 4491 patients with PD and predicted their mitochondrial haplogroup using Haplogrep2.0[16] with default parameters using the mitochondrial Revised Cambridge Reference Sequence (Supplementary Fig. 1). We next simplified the sub-haplogroups (455 sub-haplogroups) to the 34 haplogroups (Supplementary Table 1). After quality control (Supplementary material), 4064 subjects with 30 515 study visits were used for haplogroup analysis [including H, HV* (excluding H, V), I, J, K, T and U# (excluding K) haplogroups]. Out of 763 mitochondrial SNPs, 102 SNPs with allele frequency >1% were used for single SNP Cox regression analysis.

Statistical analysis

The Cox proportional hazards (Cox PH) analysis was used to estimate the influence of different mitochondrial haplogroups on time (years from onset of PD) to reaching the endpoint of global cognitive impairment (GCI) as indicated by a Serial Mini Mental State Exam (MMSE) ≤ 25 according to the recommendation the International Parkinson and Movement Disorder Society (MDS) Task Force[17] and adjusting for the covariates of age at onset, gender, years of education and polygenic hazard score (PHS) as fixed effects, and for a cohort term as a random effect. A second endpoint was time to motor disability with postural instability as indicated by Hoehn and Yahr stage 3 adjusting for age at onset, gender, *GBA* carrier status and the cohort term similar to Liu *et al.*[6] (see Supplementary material for details). For the single nucleotide variants, a similar Cox PH analysis was used (using the same co-variants as mentioned above) to investigate the effect of each SNP on time to cognitive impairment.

Generalized longitudinal mixed fixed and random effects analysis of cognitive decline was performed with MMSE scores longitudinally assessed at varying times (enrollment visit and multiple longitudinal follow-up visits) in the combined data set (Supplementary material). All analyses were conducted in the R statistical environment version 4.0.2.

Data availability

The genotype and clinical data for the Parkinson's progression markers initiative (PPMI) included in this study are publicly available upon request to ppmi@loni.usc.edu through a PPMI Whole Genome Sequencing Data Agreement. Clinical data for the Parkinson's disease biomarker program (PDBP) included in this study are publicly available through https://pdbp.ninds.nih.gov. Clinical longitudinal data and genotyping data for the other cohorts included are accessible through appropriate data sharing agreements that protect patient privacy with the institutions that conducted or are conducting study consents and clinical assessments under local institutional review board approvals.

Results

Mitochondrial haplogroup is associated with cognitive decline in patients with Parkinson's disease

The genotyped data of 4491 patients with PD across 15 cohorts from North America and Europe were used to estimate their mitochondrial haplogroups. 4447 patients with 33 068 longitudinal study visits passed quality control (Supplementary Fig. 1A) and were classified into eight groups: seven macro-haplogroups (H, HV*, I, J, T, K, U#) and a group comprising various other haplogroups (Supplementary Fig. 1B and Supplementary Table 1). Overall, 41.13%, (1829) patients belonged to macro-haplogroup H, which is a common mtDNA clade in Europe and found in approximately 43.10% of UK Biobank individuals.[18] There were no significant differences in demographic and clinical characteristics of the patients in the various macro-haplogroups (Supplementary Table 2). The proportion of the seven macro-haplogroups was consistent with a previous survey in various European countries (Supplementary Table 3) and did not differ between the 15 cohorts ($P \approx 1$, Fisher's exact test, Supplementary Fig. 2). For 4064 patients within seven macro-haplogroups, we assigned 2811 patients and 12 605 longitudinal visits to the discovery population. 1253 patients and 17 910 visits comprised the replication population.

