Title
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Journal
Brain, 145(5)

ISSN
0006-8950

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Publication Date
2022-06-03

DOI
10.1093/brain/awab402

Peer reviewed

BRAIN
ORIGINAL ARTICLE

Genetic evaluation of dementia with Lewy bodies implicates distinct disease subgroups

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The *APOE* locus is strongly associated with risk for developing Alzheimer's disease and dementia with Lewy bodies. In particular, the role of the *APOE* ε4 allele as a putative driver of α-synuclein pathology is a topic of intense debate.

Here, we performed a comprehensive evaluation in 2466 dementia with Lewy bodies cases versus 2928 neurologically healthy, aged controls. Using an *APOE*-stratified genome-wide association study approach, we found that *GBA* is associated with risk for dementia with Lewy bodies in patients without *APOE* ε4 ($P = 5.65 \times 10^{-8}$, OR = 3.21, 95% CI = 2.11–4.88), but not with dementia with Lewy bodies with *APOE* ε4 ($P = 0.034$, OR = 1.87, 95%, 95% CI = 1.05–3.37). We then divided 495 neuropathologically examined dementia with Lewy bodies cases into three groups based on the extent of concomitant Alzheimer's disease co-pathology: pure dementia with Lewy bodies ($n = 88$), dementia with Lewy bodies with intermediate Alzheimer's disease co-pathology ($n = 66$) and dementia with Lewy bodies with high Alzheimer's disease co-pathology ($n = 341$). In each group, we tested the association of the *APOE* ε4 against the 2928 neurologically healthy controls.

Our examination found that *APOE* ε4 was associated with dementia with Lewy bodies + Alzheimer's disease ($P = 1.29 \times 10^{-32}$, OR = 4.25, 95% CI = 3.35–5.39) and dementia with Lewy bodies + intermediate Alzheimer's disease ($P = 0.0011$, OR = 2.31, 95% CI = 1.40–3.83), but not with pure dementia with Lewy bodies ($P = 0.31$, OR = 0.75, 95% CI = 0.43–1.30).

In conclusion, although deep clinical data were not available for these samples, our findings do not support the notion that *APOE* ε4 is an independent driver of α-synuclein pathology in pure dementia with Lewy bodies, but rather implicate *GBA* as the main risk gene for the pure dementia with Lewy bodies subgroup.

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Keywords: dementia with Lewy bodies; APOE; Alzheimer's disease; co-pathology

Abbreviations: DLB = dementia with Lewy bodies; GWAS = genome-wide association study

Received July 12, 2021. Revised October 08, 2021. Accepted October 14, 2021. Advance access publication October 25, 2021

Introduction

Dementia with Lewy bodies (DLB) is a fatal neurological disease characterized by variable combinations of fluctuating cognition, parkinsonism, visual hallucinations and rapid eye movement behaviour disorder.[1] This form of dementia is among the most common neurological diseases in the general population, accounting for ~7.5% of all dementia cases.[2] There are currently no effective disease-modifying treatments available and the prognosis is poor. Because of the significant morbidity associated with this understudied disease, the healthcare costs associated with DLB are among the highest for any age-related disease.[3]

Clinical, neuropathological and genomic studies have shown that DLB exists along a continuum involving Alzheimer's disease and Parkinson's disease. The core neuropathological features of DLB are Lewy bodies and Lewy neurites composed primarily of abnormally phosphorylated α-synuclein deposits.[1] These pathological hallmarks are also present in Parkinson's disease, although they are typically not as widespread. The majority of DLB patients show Alzheimer's disease co-pathology consisting of amyloid-β plaques and neurofibrillary tangles.[4] Our recent genome-wide association study (GWAS) in Lewy body dementia identified five genome-wide significant risk loci: *GBA*, *BIN1*, *TMEM175*, *SNCA* and *APOE*.[5] Of these, *GBA*, *SNCA* and *TMEM175* are well-established Parkinson's disease risk loci that are crucial in the production and regulation of α-synuclein.[6–8] At the same time, *APOE* and *BIN1* are known Alzheimer's disease risk loci that affect the accumulation of both amyloid-β and neurofibrillary tangles.[9,10]

