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Apolipoprotein E ε2 genotype delays onset of dementia with Lewy bodies in a Norwegian cohort

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ABSTRACT

Background Results conflict concerning the relevance of *APOE* alleles on the development of dementia with Lewy bodies (DLB), though they are well established in connection with Alzheimer's disease (AD). The role of *APOE* alleles in a Norwegian cohort of patients with DLB was therefore examined compared with patients with AD and healthy control individuals.

Methods The study included 156 patients with DLB diagnosed according to the consensus criteria guidelines, 519 patients diagnosed with AD according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ARDRA) criteria and 643 healthy elderly volunteers. Patients were recruited through hospitals, outpatient clinics, nursing homes or from local care authorities in central and south-western parts of Norway. Healthy individuals were recruited from caregivers and societies for retired people.

Results Subjects carrying an *APOE* ε2 allele had a reduced risk for developing DLB (OR 0.4, CI 0.3 to 0.8, p=0.004), and the onset of disease was delayed by 4 years (p=0.01, Mann–Whitney U test). Conversely, the *APOE* ε4 allele increased the risk for development of DLB (OR 5.9, CI 2.7 to 13.0, p<0.0005 for homozygotes). Similar results were found for patients with AD regarding the effect of APOE ε2, though the protective effect appeared to be slightly less pronounced than in DLB. This study is one of the largest regarding DLB and *APOE* to date.

Conclusion The results indicate that *APOE* ε2, a protective factor in AD, has a clear beneficial effect on the development of DLB also.

INTRODUCTION

Several neurodegenerative diseases may arise as a consequence of sequential biochemical processes operating in more than one disease entity,[1] and could represent points on a continuum of neuropathological change, rather than being distinct nosological entities.[2] The human *APOE* gene has undergone extensive study in connection with neurodegenerative disease since the *APOE* ε4 allele was found to be the most important genetic risk factor for late-onset Alzheimer's disease (AD),[3 4] including a large Norwegian cohort,[5] as well as early-onset AD.[6] Conversely, the *APOE* ε2 isoform has been found in some studies to impart a reduced risk of AD.[7–9]

Dementia occurring before or during the first year of Parkinsonism is classified as dementia with Lewy bodies (DLB), with core features including visual hallucinations and fluctuating cognition.[10] It is the second most common neurodegenerative dementia type after AD among older patients.[11] There is overlap between the neuropathology of DLB and AD, and most DLB patients have at least some degree of plaque pathology and even tangle pathology. Risk factors for AD could therefore in theory also increase the risk of DLB.[11 12] Previous studies have suggested the *APOE* ε4 allele to be a risk factor for DLB,[13–16] though not all.[7]

Norway is a suitable country for conducting genetic analysis of neurological disease, as the ethnic population has remained relatively stable for several centuries and is comparatively homogeneous. The present study is one of the largest to date concerning the *APOE* genotype in connection with DLB, and tested the hypothesis that *APOE* genotype affects the risk for developing DLB. The results have been compared with a population of patients with AD, as well as with elderly control individuals without signs of any neurodegenerative disease.

METHODS

Subjects

The clinical material (table 1) consisted of a total of 1318 individuals: 156 patients diagnosed with DLB, 519 patients diagnosed with AD and 643 elderly control individuals, all ethnic Norwegians. Participants from central and western parts of Norway were included in one of two long-term ongoing studies of dementia (TrønderBrain or DemVest).

Caregivers not genetically related to the patients, as well as other elderly volunteers recruited from societies for retired people in central Norway, all without first-degree relatives with dementia, were enrolled as controls in the TrønderBrain study as described earlier.[5] They were healthy for their age and displayed no signs of a neurological disorder. They were age- and sex-matched to the patient groups as closely as possible.

Patients in the TrønderBrain study were recruited through the University Hospital of Trondheim, the district hospital in Namsos, nursing homes and local care authorities in central Norway. Patients with AD (diagnosed according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria[17] as described elsewhere[5]) or DLB were diagnosed by a single neurologist (SBS).

