APOE E4 is associated with cognitive decline but not with disease risk or age of onset in Nigerians with Parkinson's disease

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Abstract

The relationship between *APOE* polymorphisms and Parkinson's disease (PD) in black Africans has not been previously investigated. We evaluated the association between *APOE* polymorphic variability and cognition in 1100 Nigerians with PD and 1097 matched healthy controls. Cognition in PD was assessed using the single item cognition question (item 1.1) of the MDS-UPDRS. *APOE* genotype and allele frequencies did not differ between PD and controls ($p > 0.05$). No allelic or genotypic association was observed between *APOE* and age at onset of PD. In PD, *APOE ε4/ε4* conferred a two-fold risk of cognitive impairment compared to one or no *ε4* (HR: 2.09 (95%CI: 1.13–3.89; $p = 0.02$)), while *APOE ε2* was associated with modest protection against cognitive impairment (HR: 0.41 (95%CI 0.19–0.99, $p = 0.02$)). Altogether, our findings support previous studies in other ancestries, implying a role for *APOE ε4* and *ε2* as risk and protective factors respectively for cognitive decline in PD.

Introduction

The gene encoding apolipoprotein E (*APOE*), located on chromosome 19q13.2, has three commonly described polymorphic alleles (*ε2*, *ε3*, *ε4*) constituting six genotypes in humans (*ε2/ε2*, *ε2/ ε3*, *ε2/ ε4*, *ε3/ ε3*, *ε3/ ε4*, *ε4/ ε4*). Apolipoprotein E plays a vital role in lipid metabolism and has been linked to both vascular and neurodegenerative pathological processes. Allelic and genotypic variability in *APOE* have been extensively explored in Alzheimer's disease (AD) and other neurodegenerative conditions including Parkinson's disease (PD). [1, 2] Currently, variability in *APOE* is the strongest known common genetic risk factor for late onset AD, in which the *APOE ε4* allele increases disease risk and lowers the age at disease onset, whereas the *APOE ε2* allele confers a protective effect against AD. [2–4] In Northern European Ancestry individuals, homozygous carriers of *APOE ε4* have up to a twelve-fold increased risk for AD compared to non-carriers, whereas there is a weaker but significant effect for incident AD in persons of Yoruba ethnicity in Nigeria. [1, 5–7]

The relationship between *APOE* polymorphic variability and disease status and age at onset remains unclear for PD, with a significant number of studies yielding inconsistent results. Recent evidence from large genome wide association studies (GWAS) of Northern European ancestry participants showed no convincing link between *APOE* genotype and PD disease status or age at onset. [8] However, recent meta-analyses combining data from cohorts of varied ethnicities including Europeans, Asians and Latin-Americans showed that the association between *APOE* genotype and PD risk could be ethnicity dependent. [9] *APOE ε4* but not ε2 was shown to be a consistent risk factor for PD in Asian populations but not in Northern European ancestry individuals and Latin-Americans. [8, 9] *APOE ε4* was also shown to be consistently associated with a higher incidence of cognitive decline in patients with PD from Northern European, Asian and Latino backgrounds. [9]

Few studies have examined the role of *APOE* (and specifically *ε4*) in neurodegeneration in Africans. [10–12] To date, the link between *APOE* and PD risk and age at onset or PD related cognitive decline has not been explored in individuals of black African ancestry within or outside Africa. The objective of this study was to examine the role of *APOE* polymorphisms in the genetic susceptibility to PD in Nigerians, and to interrogate possible interactions with age at onset and cognitive status.

Results

Cohort characteristics

The study participants comprised of 1100 Nigerians with PD and 1097 cognitively normal age- and gender matched controls of similar ethnicity. Baseline characteristics are shown in Supplementary Table 1 that includes the sex distribution (female: PD – 302 (27.5%), controls – 382 (34.8%)), mean age at study (years) (PD: 64.6 ± 10.0, controls: 62.7 ± 9.0), mean age at onset of PD (59.6 ± 10.5 years), and median duration of PD (interquartile range (IQR)) 3.0 (3.0) years. A significantly higher proportion of controls in this study were female (p = 0.000). Amongst individuals with PD, mean age at study and mean age at onset did not differ by sex (p = 0.15 respectively). Disease duration, median PD stage (Hoehn and Yahr), median MDS UPDRS cognition score, and the proportions with abnormal cognition (as defined, i.e., score of 0 or 1 on the MDS UPDRS cognition question) were also similar when compared by sex (p > 0.05 for all). In non-parametric (Spearman's) correlation analysis, MDS UPDRS cognition score was significantly positively correlated with age at study (Rs = 0.145, p = 0.000), age at onset of PD (Rs = 0.094, p = 0.002) and duration of PD at study (Rs = 0.115, p = 0.000).