Despite these advances, the interplay between Alzheimer's disease, Parkinson's disease and DLB is complex and poorly understood. In particular, the role of the *APOE* ε4 allele as a possible independent driver of α-synuclein pathology in DLB remains a topic of intense debate. Two recent studies in human α-synuclein transgenic mice expressing different human *APOE* isoforms found that the *APOE* ε4 allele regulates synucleinopathies directly and independently of amyloid-β deposition.[11,12] Post-mortem human studies also reported that *APOE* ε4 is associated with DLB regardless of the severity of concomitant Alzheimer's disease pathology.[12–14] In contrast, other studies found that *APOE* ε4 is only associated with disease when there is considerable Alzheimer's disease co-pathology.[15,16] Notably, a recent population-based study showed that Lewy body pathology progresses in two distinct patterns and Alzheimer's disease co-pathology and *APOE* ε4 are only associated with one of them.[17] If true, this finding implicates the existence of multiple distinct DLB subtypes. Such disease heterogeneity may explain the disparate results discovered by previous studies.

Here, we explored the role of *APOE* ε4 in the pathogenesis of DLB. To do this, we investigated whether *APOE* ε4 is associated with risk for developing DLB regardless of the presence or absence of Alzheimer's disease co-pathology. These analyses are based on a sizable whole-genome sequencing dataset generated from patients diagnosed with DLB, providing adequate power to resolve this critical aspect of the neurological disease.[5]

Materials and methods

Sample cohorts and genome sequencing

Fig. 1 shows the analysis pipeline used in this study. We used genomic data from our recently published Lewy body dementia GWAS based on 2592 Lewy body dementia cases and 4027 neurologically healthy control subjects.[5] All study participants were of European descent and were diagnosed based on consensus criteria[1,18] or were neurologically healthy individuals as described elsewhere.[5] Whole-genome sequencing was performed on an Illumina HiSeq X Ten platform using 150-bp paired-end cycles. Alignment (using the GRCh38DH reference genome) and variant calling followed the GATK Best Practices.[19] Sample-level and variant-level quality control steps have been described elsewhere.[5] This study was approved by the appropriate institutional review boards of the participating institutions. All participants or their surrogate decision makers gave informed consent according to the Declaration of Helsinki.

The *APOE*-stratified GWASs were performed using samples selected from the overall cohort of 2466 DLB cases and 2928 neurologically healthy controls. Patients diagnosed with Parkinson's disease dementia, controls under the age of 50 years and convenience controls where the neurological status was unclear were excluded from the selection process. The pathology subtype analysis was restricted to the 495 patients who were (i) pathologically diagnosed as DLB using the McKeith criteria[1]; and (ii) for whom uniformly collected semiquantitative Alzheimer's disease co-pathology measures were available.

Neuropathological subgrouping

The 495 definite DLB cases were categorized into three subgroups based on the severity of the Alzheimer's disease co-pathology. The extent of amyloid-β pathology was quantified using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scoring[20] and neurofibrillary tangle pathology was staged using the Braak method.[21] The three subgroups were: (i) pure DLB, defined as absent or low Alzheimer's disease co-pathology (Braak stages 0–2 and CERAD scores 0–A); (ii) DLB with intermediate Alzheimer's disease co-pathology (corresponding to Braak stage 3 and CERAD scores A–C); and (iii) DLB with high Alzheimer's disease co-pathology (Braak stages 4–6 and CERAD scores B–C).

Genetic analysis

The ε4 *APOE* allele was identified based on the genotypes at two common single nucleotide polymorphisms (rs7412 and rs429358). We assessed the association of the *APOE* ε4 allele (presence or absence) with DLB by performing two GWASs. In the first GWAS, we evaluated the DLB cases without any *APOE* ε4 allele and compared them to neurologically healthy controls without *APOE* ε4. In the second GWAS, we compared the DLB cases with at least one *APOE* ε4 allele to healthy controls who were carrying at least one *APOE* ε4 allele.

In addition to the *APOE* ε4-stratified GWASs, we tested the associations of the *APOE* ε4 allele with each of the three pathologically defined subgroups (pure DLB, DLB + intermediate Alzheimer's disease and DLB + Alzheimer's disease) versus all of the controls. We also tested the associations of the rs2230288 *GBA* risk allele with each of the three pathological subgroups versus controls.

