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Assessment of APOE in atypical parkinsonism syndromes

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ABSTRACT

Atypical parkinsonism syndromes are a heterogeneous group of neurodegenerative disorders that include corticobasal degeneration (CBD), Lewy body dementia (LBD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP). The *APOE ε4* allele is a well-established risk factor for Alzheimer's disease; however, the role of *APOE* in atypical parkinsonism syndromes remains controversial. To examine the associations of *APOE ε4* and *ε2* alleles with risk of developing these syndromes, a total of 991 pathologically-confirmed atypical parkinsonism cases were genotyped using the Illumina NeuroChip array. We also performed genotyping and logistic regression analyses to examine *APOE* frequency and associated risk in patients with Alzheimer's disease (n = 571) and Parkinson's disease (n = 348). *APOE* genotypes were compared to those from neurologically healthy controls (n = 591). We demonstrate that *APOE ε4* and *ε2* carriers have a significantly increased and decreased risk, respectively, of developing Alzheimer's disease (*ε4:* OR: 4.13, 95% CI: 3.23–5.26, $p = 3.67 \times 10^{-30}$; *ε2:* OR: 0.21, 95% CI: 0.13–0.34; $p = 5.39 \times 10^{-10}$) and LBD (*ε4:* OR: 2.94, 95% CI: 2.34–3.71, $p = 6.60 \times 10^{-20}$; *ε2:* OR = OR: 0.39, 95% CI: 0.26–0.59; $p = 6.88 \times 10^{-6}$). No significant associations with risk for CBD, MSA, or PSP were observed. We also show that *APOE ε4* decreases survival in a dose-dependent manner in Alzheimer's disease and LBD. Taken together, this study does not provide evidence to implicate a role of *APOE* in the neuropathogenesis of CBD, MSA, or PSP. However, we confirm association of the *APOE ε4* allele with increased risk for LBD, and importantly demonstrate that *APOE ε2* reduces risk of this disease.

1. Introduction

The prevalence of age-related neurodegenerative diseases is a growing public health concern (World Health Organization, 2006). There exists a critical, unmet need for unraveling the genetic architectures that underlie neurodegenerative disorders. Identifying and

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validating pathogenic molecular defects can inform targets for drug-discovery efforts and disease-modifying interventions. Atypical parkinsonism syndromes are a diverse group of progressive neurological disorders characterized by the presence of parkinsonism in addition to clinical features considered atypical for Parkinson's disease (PD), such as early falls and/or early cognitive impairment (Scholz and Bras, 2015). The accurate clinical diagnosis of atypical parkinsonism disorders remains a major challenge as a result of broad phenotypic variability and the overlap with mimic syndromes.

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are characterized pathologically by the presence of neuronal and glial tau-positive inclusions, while multiple system atrophy (MSA) and Lewy body dementia (LBD) are defined by abnormal accumulation of aggregated α-synuclein as glial cytoplasmic inclusions and as neuronal Lewy bodies, respectively (Irwin et al., 2015; Spillantini and Goedert, 2016). Interestingly, AD co-pathology is observed in approximately 65 to 90% of LBD patients, placing LBD along a clinicopathological continuum between PD and AD (Dugger et al., 2014; Harding and Halliday, 2001; Merdes et al., 2003; Schneider et al., 2012).