We then investigated the effect of seven macro-haplogroups on the risk of cognitive and motor impairment during the progression of Parkinson's disease in discovery and replication populations. 'Haplogroup' was an unordered categorical variable in our Cox PH model. An omnibus test for haplogroup variation with six degrees of freedom showed that the seven haplogroups in general were differed from each other in their association with cognitive progression (the null hypothesis is that the haplogroups have the same effect) with an 'omnibus' test *P*-value < 0.001 in the discovery stage. We followed up this omnibus test with pertinent post hoc likelihood ratio tests which are the pairwise comparisons of each of the haplogroups against the 'reference' haplogroup H. J, T and U# haplogroups were associated with a reduced risk for GCI (MMSE ≤ 25) compared to the common haplogroup H with a hazard ratio (HR) of 0.65 [95% confidence interval (CI) 0.44–0.97] and *P* = 0.033, HR of 0.53 (95% CI 0.34–0.83) and *P* = 0.0052 and HR of 0.68 (95% CI 0.49–0.96) with *P* = 0.028 in the discovery stage, respectively (Fig. 1A). We further confirmed these associations in a replication population, where the HRs were 0.45 (95% CI 0.22–0.94), 0.54 (95%
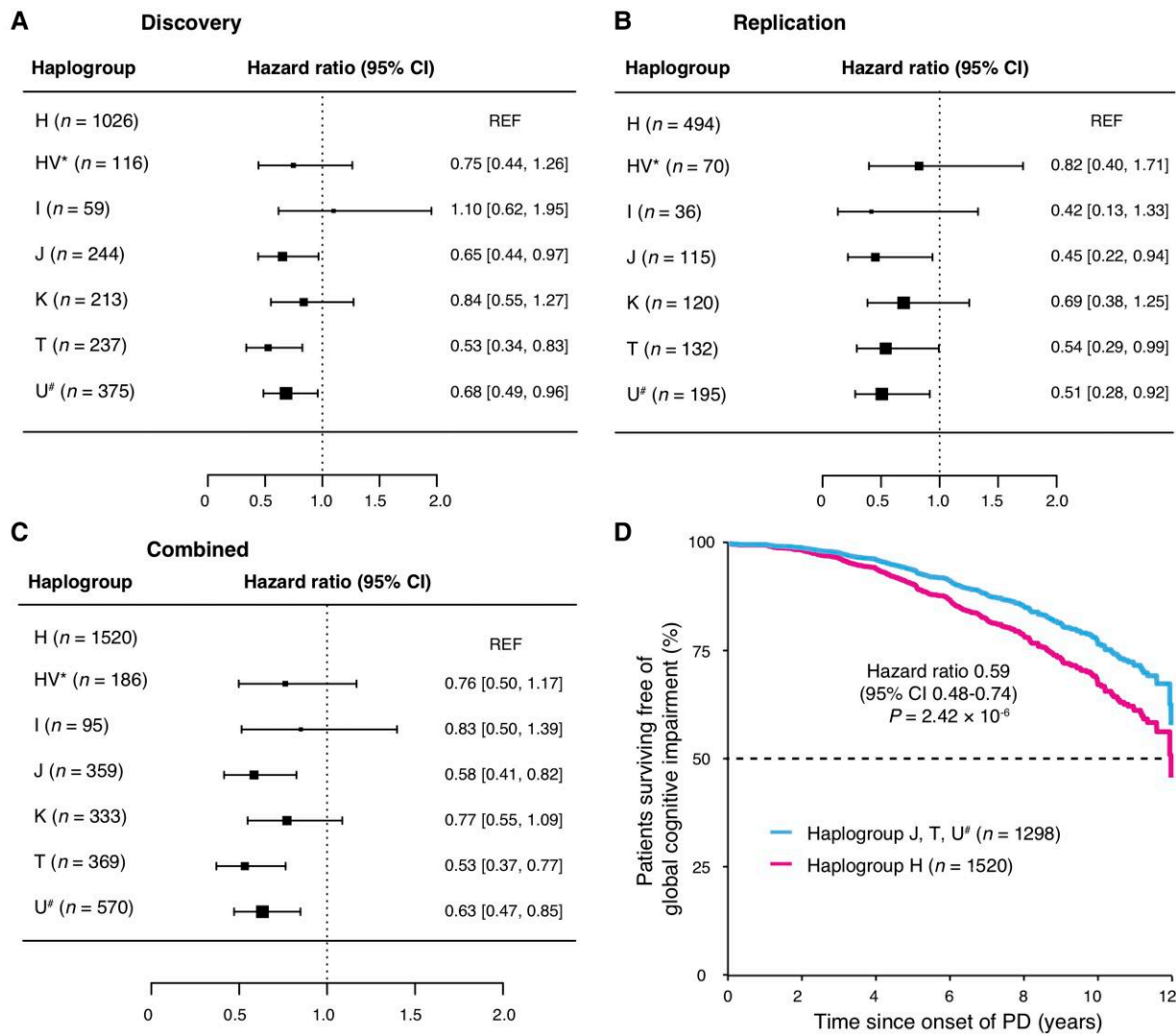
Figure 1 Mitochondrial haplogroups and risk for GCI over time in patients with PD. The forest plot shows HRs for global cognitive impairment in specific types of macro-haplogroups compared to macro-haplogroup H in patients with PD from the discovery (**A**), replication (**B**) and combined (**C**) populations. The squares represent point estimates, with the sides of the square inversely proportional to the standard error of the estimates. The horizontal lines indicate 95% CIs of the estimates. (**D**) Covariate-adjusted survival curves for patients with PD in macro-haplogroups J, T and U# (cyan line) and those in macro-haplogroups H (magenta line).