Statistical analyses

APOE ε4-stratified analyses

GWAS testing and association analysis were performed in PLINK (version 2.0) using an additive model with a minor allele frequency threshold of 1%.[22] Age, sex and relevant principal components to account for population stratification were included as covariates. The top ten principal components were calculated using FlashPCA. We determined the significant principal components to include in each analysis using the 'step' function (Ripley), as incorporated in the R (version 3.5.2, https://www.R-project.org) 'stats' package. The principal components included in these analyses were as follows: (i) principal component 1, 2, 3 and 4 in the *APOE* ε4-negative DLB cases versus controls GWAS; and (ii) 1, 2 and 10 in the *APOE* ε4-

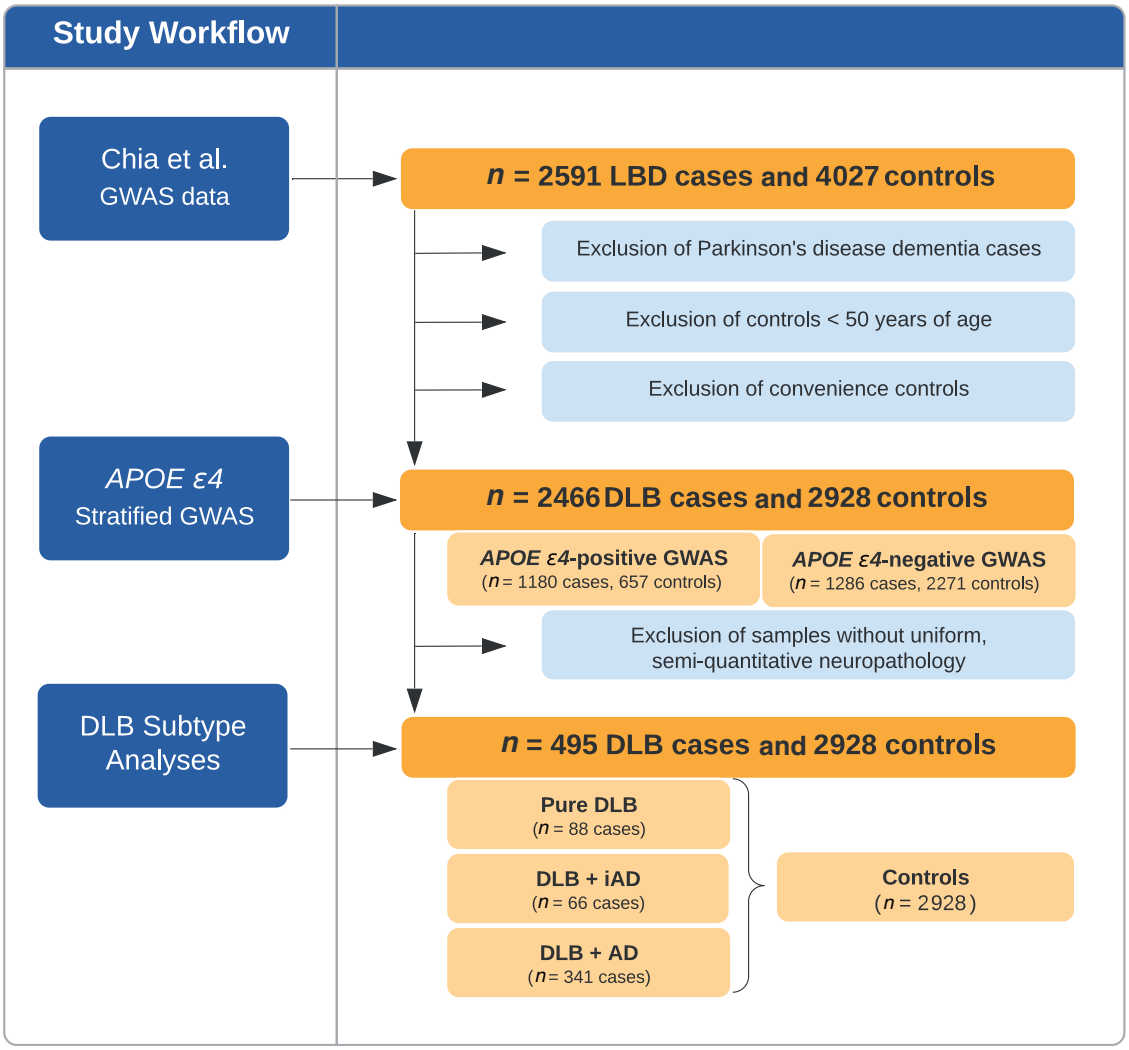

Figure 1 Analysis overview. This schematic illustration of the study workflow shows the cohort selection and analysis steps. AD = Alzheimer's disease; LBD = Lewy body dementia; iAD = intermediate-level Alzheimer's disease co-pathology.

positive DLB cases versus controls GWAS. The threshold for genome-wide significance was 5.0×10^{-8}.