Advances in modern genomic technologies have been key to the systematic dissection of the molecular etiology of neurodegenerative diseases. These efforts have revealed overlapping risk loci among atypical parkinsonism syndromes and other neurodegenerative diseases clearly suggesting that these diseases are etiologically related. Dysregulation of lipid metabolism/homeostasis has been ascertained as a contributor of degenerative disorders (Bleasel et al., 2014; Sultana et al., 2013). The *ε4* allele of apolipoprotein E (*APOE*), a well-established lipid metabolism and cholesterol transport gene, is known to be a major genetic risk determinant for sporadic, late-onset AD and LBD (Corder et al., 1993; Liu et al., 2013). Allelic dose effects for this gene have been observed among AD cases: a single copy of the *ε4* allele imparts a three-fold risk of developing disease, while subjects with an *ε4/ε4* genotype demonstrate an approximate eight-fold increase in disease risk (Corder et al., 1993; Liu et al., 2013). The *ε4* allele is also associated with a significantly decreased age at disease onset and decreased survival in a dose-dependent manner (Christensen et al., 2006; Corder et al., 1993; Schächter et al., 1994). On the other hand, the *APOE ε2* allele has been reported to have a protective effect in late-onset AD. Despite this, the role of the *ε2* allele in LBD and other atypical parkinsonism disorders remains unclear (Berge et al., 2014; Corder et al., 1994; Lovati et al., 2010; Van Cauwenberghe et al., 2016). To address this question, we investigated the allele frequencies of *APOE* in four pathologically-confirmed cohorts of atypical parkinsonism in addition to AD and PD patients. We compared our findings to neurologically healthy controls.

2. Material and methods

2.1. Study subjects

Brain tissue and/or blood samples were obtained from eighteen North American and European research centers and brain banks (Supplementary Table 1). All participants gave written, informed consent for post mortem brain or blood donation. A total of 1910 neurodegenerative disease patients of European ancestry and 591 neurologically healthy controls over the age of 50 were included (Table 1). The neurodegenerative disease cases included: AD (n = 571), PD (n = 348), LBD (total n = 525; dementia with Lewy bodies (n = 468) and Parkinson's disease dementia (n = 57)), MSA (n = 223), PSP (n = 202), and CBD (n = 41). All cases were diagnosed using consensus pathologic criteria (Dickson et al., 2002; Dickson et al., 2009; Gilman et al., 2008; Hauw et al., 1994; Hyman et al., 2012; McKeith, 2006).

2.2. NeuroChip array genotyping and quality control

Genomic DNA was extracted from frozen brain tissue or blood using standard phenol-chloroform extraction techniques. Genotyping was performed using the NeuroChip (Illumina, San Diego, CA, USA), a versatile microarray that is comprised of a tagging backbone (n = 306,670 variants) and 179,467 variants of custom "neuro" content (Blauwendraat et al., 2017). NeuroChip genotyping was conducted following the manufacturer's protocol as described elsewhere (Blauwendraat et al., 2017). The data were exported from GenomeStudio using the Illumina-to-PLINK module 2.1.4 and imported into PLINK version 1.90 (Chang et al., 2015). Quality control procedures were performed, and only samples with call rates > 95%, lack of contamination (i.e. passing heterozygosity threshold of < 0.15), concordance between reported and genotypic sex, relatedness based on PIHAT metric < 0.125, and European ancestry individuals based on the 1000 Genomes Project were included in the study (Genomes Project Consortium et al., 2015).

2.3. APOE allele genotyping

Genotype calls of two *APOE* single nucleotide polymorphisms, rs429358 and rs7412, were used to determine the *APOE* status of each sample. The combination of genotypes for rs429358 (C/T) and rs7412 (C/T) defines the three allelic variants of *APOE*: epsilon 2 (ε2), epsilon 3 (ε3), and epsilon 4 (ε4). These three allelic variants produce six genotypes, ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4. Validation of accurate *APOE* genotype calls using NeuroChip compared to standard Taqman genotyping has been previously described (Blauwendraat et al., 2017).

2.4. Statistical analysis

Association of *APOE ε2* and *ε4* alleles with risk of neurodegenerative disease (i.e.; AD, PD, CBD, LBD, MSA, and PSP) compared to controls was evaluated using PLINK version 1.90 logistic regression models, adjusted for sex and age (i.e. age at death for pathologically-confirmed samples or age at specimen collection for clinically-defined control samples).

Survival analyses were performed for each cohort using log-rank tests as implemented in the R "survival" and "survminer" packages. Only samples for which age of death information was available were included in these analyses (217/218 controls, 568/571 Alzheimer's disease cases, 523/525 LBD cases, 101/223 MSA cases, 202/202 PSP cases, 41/41 CBD cases).