CI 0.29–0.99) and 0.51 (95% CI 0.28–0.92) with P values of 0.033, 0.047 and 0.025 for J, T and U# compared with Haplogroup H, respectively (Fig. 1B). Consistently, in the combined analysis, HR were 0.58 (95% CI 0.41–0.82) with $P = 0.0023$, 0.53 (95% CI 0.37–0.77) with $P = 0.0007$, and 0.63 (95% CI 0.47–0.85) with $P = 0.0023$, respectively (Fig. 1C). For each haplogroup compared to haplogroup H, the Cochran's Q-test and the I^2 index showed that HRs across studies were homogeneous (Supplementary Table 4).

There was no difference in HR for GCI among sub-haplogroups of H (Supplementary Fig. 3). There was no difference in HR for motor progression to Hoehn and Yahr stage 3 (motor disability with postural instability in PD) for each of the seven macro-haplotypes in discovery, replication or combined populations (Supplementary Fig. 4). A PHS based on five nuclear genetic loci exhibited a substantial aggregate association with progression to PD dementia in our recent study.[5] Here, we calculated the PHS for each patient and found no association between PHS and mtDNA haplogroups (Kruskal–Wallis rank sum test $P = 0.59$; Supplementary Fig. 5). This

suggests that mitochondrial and nuclear genome variants may play independent roles in the cognitive progression of PD.

Since subjects with macro-haplogroups J, T and U# showed a protective effect compared to haplogroup H, we combined these subjects into a super-group ($n = 1298$) and showed reduced risk for GCI with HR = 0.59 (95% CI 0.48–0.74) and $P = 2.42 \times 10^{-6}$ (Fig. 1D) (macro-haplogroup H as reference) after adjusting for covariates. A linear mixed model analysis indicated that serial MMSE scores in patients with macro-haplogroups J, T and U# declined more slowly over time compared to patients in the common macro-haplogroup H ($P = 0.018$).

Exploratory analysis of single nucleotide polymorphisms in mtDNA and cognitive decline in PD

We next carried out an exploratory analysis to investigate the effect of single nucleotide polymorphisms in mtDNA on cognitive

impairment during the progression of PD in the combined population (see 'Methods' section). We observed that two variants, m.2706A>G and m.14766C>T, were associated with cognitive decline (Fig. 2A). The common m.2706A>G variant (G allele carriers, 58.3% in our cohorts) is located in the 16S rRNA locus. Patients with the m.2706G allele had a reduced risk of developing GCI with an HR = 0.68 (95% CI 0.56–0.81) and $P = 2.46 \times 10^{-5}$ compared to patients with the A allele (Fig. 2B). The common variant m.14766C>T (C allele carrier, 47.5% in our cohorts) codes for an amino acid substitution of an isoleucine for threonine at amino acid site 7 in *CYTB*. Patients with PD and m.14766T had a reduced risk of developing GCI with a HR = 0.70 (95% CI 0.58–0.84) and $P = 1.15 \times 10^{-4}$ compared to patients carrying the C allele. For m.2706A>G and m.14766C>T, proportional HRs across studies were homogeneous with $P = 0.46$ ($I^2 = 0\%$) and $P = 0.44$ ($I^2 = 0.96\%$), respectively, according to a Cochran's Q-test for heterogeneity. Associations of these two variants remained significant after considering multiple-testing with both P values lower than the Bonferroni-corrected significance threshold (0.05/102 variants tested = 4.9×10^{-4}). Twelve additional variants were associated with cognitive decline during the course of PD with $P < 0.05$ (Fig. 2A and Table 1).