Subgroup analysis

We performed the *APOE ε4* analysis in DLB subgroups using the 'glm' function under a dominant association model, as implemented in the R stats package.[23] The principal components included in the subtype analyses were as follows: (i) 1, 2 and 6 in the *APOE* and *GBA* allele analysis in the pure DLB cohort versus controls; (ii) 1, 4, 5, 6, 7 and 10 in the *APOE* and *GBA* allele analysis in the DLB + intermediate Alzheimer's disease cohort versus controls; and (iii) 1, 2, 3, 4, 5, 6 and 7 in the *APOE* and *GBA* allele analysis in the DLB + Alzheimer's disease cohort versus controls. Association results for Bonferroni-corrected for multiple testing using a *P*-value threshold of 0.017 (= 0.05/3 groups tested).

Data availability

Individual-level sequence data are available on dbGaP (accession number: phs001963.v1.p1). The analysis presented here has not been previously published elsewhere.

Results

APOE ε4-stratified GWAS

We explored the genetic risk factors among DLB patients carrying and not carrying the *APOE ε4* allele. To perform this stratified GWAS, we compared the 1286 DLB cases without *APOE ε4* to the 2271 controls without *APOE ε4*. The genomic inflation factor λ_{1000} was 1.009, indicative of only minimal residual population stratification. *GBA* was the only locus that nearly reached genome-wide significance in this analysis (rs2230288, $P = 6.58 \times 10^{-9}$, OR = 3.41, 95% CI = 2.25–5.17; Fig. 2). When we compared the 1180 DLB cases with *APOE ε4* to the 657 controls with *APOE ε4*, the *GBA* locus signal did not achieve genome-wide significance ($P = 0.034$, OR = 1.87, 95% CI = 1.05–3.37), suggesting that *GBA* is not a major determinant of disease risk in *APOE ε4* carriers. However, we noted a subsignificant association signal within the histamine receptor H1 (*HRH1*) gene (rs9858388, $P = 2.0 \times 10^{-7}$, OR = 1.47, 95% CI = 1.27–1.71). Furthermore, no association signals exceeded the Bonferroni threshold for multiple testing in the *APOE ε4*-positive GWAS. The λ_{1000} for this GWAS was 1.012. These findings confirmed the importance of *GBA* as a significant driver of α-synuclein pathology in the *APOE ε4*-negative DLB patients.