3. Results

We demonstrated that *APOE ε4* carriers (genotypes: *ε2/ε4*, *ε3/ε4*, and *ε4/ε4*) had a statistically significant increased risk of developing AD (OR: 4.13, 95% CI: 3.23–5.26, $p = 3.67 \times 10^{-30}$) and LBD (OR: 2.94, 95% CI: 2.34–3.71, $p = 6.60 \times 10^{-20}$). Both of these results surpassed the Bonferroni threshold for multiple comparisons (Table 2). In contrast, carriers of the *APOE ε2* allele, as defined by *ε2/ε2* and *ε2/ε3* genotypes, had a significantly decreased risk of developing AD (OR: 0.21, 95% CI: 0.13–0.34; $p = 5.39 \times 10^{-10}$) or LBD (OR: 0.39, 95% CI: 0.26–0.59; $p = 6.88 \times 10^{-6}$) (Table 2). There were no significant associations of *APOE ε4* and *ε2* with altered risk of developing CBD, MSA, PSP, or PD (Table 2, Supplementary Table 2). Additionally, a dose-response association between increasing *APOE ε4* allele dose and reduced survival was observed in AD ($p < 0.0001$) and LBD ($p = 0.0022$); the association with PSP did not surpass the Bonferroni threshold (Supplementary Fig. 1).

4. Discussion and conclusions

The *APOE ε4* allele has been widely and consistently implicated in the pathogenesis of AD and LBD (Galasko et al., 1994; Robinson et al., 2018; Singleton et al., 2002; St Clair et al., 1994; Tsuang et al., 2013).

Table 1
Cohort characteristics and distribution of *APOE* genotypes in study populations.

	Controls	AD	PD	CBD	LBD	MSA	PSP
N	591	571	348	41	525	223	202
Mean Age ± SD (years)[a]	71.7 ± 11.0	81.8 ± 10.1	78.2 ± 9.4	74.8 ± 9.3	77.5 ± 8.2	66.1 ± 10.8	78.1 ± 9.7
Age range (years)[a]	(50, 105)	(41, 103)	(19, 107)	(51, 96)	(49, 99)	(20, 90)	(55, 102)
No. Male (%)	318 (53.8)	221 (38.7)	234 (67.2)	18 (43.9)	338 (64.4)	109 (48.9)	113 (55.9)
No. Female (%)	273 (46.2)	350 (61.3)	114 (32.8)	23 (56.1)	187 (35.6)	114 (51.1)	89 (44.1)
No. Pathologically-confirmed	218 (36.9)	571 (100)	348 (100)	41 (100)	525 (100)	223 (100)	202 (100)
No. Clinically-defined	373 (63.1)[b]	N/A	N/A	N/A	N/A	N/A	N/A
No. with ε2/ε2 (%)	5 (0.8)	0 (0)	0 (0)	0 (0)	2 (0.4)	0 (0)	3 (1.5)
No. with ε2/ε3 (%)	83 (14.0)	29 (5.1)	54 (15.5)	4 (9.8)	35 (6.7)	25 (11.2)	20 (9.9)
No. with ε2/ε4 (%)	14 (2.4)	11 (1.9)	6 (1.7)	1 (2.4)	14 (2.7)	6 (2.7)	5 (2.5)
No. with ε3/ε3 (%)	368 (62.3)	208 (36.4)	203 (58.3)	28 (68.3)	239 (45.5)	141 (63.2)	138 (68.3)
No. with ε3/ε4 (%)	104 (17.6)	252 (44.1)	82 (23.6)	6 (14.6)	187 (35.6)	48 (21.5)	33 (16.3)
No. with ε4/ε4 (%)	17 (2.9)	71 (12.4)	3 (0.9)	2 (4.9)	48 (9.1)	3 (1.3)	3 (1.5)

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; CBD, corticobasal degeneration; LBD, Lewy body dementia; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; SD, standard deviation; N/A, not applicable.