APOE allelic and genotypic frequency proportions in Nigerians with PD and controls

Table 1 compares frequency distributions of *APOE* alleles and genotypes in Nigerian PD patients and controls in this study to data from previous reports describing these frequencies in general populations from different ethnicities. [13–15] *APOE* allelic and genotypic frequencies for our entire cohort had similar distribution to that reported in populations of black ancestry except for the *ε4/ε4* genotype which was higher than the global average (5.7% in the present study versus 1.41% global) and higher than the average frequency in other black populations (3.44%) (Table 1). The allele frequencies of *APOE* in all our participants (n = 2197) were: ε3 (58.9%), ε4 (29%) and ε2 (12.1%) (Table 1). The genotypic frequencies of the *APOE* were as follows for homozygotes (*ε3/ ε3* (43.2%), *ε4/ ε4* (5.7%), *ε2/ε2* (1.4%)) and heterozygotes (*ε3/ε4* (33%), *ε2/ ε3* (12%), *ε2/ ε4* (12%)) respectively. No gender differences were observed (p > 0.05).

Table 1

APOE genotype and allele frequency distributions in Nigerians with PD and controls in comparison to other normal global and ethnic populations

Allele *n (%)*									
	All *n* = 2197	PD *n* = 1100	Controls *n* = 1097	Global (21)	Africans (22)	Europeans (22)	Asians (22)	Native Americans (22)	Oceanians (22)
ε2	397 (12.1)	204 (12.3)	193 (11.8)	0–38	2.7–11.6	4.4–11.9	0.4–14.0	0.0–1.4	0.0–14.5
ε3	1937 (58.9)	959 (57.9)	978 (59.9)	48–94	53.6–85.0	64.0–89.8	62.0–87.0	72.0–91.1	48.6–74.0
ε4	955 (29.0)	494 (29.8)	461 (28.2)	3–41	14.3–40.7	6.8–31.0	7.1–24.0	8.9–28.0	26.0–68.0
Genotype n (%)									
	All *n* = 2197	PD *n* = 1100	Controls *n* = 1097	Global (23)	Black (23)	Whites (23)			
ε2/ε2	30 (1.4)	18 (1.6)	12 (1.1)	0.53	1.23	0.50			
ε2/ε3	263 (12.0)	129 (11.7)	134 (12.2)	11.99	13.38	12.71			
ε2/ε4	104 (4.7)	57 (5.2)	47 (4.3)	1.78	3.44	2.21			
ε3/ε3	949 (43.2)	459 (41.7)	490 (44.7)	65.68	47.86	60.16			
ε3/ε4	725 (33.0)	371 (33.7)	354 (32.3)	18.61	30.65	22.43			
ε4/ε4	126 (5.7)	66 (6.0)	60 (5.5)	1.41	3.44	1.99			

Footnote: Denominator for allele frequencies is total allele count (Nigerian cohort present study: all = 3289, PD = 1657, controls = 1632). No significant difference in allele or genotype frequencies in PD versus controls in this study. Odds ratios (95% CI) PD versus controls (e2: 0.97 (0.87–1.08), p = 0.56; e3: 1.10 (0.97–1.24), p = 0.15; e4: 0.94 (0.97–1.03), p = 0.17). P value for comparison of genotype frequencies in present study (i.e. PD v. controls) = 0.56. Global data for alleles from references 21 and 22. Global data for alleles (not shown) from reference 22 (Corbo RM, *et al*) (e2: 0.0–37.5; e3: 8.5–98.0; e4: 0.0–49.0). Genotype frequencies for controls as reported by Qin W *et al* (23) for global and race categorization reported as stated in the publication ('Black' and 'White').

Association between APOE and PD risk, age at onset, and cognition status

As shown in Table 1 and Supplementary Tables 2 and 3, there was no significant difference in allele or genotype frequencies (p = 0.65) in PD versus controls in this study (either overall or by sex). The Odds ratios (95% CI) for the comparison between PD versus controls for allele distribution (Supplementary Table 3) was as follows: ε2: 0.97 (0.87–1.08), p = 0.56; ε3: 1.10 (0.97–1.24), p = 0.15; ε4: 0.94 (0.97–1.03), p = 0.17. Supplementary Table 4

provides data on the association between ε2 and ε4 dose to disease status, demonstrating the lack of association with PD status ($p > 0.05$ for all comparisons).