The TrønderBrain DLB patients and/or a suitable proxy gave a case history, including occurrence of core features of DLB. The neurological examination included Mini Mental State Examination (MMSE), Clock Drawing Test and the motor examination part of Unified Parkinson's Disease Rating Scale

Table 1 Demographic data for the study groups

	DLB (total)	DLB (TrønderBrain)	DLB (DemVest)	AD (TrønderBrain)	Healthy controls (TrønderBrain)
Cases (total)	156	103	53	519	643
Probable/possible DLB	135/21	88/15	47/6		
Females (%)	67 (42.9)*,†	44 (42.7)	23 (43.4)	351 (67.6)*	388 (60.3)
Age at onset (y)	72.3±7.9	72.3±7.7	72.1±8.3	71.3±9.3	NA
Age at inclusion (y)	76.3±7.6*	76.9±7.7	75.3±7.4	76.0±9.9*	74.8±7.2
Duration (y)	4.2±3.0†	4.5±3.1	3.5±2.5	4.7±3.2	NA
Range of onset (y)	46–89	46–88	50–89	47–88	NA
Mean education (y)	9.8±3.1	9.9±3.1	9.6±3.0	9.5±3.1*	9.8±2.9
MMSE	19.6±7.5	17.9±8.4‡	22.9±3.3	17.8±8.1†	NA
UPDRS III	16.9±12.9†	18.7±12.3‡	13.9±13.6	3.3±6.0 (n=294)	NA

Statistical analysis was initially made using the Kruskal–Wallis test for multiple groups. Where values of $p<0.05$ were found, subsequent individual group comparisons were made with the Mann–Whitney U test.
All p values ≤0.03.
*Significant difference between a patient group and the control group.
†Significant difference between the groups of patients with DLB or AD.
‡Significant difference between the two DLB cohorts.
AD, Alzheimer's disease; DLB, dementia with Lewy bodies; MMSE, Mini Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale.

(UPDRS). Diagnosis of probable or possible DLB was based on the original consensus criteria guidelines,[18] but for the purposes of analysis were considered as a single group. About 20% of the TrønderBrain cases with clinically diagnosed DLB had a dopamine-transporter SPECT (^{123}I-Ioflupane) to support the diagnosis. Pathological confirmation of the clinical dementia diagnosis was available for two patients with DLB.

Patients included in the multicentre DemVest study were recruited from outpatient clinics in the counties of Hordaland and Rogaland. DLB patients with mild dementia (n=53) were examined by a licensed specialist in geriatrics or psychiatry, and diagnosis was made after discussion by a consensus panel, and according to the new criteria.[19] Each patient was interviewed at inclusion, usually with a caregiver attending who could provide supplementary information. Medical history, neurological and neuropsychological examinations were performed. All patients were assessed for diagnostically relevant information, including the motor examination part of UPDRS, the Neuropsychiatric Inventory. The Mayo fluctuating cognition scale and Mayo sleep scale were administered to assess visual hallucinations, fluctuating cognition and REM-sleep behavioural disorder. Supplemental investigations included routine blood tests, brain MRI or CT, as well as cerebrospinal fluid assessment in some of the cases. Overall, 28% of the DemVest cases had a dopamine-transporter SPECT (^{123}I-Ioflupane) to support the diagnosis, and pathological confirmation of the clinical dementia diagnosis was available for the first seven cases from the DemVest material.

APOE genotyping

APOE genotyping was performed on blood samples from all patients and control individuals. Fresh whole blood was drawn into 6 mL EDTA-vacutainers, and DNA isolated using the QIAamp DNA Blood Mini Kit (QIAGEN), together with the spin protocol provided. Random samples of isolated DNA were checked for purity using NanoDrop technology, and all samples were frozen and stored at −80°C. *APOE* analysis was either performed according to the protocol described elsewhere[5] or using the Fast Start DNA Master HybProbe Kit (Roche) in combination with the LightMix ApoE C112R R158C kit from TiB MolBiol (Berlin, Germany) according to the manufacturer's instructions, followed by *APOE* genotyping with LightCycler technology (Roche).

Statistical analyses

No difference in the frequency of *APOE* alleles was found between the two DLB cohorts, and the genotype data were therefore pooled. Statistical analyses were performed using SPSS V.21.0. Categorical variables were compared using Pearson's χ^2 test. The Kruskal–Wallis test (KW) was used for comparisons between multiple groups, followed by the Mann–Whitney U test (MW) between individual groups. OR were calculated for *APOE* alleles by binary logistic regression, using the *APOE* ε3/ε3 genotype as reference value, both unadjusted and adjusting for potential confounders (age and gender). Two-sided p values <0.05 were considered significant. Where applicable, the mean±SD is given.

Ethical considerations

Written, informed consent was obtained from all patients or suitable proxies, and from all control individuals. The biobanks are licensed by the Norwegian Directorate for Social and Health Affairs, and the research project was approved by the relevant Regional Committee for Medical Research Ethics.