[a] Age was defined as age at death for pathologically-confirmed samples and age at specimen collection for clinically-defined control samples. Age information was available for 590/591 controls, 568/571 AD samples, 342/348 PD samples, 41/41 CBD samples, 523/525 LBD samples, 101/223 MSA samples, and 202/202 PSP samples.

[b] DNA from clinically defined control samples was extracted from blood as opposed to brain tissue from all other cohorts.

The main objective of this study was to determine the frequency and risk of disease associated with the *APOE ε4* and *ε2* alleles in pathologically-confirmed atypical parkinsonism subjects compared to neurologically healthy individuals. We confirmed the well-known effect of *APOE* on AD and LBD risk. In addition, we also compared autopsy-confirmed AD and PD cohorts to controls. We found that *APOE ε4* carrier status is significantly associated with increased risk of developing AD and LBD, while *APOE ε2* carriers have a decreased relative risk of developing these degenerative dementias. A prior study of *APOE ε2* in clinically-diagnosed DLB patients also demonstrated a protective *ε2* effect (Berge et al., 2014). Recently, Dickson et al. reported that *APOE ε4* is associated with greater severity of Lewy body pathology independent of Alzheimer's disease pathology (Dickson et al., 2018). Interestingly, another recent study demonstrated similar decreases in methylation at the *APOE* locus in post mortem brain tissues of neuropathological pure LBD and AD suggesting that this epigenetic alteration may also be contributing to disease risk (Tulloch et al., 2018).

Our data indicate that *APOE* is not a risk factor for PD nor MSA or for the tauopathies CBD and PSP. Our results confirmed previous studies of *APOE* in PD and MSA (Federoff et al., 2012; Morris et al., 2000; Morris et al., 2001; Ogaki et al., 2018; Sailer et al., 2016; Toji et al., 1998). A genome-wide association study (GWAS) performed on a small cohort of CBD also found no association of *APOE* with CBD (Kouri et al., 2015). Recently, a study of 134 CBD cases found no significant associations of *ε2* or *ε4* with disease risk (Zhao et al., 2018). The role of *APOE* variants in risk of developing PSP has been controversial (Anouti et al., 1996; Baba et al., 2006; Morris et al., 2000; Morris et al., 2001; Pickering-Brown et al., 2000; Tabaton et al., 1995). A higher frequency of *APOE ε2* allele, but not *ε4* allele, in PSP was found in a Japanese cohort (Sawa et al., 1997). The first PSP GWAS, including 1150 autopsy-confirmed cases, demonstrated that the *ε4* frequency is reduced in PSP (Höglinger et al., 2011). A recent study by Zhao and colleagues of a series of 994 PSP patients found that *APOE ε2/ε2* carriers have a significantly increased risk of developing disease (OR = 4.41) (Zhao et al., 2018). Similarly, our study shows a higher frequency of *APOE ε2/ε2* carriers in PSP (1.5%) versus controls (0.8%), but no significant association of the *ε2* allele with risk of disease. Additionally, possession of the *APOE ε4* allele has not been shown to affect age of disease onset in MSA or PSP (Morris et al., 2001).

A notable strength of this study is the use of large, pathologically-proven cohorts of atypical parkinsonism syndrome patients. This approach effectively eliminates diagnostic uncertainty due to heterogeneous clinical presentations and possible presence of mimic syndromes.

There are a number of limitations to this study. First, age information was not available for 134 subjects and most of the patients (122/

Table 2
Association of *APOE* ε4 and ε2 with risk of neurodegenerative diseases.