Both m.2706A and m.14766C are largely specific to the H or HV* haplogroup. The alternative alleles m.2706G and m.14766T occur in other haplogroups (Fig. 2C). These results are consistent with our haplogroup analysis as patients within haplogroups J, T and U# have a lower risk for cognitive progression compared to those with haplogroup H. We found high correlation ($r^2 = 0.78$) of these two common variants in our cohorts and 94.1% of patients carried the same risk/protective alleles (m.2706A/m.14766C or m.2706G/m.14766T). After correcting for the effect of m.2706A>G, conditional Cox PH analysis no longer showed an association of m.14766C>T with cognitive decline [HR = 0.92 (95% CI 0.62–1.38), $P = 0.7$]. Thus, m.14766C>T was dependent with m.2706A>G in our cohorts.

Age at disease onset, years of education, sex, MMSE at enrollment, Movement Disorder Society Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) score at enrollment and depression at enrollment are clinical variables associated with cognitive decline in PD.[7] A total of 2629 patients were included in both our previous[7] and current studies, and we used these 2376 patients (253 left censored patients were removed) for further analyses (Supplementary material). m.2706A and m.14766C carriers showed significant HRs of 1.48 (95% CI 1.18–1.86, $P = 8.21 \times 10^{-4}$) and 1.38 (95% CI 1.09–1.74, $P = 7.23 \times 10^{-3}$) for risk of progression to GCI, respectively, adjusting for all six clinical predictors (Supplementary Fig. 6).

Consistent with our previous genome-wide survival analysis for progression from PD to PD dementia, *GBA* carriers had an HR of 1.91 (95% 1.39–2.64) with $P = 7.76 \times 10^{-5}$ and *APOE* ε4 carriers had an HR of 1.29 (95% 1.03–1.62) with $P = 0.028$ for cognitive decline (without accounting for mitochondrial variants; Supplementary Fig. 6). *GBA* carriers who carried the mitochondrial m.2706A allele (linked to relatively more 'rapid' progression compared to the m.2706G allele) had an HR of 2.92 (95% CI, 1.87–4.55, $P = 2.23 \times 10^{-6}$). *GBA*-positive non-m.2706A carriers had the second highest HR of 1.84 (95% CI 1.15–2.93, $P = 0.011$), and *GBA*-negative m.2706A carriers had an HR of 1.46 (95% CI 1.14–1.88, $P = 0.0028$) compared to patients carrying neither *GBA* variants nor the m.2706A variant (Fig. 3). Thus, m.2706A>G and *GBA* variants may have additive effects. Moreover, patients homozygous for the *APOE* ε4 allele and carrying m.2706A had a substantially elevated risk for longitudinal cognitive decline with HR = 5.09 (95% CI 2.04–12.56 $P = 0.0005$) compared to patients carrying neither the *APOE* ε4 allele nor the m.2706A variant (Supplementary Fig. 7).