RESULTS

The demographic data are shown in table 1. Significant differences were found in gender between the test groups, with more men among patients with DLB compared with both AD and control groups ($p<0.0005$, KW), but more females among patients with AD compared with controls ($p=0.01$, MW) as is typically found.[20] Mean education was significantly lower in the group with AD compared with the controls ($p=0.002$, MW), though only by a few months. Regarding age at inclusion, no significant difference was found between the patient groups, but both were significantly older than controls ($p<0.0005$, KW), though by less than 2 years. No significant difference was found between the DLB and AD groups for age at onset of disease, but patients with DLB had a significantly shorter duration of disease at inclusion compared with those with AD ($p=0.03$, MW). UPDRS scores were significantly increased in patients with DLB compared with those with AD ($p<0.0005$, MW). The latter group had significantly lower scores on the MMSE ($p=0.015$, MW). Consistent with selecting only patients with mild DLB, the DemVest DLB patients had less cognitive ($p=0.001$, MW) and motor impairment ($p=0.017$, MW) than the TrønderBrain DLB patients. In the cohort of patients with DLB, 87.2% of the

Table 2 APO*E* allele and genotype frequency in patients with DLB or AD, and healthy control individuals

		Allele frequency (%)			Genotypes (%)					
Group	**n**	**ε2**	**ε3**	**ε4**	**ε2/ε2**	**ε2/ε3**	**ε2/ε4**	**ε3/ε3**	**ε3/ε4**	**ε4/ε4**
DLB	**156**	**5.1**	**62.8**	**32.1**	**0.6**	**4.5**	**4.5**	**41.0**	**40.4**	**9.0**
F	67	7.5	57.5	35.0	1.5	7.5	4.5	34.3	38.8	13.4
M	89	3.4	66.8	29.8	0.0	2.2	4.5	46.1	41.6	5.6
AD	**519**	**5.8**	**51.3**	**42.9**	**0.2**	**6.2**	**5.0**	**27.2**	**42.2**	**19.3**
F	351	5.7	51.7	42.6	0.3	5.1	5.7	28.2	41.9	18.8
M	168	6.0	50.6	43.4	0.0	8.3	3.6	25.0	42.9	20.2
Healthy controls	**643**	**10.6**	**75.0**	**14.4**	**0.6**	**16.3**	**3.6**	**56.8**	**20.4**	**2.3**
F	388	10.2	75.5	14.3	0.5	15.7	3.6	57.2	20.9	2.1
M	255	11.2	74.3	14.5	0.8	17.3	3.5	56.1	19.6	2.7

No significant difference in *APOE* allele and genotype frequencies between the TrønderBrain and DemVest cohorts, so all DLB patients have been pooled to a single group.
The *APOE ε4* allele was significantly increased in both the DLB ($p<0.0005$) and AD patient groups ($p<0.0005$) compared with healthy controls, and was more common in AD than DLB ($p=0.004$). Conversely, the *APOE ε2* allele was reduced in the DLB ($p=0.002$) and AD ($p<0.0005$) patient groups compared with controls (Pearson's χ^2 test).
AD, Alzheimer's disease DLB, dementia with Lewy bodies.

SPECT analyses supported the clinical diagnosis. No SPECT results were available for AD or healthy controls. The percentage of scans not supporting the clinical diagnosis of DLB (12.8%) is similar to recently published data.[21]

APOE allele and genotype frequency with p values are shown in table 2. Although the frequency of the *APOE* ε4 allele was significantly increased in both patients with DLB and AD, it was less frequent in the group with DLB compared with AD (32% in DLB, 43% in AD, against 14% in controls). Conversely, the highest frequency of the *APOE* ε2 allele was found in the control group (10.6%) compared with both patient groups (DLB and AD between 5% and 6%), though no significant difference between the patient groups was found. In the overall cohort of patients with DLB, 10% were homozygous or heterozygous for *APOE* ε2. In those patients given a dopamine-transporter SPECT, the number carrying *APOE* ε2 was 9%. The allele frequencies for men and women did not differ significantly either in controls or patients.

The OR for developing DLB or AD were calculated for *APOE* ε2 and ε4, with respectively zero alleles as the reference value, as shown in table 3. Due to the low number of homozygotic *APOE* ε2 carriers, OR values were only calculated for bearers of one or two alleles combined. The *APOE* ε2 allele significantly reduced the risk of developing either DLB or AD. In the case of *APOE* ε4, an allele–dose dependent relationship was found for increasing the risk of DLB, though not as strongly as the increased risk for AD.

When these results were corrected for age and gender, the reduced risk of developing DLB or AD in carriers of the *APOE* ε2 allele was maintained, as shown in table 4. Similarly, an increased risk was still found for developing DLB or AD in carriers of the *APOE* ε4 allele after correction.