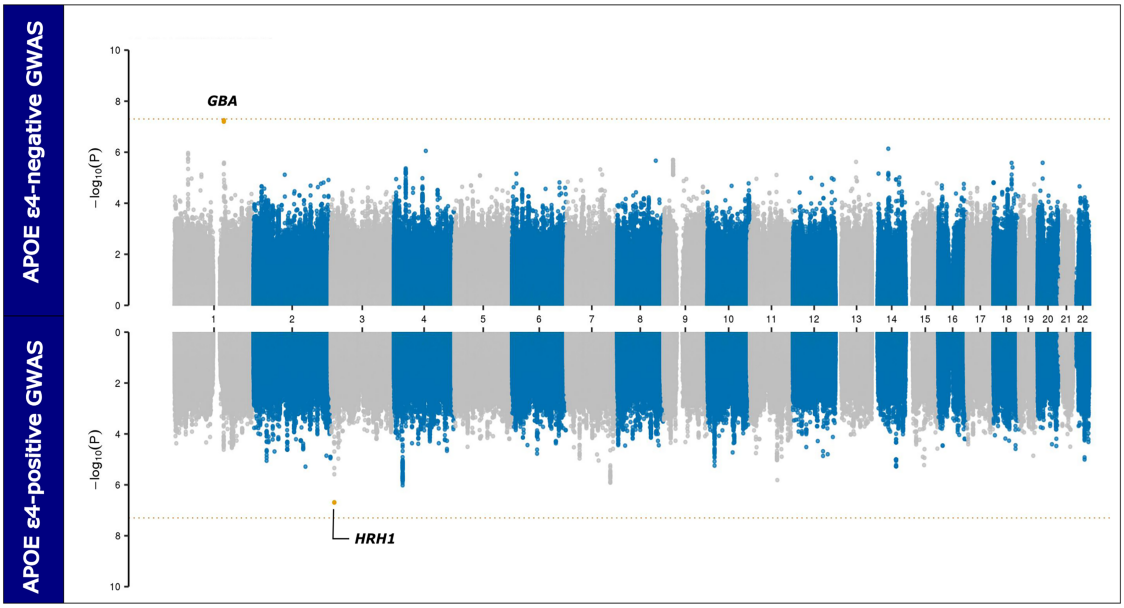

Figure 2 Miami plot depicting the APOE-stratified GWAS results. The upper panel shows the GWAS results comparing *APOE* ε4-negative DLB cases with *APOE* ε4-negative controls ($n = 1286$ cases versus 2271 controls). The *bottom* panel shows the association test results comparing *APOE* ε4-positive *DLB* cases with *APOE* ε4-positive controls ($n = 1180$ cases versus 657 controls). The x-axis depicts the chromosomal position for 22 autosomes in hg38 and the y-axis denotes the association *P*-values on a $-\log_{10}$ scale. The dotted, horizontal line indicates the conservative Bonferroni threshold for genome-wide significance. Suggestive variants are indicated by orange dots, while red dots highlight genome-wide significant associations.

Table 1 DLB subgroups and demographic characteristics

	Pure DLB	DLB + intermediate Alzheimer's disease	DLB + Alzheimer's disease	Controls
n	88	66	341	2928
Mean age (SD)	73 (11)	79 (10)	76 (11)	78 (11)
Age range, years	40–95	55–100	39–103	50–110
% Male	81	59	52	46
APOE ε4 carriers				
Homozygous (%)	0 (0%)	2 (3%)	47 (14%)	42 (1%)
Heterozygous (%)	17 (19%)	25 (38%)	148 (43%)	615 (21%)
GBA rs2230288T carriers (%)[a]	7 (8%)	3 (5%)	9 (3%)	51 (2%)

[a]One pure DLB case was homozygous for the rs2230288T risk allele, while all other *GBA* risk allele carriers were heterozygous.

APOE associations with DLB subgroups

Of the 495 DLB cases with available co-pathology measures, 88 (17.8%) were classified as pure DLB cases, 66 (13.3%) cases were categorized as having intermediate AD co-pathology and 341 (68.9%) were identified as having severe AD co-pathology. Table 1 shows the clinical and demographic details of these subgroups. Men were overrepresented in the pure DLB group (81%). Only limited phenotype data were available for these individuals.

APOE ε4 was strongly associated with disease in the DLB with severe Alzheimer's disease co-pathology subgroup ($P = 1.29 \times 10^{-32}$, OR = 4.25, 95% CI = 3.35–5.39) and the DLB with intermediate AD co-pathology subgroup ($P = 0.0011$, OR = 2.31, 95% CI = 1.40–3.83). In contrast, *APOE* ε4 was not associated with disease in the pure DLB cohort ($P = 0.31$, OR = 0.75, 95% CI = 0.43–1.30). Moreover, DLB patients with high Alzheimer's disease co-pathology were more likely to be homozygous for the *APOE* ε4 allele than the other subgroups displaying less severe Alzheimer's disease co-pathology [$n = 47$ (13.8%) in the DLB + Alzheimer's disease group, $n = 2$ (3.0%) in the DLB + intermediate Alzheimer's disease group and $n = 0$ (0.0%) in the pure DLB group; Fisher *P*-value = 4.4×10^{-6}], consistent with dose-dependent effects on disease risk. Taken together, these findings do not support a role of *APOE* ε4 as an independent driver of human α-synuclein pathology.

In contrast to the *APOE* ε4 subgroup associations, we found a statistically significant association of the *GBA* rs2230288 risk allele with the pure DLB subgroup ($P = 0.0004$, OR = 4.52, 95% CI = 1.94–10.44). Interestingly, we did not identify an association within the intermediate or high Alzheimer's disease co-pathology subgroups (DLB + intermediate Alzheimer's disease: $P = 0.11$, OR = 2.67, 95% CI = 0.80–8.89; DLB + Alzheimer's disease: $P = 0.32$, OR = 1.45, 95% CI = 0.69–3.01). These findings support the existence of distinct genetic architectures within each DLB subtype.