Discussion

This genetic survival study overall indicates that mitochondrial macro-haplogroups are associated with reduced risk of cognitive disease progression in PD. *Post hoc* analyses identified the haplogroups J, T and U# as the haplogroups associated with reduced risk compared to the macro-haplogroup H in Parkinson's patients, but further research is required to definitively identify the contribution and statistical significance of each individual haplogroup. Previous meta-analyses found that the haplogroups J, K and T are associated with reduced susceptibility for PD and the haplogroup H is linked to elevated susceptibility for PD.[15]

About 41% of patients with PD in this study belong to the macro-haplogroup H, the most common genotype in Europeans. The European mtDNA haplogroup H is associated with a higher survival ratio after sepsis,[19] but is linked to higher risk of developing PD in late life.[15] On the flip side, our findings are consistent with a relatively more deleterious effect of haplogroup H on the progression of PD compared to haplogroups J, T and U#. This may represent an evolutionary trade-off,[20] whereby genetic variants that increase the chance of surviving early-life illness such as sepsis might contribute to pathogenic events later in life.[20]

Alzheimer's disease-associated plaques and tangles are found in a substantial proportion of brains with of patients with PD dementia in addition to Lewy bodies.[21] H and HV are risk haplogroups for Alzheimer's disease,[22] while the JT haplogroup was protective in a prior study[23]; evidence for the other haplogroups (K, J, T, U) is limited and controversial (e.g. J[22,24]; Supplementary Table 5). This is also consistent with our study, where H carriers had a relatively more rapid cognitive progression compared to the protective haplogroups J, T and U#.

Two common significant mtSNPs showed effects on the risk of global cognitive impairment and are related to the haplogroups (Fig. 2C). The common m.2706A>G variant, located at 16S rRNA gene, is close to the ribosomal peptidyl transferase center, and might be relevant to many diseases, such as mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), Alzheimer's disease and PD.[25] This variant can induce substantial alterations in the mitochondrial 16S rRNA secondary structure.[26] The m.14766C variant might increase the risk for late-onset Alzheimer's disease[23] consistent with our findings. Interestingly, contrary to our data, m.2706G was associated with faster cognitive ageing in a large longitudinal cohort of African Americans but not Caucasian Americans.[27]

Our study is limited in sample size and statistical power. P values for individual haplogroups were not adjusted for multiple testing. Another limitation of this study is that we evaluated the effects of mitochondrial genetic variants in patients with European ancestry only. The mtSNPs (m.2706A>G or m.14766C>T) are rare in populations from East Asia or Africa (Table 1). Further studies in other populations are urgently needed because of differences in mtDNA haplogroups, considering that more than 60% of PD patients are expected to live in the Western Pacific Region by 2030,[28] most of them belonging to haplogroups A, B, C, D, F and G. Moreover, replication of our exploratory findings in additional longitudinal patient populations of European ancestry is needed.