The effect of the *APOE* ε2 allele on age at onset with p values in patients with DLB and patients with AD is shown in table 5. For the patients with DLB, carriers of *APOE* ε2 developed the disease on average 4 years later than those without the allele. Patients with AD carrying *APOE* ε2 developed the disease on average around 3 years later than those without the allele. Both these results were significant. Regarding the *APOE* ε4 allele, only a weak trend towards a reduction in age at onset was found in patients with DLB. For the patients with AD, a significantly lower age at onset was detected for carriers of *APOE* ε4.

To control for the effect of age, *APOE* allele frequencies were also examined with respect to onset of disease in three separate age groups for the patients, and compared with age at inclusion for control individuals, as shown in table 6. The youngest age

Table 3 OR for developing DLB or AD relative to *APOEε2* and *APOEε4* alleles

	DLB vs CTR	AD vs CTR
No. of *APOE* alleles		
1 or 2 *APOE* ε2 alleles		
OR	0.4	0.5
CI	0.2 to 0.7	0.4 to 0.7
p Value	0.002	<0.0005
1 *APOE* ε4 allele		
OR	3.0	4.3
CI	2.1 to 4.3	3.3 to 5.7
p Value	<0.0005	<0.0005
2 *APOE* ε4 alleles		
OR	6.0	19.3
CI	2.8 to 13.1	10.8 to 34.2
p Value	<0.0005	<0.0005

AD, Alzheimer's disease; CTR, healthy controls; DLB, dementia with Lewy bodies.

Table 4 OR for developing DLB or AD relative to *APOEε2* and *APOEε4* alleles adjusted for age and gender

	DLB vs CTR	AD vs CTR
No. of *APOE* alleles		
1 or 2 *APOE* ε2 alleles		
OR	0.4	0.5
CI	0.3 to 0.8	0.4 to 0.8
p Value	0.004	<0.0005
1 *APOE* ε4 allele		
OR	2.9	4.2
CI	2.2 to 4.6	3.2 to 5.4
p Value	<0.0005	<0.0005
2 *APOE* ε4 alleles		
OR	5.9	15.2
CI	2.7 to 13.0	8.5 to 27.2
p Value	<0.0005	<0.0005

AD, Alzheimer's disease; CTR, healthy controls; DLM, dementia with Lewy bodies.

Table 5 The effect of *APOE* ε2 and *APOE* ε4 alleles on AAO of DLB and AD

	0		1 or 2		p Value, Mann–Whitney U test
	AAO	n	AAO	n	
Number of *APOE ε2* alleles					
DLB	71.9±7.7	141	76.1±8.6	15	0.01
AD	71.0±9.1	460	73.9±10.5	59	0.006
Number of *APOE ε4* alleles					
DLB	73.1±8.3	72	71.5±7.5	84	0.08
AD	73.6±10.0	174	70.1±8.7	345	<0.0005

AAO, age at onset; AD, Alzheimer's disease; DLB, dementia with Lewy bodies.

group included the individuals aged 65 or less, corresponding to young-onset dementia. In this subset, a significant increase in the frequency of the *APOE* ε4 allele was found between the AD and control groups ($p<0.0005$, Pearson's χ^2 test), and between the patients with DLB and the controls ($p=0.03$, Pearson's χ^2 test). No other significant differences were found.

In the 66–79-year age group, which included most individuals, strongly significant increases in the frequency of the *APOE* ε4 allele were again found in patients with AD or DLB compared with the controls ($p<0.0005$, Pearson's χ^2 test), and the frequency was higher in AD compared with DLB ($p=0.0001$, Pearson's χ^2 test). The frequency of the *APOE* ε2 allele was similar in both patient groups, with a significant reduction being observed relative to the controls (DLB: $p=0.006$; AD: $p<0.0005$, Pearson's χ^2 test). In the oldest group of participants (80 years and above), the only significant change found was an increase of the *APOE* ε4 allele in patients with AD compared with the control group ($p=0.003$, Pearson's χ^2 test).

Allele frequencies in the three age categories were also compared within each study group. The greatest differences were found between the youngest and oldest individuals. Although no differences in the occurrence of the three *APOE* alleles were found at any age in the control group, the occurrence of the *APOE* ε2 allele increased with age at onset in patients with AD ($p=0.014$, Pearson's χ^2 test), whereas the *APOE* ε4 allele decreased significantly with age at onset ($p<0.0005$, Pearson's χ^2 test).