Cohort	N	*APOE* ε4 carriers			*APOE* ε2 carriers		
		N. samples (%)[a]	OR (95% CI)	*p* value	No. samples (%)[b]	OR (95% CI)[c]	*p* value
Controls	591	135 (22.8)	1.00 (Reference)	N/A	102 (17.3)	1.00 (Reference)	N/A
AD	571	334 (58.5)	**4.13 (3.23, 5.26)**	$\mathbf{3.67 \times 10^{-30}}$	40 (7.0)	**0.21 (0.13, 0.34)**	$\mathbf{5.39 \times 10^{-10}}$
PD	348	91 (26.1)	1.18 (0.88, 1.59)	0.27	60 (17.2)	0.88 (0.60, 1.29)	0.52
CBD	41	9 (22.0)	1.10 (0.59, 2.04)	0.76	5 (12.2)	0.57 (0.20, 1.60)	0.29
LBD	525	249 (47.4)	**2.94 (2.34, 3.71)**	$\mathbf{6.60 \times 10^{-20}}$	51 (9.7)	**0.39 (0.26, 0.59)**	$\mathbf{6.88 \times 10^{-6}}$
MSA	223	57 (25.6)	1.11 (0.74, 1.67)	0.62	31 (13.9)	0.80 (0.43, 1.49)	0.48
PSP	202	41 (20.3)	0.95 (0.66, 1.35)	0.77	28 (13.9)	0.72 (0.45, 1.14)	0.16

ORs, 95% CIs, and p value results from logistic regression models adjusted for sex and age at death for pathologically-confirmed samples or age at collection for clinically-defined control samples.

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; CBD, corticobasal degeneration; LBD, Lewy body dementia; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; OR, odds ratio; CI, confidence interval; N/A, not applicable.

[a] ε4 allele carriers included individuals with genotypes ε2/ε4, ε3/ε4, and ε4/ε4.

[b] ε2 allele carriers included individuals with genotypes ε2/ε2, ε2/ε3, and ε2/ε4.

[c] When calculating the OR, individuals with the ε2/ε4 genotype were excluded from the ε2 relative risk analyses since ε2 is predicted to be protective and ε4 is shown to be a risk factor.

134) were within the MSA cohort. Second, although our CBD cohort consisted of only 41 subjects, previous non-GWAS studies investigating *APOE* allele frequencies in CBD have been limited to 18 patients or fewer (Borroni et al., 2006; Josephs et al., 2004; Pickering-Brown et al., 2000; Schneider et al., 1997). We acknowledge that our CBD cohort has only low power for identifying significant associations, and thus the results of the *APOE* analysis in this cohort should be interpreted with caution. Additionally, it is possible that our clinically-defined controls (n = 373/591 subjects) may develop a neurodegenerative disease later in their life. To counter this limitation, logistic regression analyses performed with inclusion of only pathologically-confirmed controls mirrored the results in Table 2.

Taken together, our findings did not implicate *APOE ε4* as a major genetic risk determinant for atypical parkinsonism syndromes, including CBD, MSA, and PSP. In contrast, we replicate association of the *APOE ε4* allele and risk for LBD, and importantly demonstrate that possession of the *ε2* allele is associated with a lower relative risk. Additional functional studies are required to elucidate the biological mechanism underlying this effect. Our findings support the notion of overlapping pathogenetic mechanisms between AD and LBD. Further investigation of other genetic loci associated with the spectrum of neurodegenerative diseases, particularly of AD- and PD-related loci, is essential for improving the diagnostic, prognostic, preventative and therapeutic management of atypical parkinsonism syndromes.

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Authors' roles

Research Project: A. Conception (SWS), B. Organization (SWS), C. Sample Contributors (GES, TGB, MP, ACR, EM, CMM, LP, AP, SR, MRC, DGH, MA, TMD, LSR, HH, OP, JT), D. Execution (MSS, CB, SA, SWS). Statistical Analysis: A. Design (MSS, CB, SWS) B. Execution (MSS), C. Review and Critique (MSS, CB, SWS). Manuscript: A. Writing of the first draft (MSS), B. Review and Critique (CB, SA, GES, TGB, MP, ACR, EM, CMM, LP, AP, SR, MRC, DGH, MA, TMD, LSR, HH, OP, JT, SWS).

Disclosure statement

The authors report no conflicts of interest.

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