This study suggests that mitochondrial genotypes may not be innocent bystanders in the progression of PD, but might play a role in modulating disease progression. Our study provides evidence for the role of mitochondrial haplogroups in the progression of PD towards Lewy body dementia, and this association appears independent of *GBA* and *APOE*.
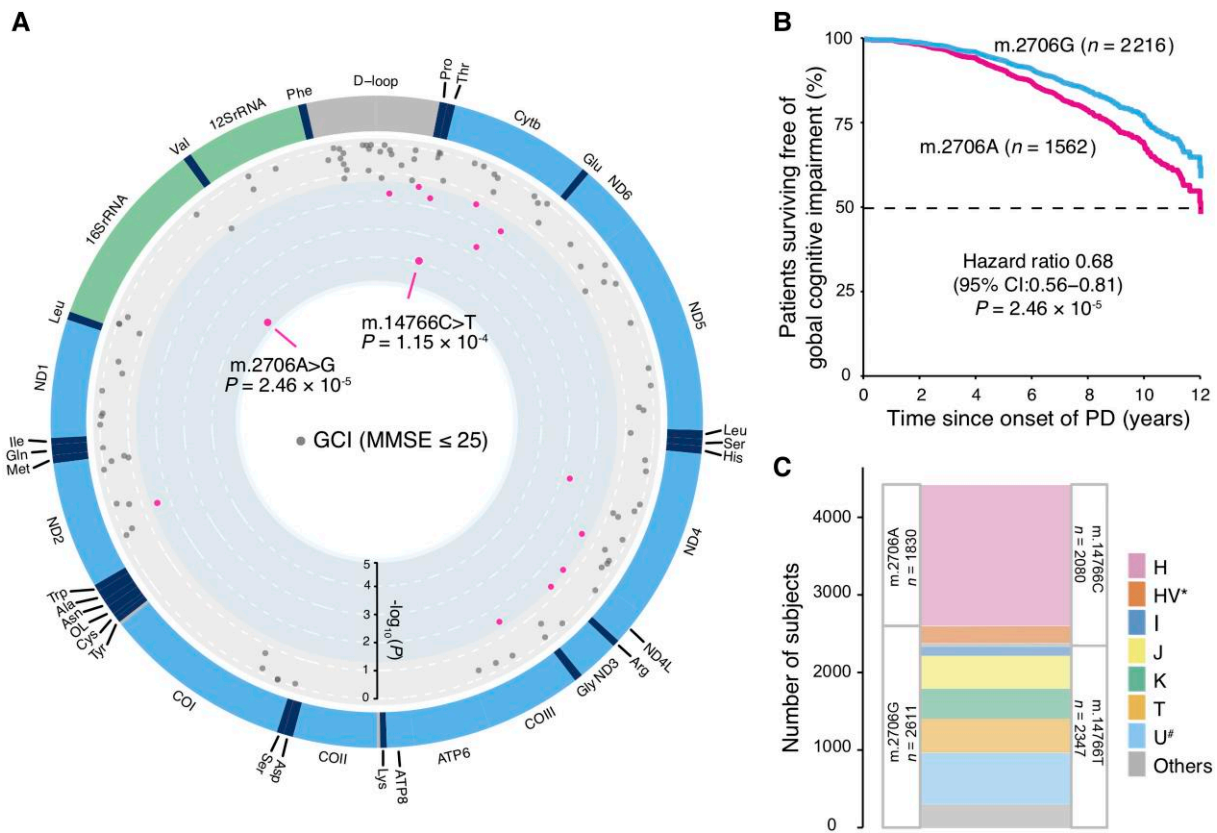
Figure 2 mtSNPs associated with cognitive progression in patients with PD. (**A**) Association plot of SNPs in mtDNA associated with risk of developing global cognitive impairment (dot) in the combined population. The outside labels indicate mitochondrial genes; circular axis from outside to inside represents the value of -log10(P) from 0 to 5; SNPs with $P < 0.05$ are shown in magenta, while SNPs with $P \geq 0.05$ are shown in grey. (**B**) Covariate-adjusted survival curves for patients with PD carrying mtDNA m.2706G (cyan line) and those with m.2706A (magenta line). m.2706A was used as the reference allele to calculate the HR from the Cox PH analysis; P values from two-sided Wald tests. (**C**) Overlap between carriers of the m.2706A>G and the m.14766C>T variant. Out of 2611 m.2706G allele carriers and 2347 m.14766T allele carriers, 2342 individuals carried both alleles. Out of 1830 m.2706A allele carriers and 2080 m.14766C allele carriers, 1819 individuals carried both alleles.

Table 1 Association of mtDNA SNPs with global cognitive impairment during the progression of PD

rCRS	Effect allele	Alternative allele	P	P[a]	HR (95% CI)	EAF[b]	EAF in European	EAF in East Asian	EAF in African
m.2706A>G	G	A	2.46×10^{-5}	0.003	0.68 (0.56–0.81)	0.5826	0.5746	0.9960	0.9970
m.14766C>T	T	C	1.15×10^{-4}	0.012	0.70 (0.58–0.84)	0.5249	0.5169	0.9960	0.9985
m.11251A>G	G	A	0.002	0.204	0.67 (0.52–0.86)	0.1942	0.1610	0.0000	0.0015
m.15452C>A	A	C	0.002	0.204	0.67 (0.52–0.87)	0.1951	0.1610	0.0000	0.0000
m.15607A>G	G	A	0.017	1	0.65 (0.46–0.93)	0.0984	0.0875	0.0000	0.0015
m.16162A>G	G	A	0.019	1	1.95 (1.12–3.40)	0.0235	0.0199	0.0417	0.0015
m.15928G>A	A	G	0.021	1	0.66 (0.47–0.94)	0.0998	0.0875	0.0080	0.0000
m.11812A>G	G	A	0.029	1	0.65 (0.44–0.96)	0.0787	0.0696	0.0000	0.0045
m.4917A>G	G	A	0.030	1	0.66 (0.46–0.96)	0.0971	0.0875	0.0000	0.0000
m.9477G>A	A	G	0.031	1	0.66 (0.46–0.96)	0.0926	0.1392	0.0000	0.0061
m.10589G>A	A	G	0.041	1	1.89 (1.03–3.47)	0.0110	0.0060	0.0020	0.0530
m.16482A>G	G	A	0.043	1	1.62 (1.02–2.59)	0.0200	0.0139	0.0020	0.0000
m.15218A>G	G	A	0.045	1	0.55 (0.31–0.99)	0.0453	0.0437	0.0119	0.0000
m.10463T>C	C	T	0.048	1	0.71 (0.51–1.00)	0.1030	0.0875	0.0040	0.0000