Supplementary Table 5 and Supplementary Fig. 3 explore the allelic and genotypic relationship of *APOE* to age at onset of PD. Genotypic and allelic genotypes in *APOE* did not influence age at onset of PD, and neither did ε2 or ε4 dose (data not shown; $p > 0.05$ for all iterations).

Table 2 provides data on the relationship of allelic and genotypic variability and ε2 and ε4 dose to cognition status in PD. Homozygosity for ε4 conferred a two-fold increased risk for cognitive decline in PD (Hazards ratio 2.09 (95% CI 1.13–3.89), $p = 0.02$), whereas the presence of at least one ε2 allele reduced the likelihood of cognitive impairment (HR 0.41 (95% CI 0.19–0.88), $p = 0.023$). None of the 18 PD participants homozygous for ε2 had cognitive impairment.

Table 2
Relationship between APOE ε4 genotype dose and cognition status among Nigerians with Parkinson's disease

	PD with normal cognition n = 922	**PD with impaired cognition n = 121**	**Hazard ratio (95% CI)**	***p-value**
ε4 dose				
0	546 (90.1)	60 (9.9)	Reference	
1	322 (86.8)	49 (13.2)	1.38 (0.95–2.03)	0.094
2	54 (81.8)	12 (18.1)	2.09 (1.13–3.89)	0.020
ε2 dose				
0	782 (87.3)	114 (12.7)	Reference	
1	122 (94.6)	7 (5.4)	0.41(0.19–0.88)	0.023
2	18 (100.0)	0 (0.0)		

Footnote: ε4 dose : 0 = ε2/ε2, ε2/ ε3, ε3/ ε3, 1 = ε3/ ε4, 2 = ε4/ ε4; ε2 dose: 0 = ε3/ ε3, ε3/ ε4, ε4/ ε4, 1 = ε2/ ε3, 2 = ε2/ ε2. ε2/ ε4 excluded as they are nor risk neither protective factor. *Adjusted for gender and age at onset

Discussion

This is the largest dataset from individuals of black African ancestry investigated to date describing genetic variability in *APOE* in the context of PD and providing a comparison to ethnically matched otherwise healthy subjects from the same geographical location. In addition, we provide further insight into the distribution of *APOE* in modern populations by adding to the existing data on the frequency of *APOE* alleles and genotypes from the healthy population in Nigeria. As it has been described in other publications, the *APOE* ε3 was the most frequent allele, present in 59.9% of the healthy controls in this study (compared to the widely variable global range of 8.5–98.0% derived from populations across all continents) [13], and within the range of rates reported from modern African populations (48–94%). [13–16] The frequency of ε4 in our healthy controls (28.2%) is also mid-range of the typical rates (14.3% – 40.7%) for Africa, in which the highest frequencies are in Central Africans (from 29% in Fon to 40% in Aka pygmies). [13] The least frequent allele was ε2 (present in 11.8%) and also coincides (though at the

higher end of the range) with earlier reports from Africa (2.7–11.6%). [13, 17] The genotype distributions in our healthy controls (ε3/ε3 and ε3/ε4 most common) followed a similar trend with the most recent data for individuals of black ethnicity included in the systematic review by Qin *et al*. [15]

Regarding the specific objectives of our study, we found no association between any specific *APOE* allele or genotype and the risk of PD in our population. Our findings corroborate previous observations in other populations, indicating that the distribution of *APOE* alleles (including specifically ε4 carrier rates), ε4 or ε2 allele dosage, and *APOE* genotypes are not significantly different between PD and controls. [18, 19] We did not observe the significant over-representation of *APOE* ε2 carriers in PD reported in previous meta-analysis, and our observation is similar with the data presented by William-Gray *et al* for the primary cohort of 528 PD and 512 controls, in which the frequency of ε2 was 8.3% for both PD and controls. [18 – 20]