Table 6 *APOE* allele frequencies according to age (age at onset for patients and age at inclusion for healthy controls)

			Allele frequencies (%)		
	Age (years)	n	ε2	ε3	ε4
DLB	≤65	30	3.3	60.0	36.7*
	66–79	100	4.0*	62.0	34.0*
	≥80	26	11.5	69.3	19.2
AD	≤65	144	4.5	41.3	54.2*
	66–79	263	4.7*	50.8	44.5*,†
	≥80	112	9.8‡	65.6	24.6*,‡
Healthy controls	≤65	59	10.2	72.0	17.8
	66–79	426	9.9	76.3	13.8
	≥80	158	12.7	72.7	14.6

*Significant difference between a patient group and the control group.
†Significant difference between the groups of patients with DLB or AD.
‡Significant difference in allele frequency according to age within the respective group (Pearson's χ^2 test).
AD, Alzheimer's disease; DLB, dementia with Lewy bodies.

DISCUSSION

The most important finding of the present data was the beneficial effect of the *APOE* ε2 allele in reducing the risk of DLB, an effect that was maintained after correction for age and gender. In our material, the *APOE* ε2 allele reduced the risk for DLB, and delayed the onset of disease by around 4 years. It is well known that the *APOE* ε2 allele reduces the risk of AD[9] and this was clearly found also in the present study.

Conversely, the *APOE* ε4 allele increased the risk for disease in a dose-dependent manner, and reduced the age at onset of DLB and AD, which has been demonstrated in previous studies[22 23] including a recent large series of DLB patients.[24] In our study, although the onset of AD was accelerated by around 3.5 years, the effect on the onset of DLB was less pronounced with an earlier start of around 1.6 years.

The beneficial effect of the *APOE* ε2 allele on the risk for, and onset of, DLB may be particularly pronounced in this study as it has already been established that the *APOE* ε2 allele has a high frequency in Norway[5] compared with data from a wider meta-analysis.[25] This infers that the difference might be less clear in populations of mixed ethnicity.

These results were also supported by data when control and patient groups were divided into three separate age groups. A significant reduction in the frequency of *APOE* ε2 was only observed for the 66–79 age group, whereas the frequency in the age group 80 years and over was similar to the level in the control group. Although not significant due to the low number of individuals in the group, the data tentatively suggest that the protective effect of *APOE* ε2 is lost by age 80 years, perhaps due to multiple comorbidities.[26] Similarly among the oldest patients with AD, no reduction in the frequency of *APOE* ε2 was found, complementing the data from patients with DLB. Similar results were observed with the *APOE* ε4 allele, and support existing evidence[27] that for patients who develop AD in more extreme old age, the *APOE* ε4 allele is less relevant as a risk factor, perhaps because most affected individuals have developed AD at an earlier age.

It is debatable how the *APOE* genotype affects dementia development. Considerable attention has been focused on the chaperone ability of ApoE to clear Aβ deposition in connection with AD.[28 29] Several aspects suggest that *APOE* is important for the clearance of Aβ, but the *APOE* ε4 genotype is least effective, and thus accelerates Aβ deposition into plaque.[29] These data are further supported by recent findings that anti-*APOE* immunotherapy inhibits Aβ deposition in a transgenic mouse model.[30]

Although the hallmark of DLB is Lewy body pathology with lesions rich in α-synuclein, several clinical and neuropathological features of DLB overlap with AD, including senile plaque and neurofibrillary tangles. However, these latter features are much more sparse in DLB,[31] though the *APOE* ε4 allele may accelerate this process in connection with disease. Since the *APOE* ε2 genotype is much less common than *APOE* ε4, fewer studies have been carried out on the mechanism behind its protection in AD. The *APOE* ε2 genotype may remove Aβ accumulation more efficiently, a hypothesis that has received some support,[32] but in the absence of more data, this possibility, as well as other possible mechanisms, remains speculative. Recent data supports the parallels between DLB and AD.[33]

A limitation of the present study is the absence of neuropathological confirmation of the diagnosis for the majority of cases, and we lack data in vivo on the extent of brain load of deposited Aβ, so we cannot distinguish between pure and mixed DLB cases. However, results from a recent study supported by

neuropathology[34] show an increased risk for pure DLB due to the *APOE* ε4 allele that is similar to the present results. This suggests that our results concerning the *APOE* ε2 allele are also likely to be reliable. DLB patients were drawn from two cohorts, with slightly different selection and diagnostic procedures. However, demographic factors such as age, gender, and education were similar suggesting that the groups are comparable, as was supported by the similar genotype distribution.

Our results also agree with recent data[24] demonstrating that many risk factors for AD, including the *APOE* ε4 allele, are also risk factors for DLB. Such similarities may extend to the *APOE* ε2 allele, long recognised as a protective factor in AD,[6 9] and apparently also a protective factor reducing the risk, and raising the average age at onset of DLB.

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