P from the Cox proportional hazards statistic used to estimate the influence of SNP on time (years from onset of PD) to reaching the endpoint of GCI as indicated by a MMSE ≤ 25 in exploratory analyses using the combined population; age at onset of PD, sex, years of education and PHS (including *GBA* mutation status, *APOE* ε4 allele haplotype, and rs182987047, rs138073281 and rs8050111) were included as covariates in the Cox analyses. A 'cohort' term was included as a random effect. rCRS = revised Cambridge Reference Sequence.
[a]Bonferroni correction based on the result of 102 mtDNA SNPs from combined analysis was performed using the p.adjust function with the 'Bonferroni' method in R.
[b]Based on 4491 patients with PD across 15 cohorts. EAF in 503 European, 503 East Asian or 661 African was calculated based on dataset of Phase 1 and 3 of the 1000 Genome Project mitochondrial variants calling by the MToolbox pipeline. EAF = Effect allele frequency.
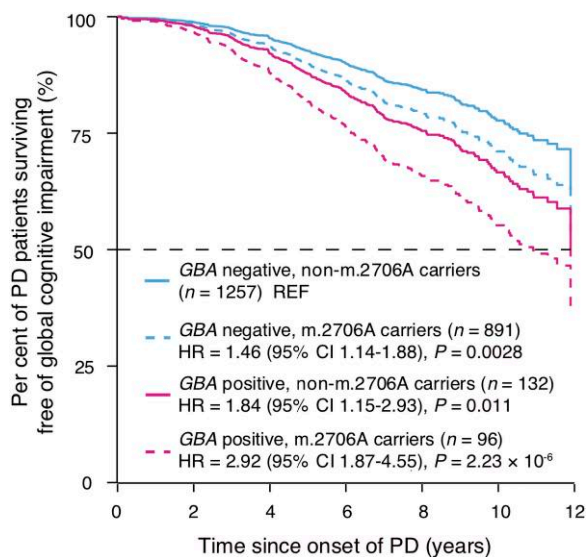
Figure 3 Effects of GBA variants and mtSNPs on global cognitive impairment in patients with PD. Covariate-adjusted survival curves for patients with PD stratified into four subgroups: *GBA*-negative and non-m.2706A carriers (*n* = 1257), *GBA*-negative and m.2706A carriers (*n* = 891), *GBA*-positive and non-m.2706G carriers (*n* = 132) and *GBA*-positive and m.2706A carriers (*n* = 96). HR and *P*-values were calculated adjusting for clinical covariates and study cohort as a random term. The group of *GBA*-negative and non-m.2706A carriers is denoted as reference group (REF) in this Cox PH analysis.

Mitochondrial dysfunction[14] and alpha-synuclein accumulation are two pathologically and biologically linked culprits of PD. Alpha-synuclein triplication causes mitochondrial bioenergetics dysfunction.[29] Conversely, the mitochondrial toxin rotenone leads to alpha-synuclein accumulation.[30] Taken together with our new findings, this body of evidence suggests that mitochondria might play a role not only in the onset, but also in the progression of Parkinson's disease.

Acknowledgements

Funding

Competing interests

Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

International Genetics of Parkinson Disease Progression (IGPP) Consortium

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