We found a modest but significant (protective) association of the *APOE* ε2 allele with cognitive status in our cohort, with higher ε2 dosage conferring a lower (but small) risk of cognitive impairment in individuals with PD. On the other hand, the presence of the ε4 allele conferred a two-fold increased risk of abnormal cognition. These findings align with the postulate of a modest protective effect of ε2 and detrimental impact of ε4 on cognition in PD. Several studies and meta-analyses have demonstrated an over-representation of *APOE* ε4 carriers amongst individuals with PD cognitive impairment and dementia, although others have been equivocal or provided only modest evidence. [19, 21 – 24]. Studies including GWAS of neuropathologically confirmed PD have also strengthened the credibility of an association between *APOE* e4 carrier status by demonstrating a significant association with cognitive decline in PD. [25, 26] The more appealing explanation of the effect of genetic variability on cognition in PD is that of a cumulative effect conferred by multiple common (often independently low risk) variants (polygenic risk) such as *APOE* ε4. A recent longitudinal genome-wide survival study not only confirmed the notion of an association between *APOE* and cognition in PD, but demonstrated a substantial aggregate association of polygenic progression scores (but not polygenic susceptibility scores) with dementia risk, and proposed diverging genetic architectures of cognitive disease progression and susceptibility. [27] We acknowledge the limitations with respect to the measure of cognitive function utilized in this analysis, and understand the inherent challenge with specifically comparing our data with studies that have used more widely recommended and robust measures such as the Montreal Cognitive Assessment (MoCA) and other extensive cognition batteries. [28] The aspiration to provide an albeit exploratory impression of the relationship of *APOE* status to cognition in our population where no prior data exists, coupled with the precedence for the use of the MDS UPDRS single patient-reported cognition question in the absence of more robust assessments provided the rationale for this approach. [29] This single item reportedly is most strongly associated with visuospatial/executive function and delayed recall on the MoCA. [29] We share the sentiment of Mills and colleagues that the less complicated, more global patient-reported cognitive measure is externally valid and inherently useful. Our study is informative in that with only one question about global cognition, the patient had to sum his or her experiences and give a general response based on the degree of self-assessed severity while avoiding the distraction of more interrogative approaches. In addition, our observations are likely credible because the trend of association between *APOE ε*4 and cognitive impairment occurred despite the similarity in potential clinical confounders such as age at onset, duration of PD, and age at study. Although the proportion of PD with cognitive impairment at the median duration of disease in this study using the single MDS UPDRS cognition screen is similar to previous studies employing more robust assessments of cognition, the interpretation of our findings must be cautious. A validation study of the MDS-UPDRS Part 1 for non-motor symptoms compared the single item cognition question to Addenbrooke's Cognitive Examination (ACE), Scales for

Outcome of Parkinson's disease (SCOPA)-cognitive scale (SCOPACOG), and Frontal Assessment Battery (FAB) found a weak (though positive and statistically significant) correlation for all three cognitive scales (ACE, SCOPA-COG, and FAB). The study alluded to the possibility of heterogeneity in cognitive profiles in PD, which makes demonstrating a stronger correlation with a single screening question difficult. [30] Our study is also limited by the draw-back of providing a comparison of cognitive profile derived from a static snapshot whereas cognitive decline is an inherently dynamic clinical variable which can occur with disease progression in neurodegenerative disorders such as PD.

In conclusion, our study provides the first (and largest to date) study describing the association between *APOE* and PD in individuals of black African ancestry, demonstrating a lack of association with disease risk and age at onset and indicating a trend of association of cognitive impairment with *APOE ε*4 and protection by higher doses of *APOE* ε2.

Methods

Participant recruitment and clinical assessments

A total of 1100 Nigerians with PD and 1097 healthy controls matched by age, gender and ethnicity were included in this cohort study. We excluded 83 participants (31 controls and 52 PD participants) with incomplete genotyping data. The excluded participants did not differ from those included based on age at study (p = 0.998), male/female ratio (p = 0.98), or age at onset of PD (p = 0.56). Participants were recruited from an ongoing study being conducted by the Nigeria Parkinson's Disease Research (NPDR) network in collaboration with the International Parkinson's Disease Genomics Consortium Africa (IPDGC Africa). [31, 32] The NPDR includes participating sites from tertiary neurology clinics covering all 6 geopolitical regions in Nigeria. [31] Approval of the study protocol was obtained from the institutional health research ethics committees, the National Health Research Ethics Committee (NHREC) in Nigeria and the ethics committee of the University College London and the National Hospital for Neurology and Neurosurgery, London, United Kingdom.

PD diagnosis was based on the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria. [33] Data available for analysis in this study include baseline demographics (age at study, gender, age at onset of PD, duration of PD (years), disease stage (Hoehn and Yahr), and patient-reported cognitive status. Cognitive status was assessed in individuals with PD using the Movement Disorder Society (MDS) Unified Parkinson's Disease Rating Scale (UPDRS) (n = 987) or the earlier version of the UPDRS (n = 113) single item question on cognitive status (Part 1 item 1.1 of the instrument). The response is rated as 0: Normal: No cognitive impairment; 1: Slight: Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions; 2: Mild: Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions; 3: Moderate: Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions; and 4: Severe: Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions. The responses for the small sample of 113 with old UPDRS scores were recoded to the most approximate MDS UPDRS score (0◊0, 1◊1, 2◊3, and 3 or 4◊4). This convenience was adopted because the previously published formulae for calibration of data allows archival UPDRS Parts II and III data to be accurately transferred to MDS-UPDRS scores but are not accurate for Part I and IV scores. [34] In this study, cognition scores of

0 and 1 were interpreted as PD with normal cognition, whereas scores of 2 to 4 were regarded as abnormal cognition.

APOE **genotyping**

DNA was extracted from saliva samples collected using DNA Genotek® saliva kits or from venous whole blood samples using standard protocols. *APOE* genetic variation was determined by genotyping two well established non-synonymous single nucleotide polymorphisms (SNPs): rs429358 and rs7412. The Kompetitive Allele-Specific Polymerase Chain Reaction (PCR) assay (KASP™, LGC Genomics. Herts, UK) was used as described elsewhere to genotype both SNPs in 987 participants with PD and 1050 controls. [35] In addition, 113 samples from individuals with PD and 47 controls were genotyped using the Infinium® NeuroChip Consortium Array (Illumina, San Diego, CA, USA).[36, 37] NeuroChip array description and validation of its ability to accurately identify *APOE* genotype calls compared to standard Taqman genotyping is well established. [38] Quality control assessments for the arrays were carried out using PLINK version 1.9 and genotype calls of the rs429358 and rs7412 SNPs were extracted to define the *APOE* alleles as described previously. [36, 37] SNPs genotypes were assessed for Hardy-Weinberg equilibrium (HWE) using Fisher exact test.

Data analyses

Cohort characteristics are expressed as counts (%), mean ± SD or medians and compared between groups (PD and controls) using two tailed X^2 test for categorical variables (or) analysis of variance (ANOVA) or non-parametric alternative for continuous variables as relevant. Frequency proportions in percent of *APOE* alleles (*ε*2, *ε*3, *ε*4) and genotypes (*ε*2/*ε*2, *ε*2/ *ε*3, *ε*2/ *ε*4, *ε*3/ *ε*3, *ε*3/ *ε*4, *ε*4/ *ε*4) were calculated and compared to published data in subjects from other populations. Logistic regression was used to analyze the association between *APOE* and PD risk, and cognitive performance (in individuals with PD with normal cognition versus PD with impaired cognition). The differences in the frequencies of genotypes and allele between persons with PD and controls,

and Hardy Weinberg equilibrium (HWE) was tested using the Pearson's Chi-square test. SNP rs429358 was in HWE for both control and cases (p = 0.76 and p = 0.40 respectively). For SNP rs7412, HWE was preserved in controls (p = 0.56) but not in (cases p = 0.03) (See Supplementary Figs. 1 and 2). Cox proportional hazards regression was used to investigate the influence of *APOE* on age of onset of PD. For all analyses, PD cases and (or) controls were used as the dependent variable and the relevant *APOE* allele, genotype and *ε*4 dose as the independent variables, adjusting were relevant for gender, age at onset or at study in PD, and age at recruitment for controls. *APOE ε*4 dose was defined as 0 dose = ε2/ε2, ε2/ ε3 and ε3/ ε3, 1 dose = ε3/ ε4 and 2 doses = ε4/ ε4. Genotype ε2/ε4 was excluded from the analysis because ε2 is considered protective and ε4 is considered a risk variant. Data were analysed using Stata/MP version 16.0 statistical software (Stata Corporation, College Station, TX: StataCorp LLC).

Declarations

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Mie Rizig: University College London; grants

ETHICAL COMPLIANCE STATEMENT

The study was approved by the institutional research ethics committees of the participating centers and the National Health Research Ethics Committee of Nigeria. All participants provided written informed consent prior to inclusion in the registry and study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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