Discussion

The influence of genetic association signals implicated in Lewy body dementia on Alzheimer's disease co-pathology has been unclear. *APOE* ε4 is the most common genetic risk factor for late-onset Alzheimer's disease, and it has also been consistently the top association signal for Lewy body dementia.[5,14,24,25] Controversial evidence exists implicating *APOE* ε4 as an independent driver of α-synuclein pathology. Here, we show that the association of *APOE* ε4 with DLB is dependent on the severity of Alzheimer's disease co-pathology, as *APOE* ε4 was associated with DLB only when there were intermediate or high levels of Alzheimer's disease co-pathology. No associations were found for

APOE ε4 with pure DLB, arguing against the notion that *APOE ε4* is an independent driver of α-synuclein pathology.

We made several additional observations. First, in the *APOE*-stratified GWAS, we found that the *GBA* risk variant rs2230288 nearly reached genome-wide significance when comparing DLB cases without *APOE ε4* to healthy controls without APOE *ε4*. In contrast, we did not detect any genome-wide significant loci when examining DLB cases with *APOE ε4*. Taken together, these findings demonstrate a clear relationship between *GBA* and *APOE ε4*-negative DLB, whereas the association with *APOE ε4*-positive DLB is equivocal. However, we noticed a subsignificant signal within the *HRH1* gene, encoding the histamine receptor H1 that is widely expressed within the central nervous system. Histaminergic dysregulation is a crucial feature of Alzheimer's disease and DLB,[26,27] making *HRH1* a plausible risk gene. However, additional genetic association studies will be required to determine the importance of this observation. Furthermore, the rs2230288 variant located within the *GBA* locus was associated with pure DLB (*P*-value = 0.0004, OR = 4.52, 95% CI = 1.95–10.44) but not with DLB with Alzheimer's disease co-pathology (*P*-value = 0.32, OR = 1.45, 95% CI = 0.69–3.01). Overall, these findings suggest the existence of DLB subgroups with distinct genetic architectures, perhaps hallmarked by the *APOE* and *GBA* loci.

Only a limited number of DLB research studies have previously accounted for the severity of Alzheimer's disease co-pathology. While some studies reported the association of *APOE* with DLB to be dependent on the presence of Alzheimer's disease co-pathology,[15,16] others did not.[12–14] One possible explanation for this discrepancy in the literature may be the small sample sizes and varying neuropathological definitions for pure DLB. In addition, each study employed different inclusion and exclusion criteria and methodologies to group the neuropathological changes. For example, in one of the previous studies, the aged controls had to be free of cognitive impairment both at study enrolment and at the last evaluation. Such criteria may have led to a selection bias against *APOE ε4*, and the results may be attributed to the lack of *APOE ε4* in cognitively intact aged individuals rather than its association with DLB. Other co-pathologies, such as microvascular disease and TDP-43 inclusions, could be present in this aged cohort and may explain the disparate results in the studies. Such co-pathologies were more likely to have emerged if the patients had survived longer. These data were not available for the samples that were included in our analysis.

The relationship of *APOE* to other genetic and non-genetic risk factors is complex. For example, transgenic mouse models expressing the human *APOE ε4* allele and a pathogenic mutation in *SNCA*, encoding the α-synuclein protein, showed increased α-synuclein aggregation.[12] However, it is difficult to extrapolate from artificial model systems to human patients. Additional factors, such as ageing, sex, polygenic genetic contributions of small effect size, cerebrovascular disease, mitochondrial impairment, neuroinflammation and dysfunctional lysosomes may interact with *APOE*, and the outcome likely depends on the integrated sum of these factors.[28] Our study highlights the value of studying neurological diseases directly in pathology-derived human tissue as a means to understand the primary drivers underlying co-pathologies.

Aside from genetic differences, we observed that 81% of the pure DLB group were male, compared to the DLB + Alzheimer's disease group, where the male-to-female ratio was ∼1. This observation is in line with previous studies of DLB with varying severity of Alzheimer's disease co-pathology.[13,14,16] Because all studies, including ours, have potential selection biases and confounding factors that affect sex, we cannot conclude that sex influences the DLB phenotype. However, the consistency with which males form the majority of pure DLB cases is noteworthy. Interestingly, the male sex has also been implicated as a risk factor for Parkinson's disease with the same neuropathological changes as pure DLB.[29]

A strength of our study is the availability of neuropathological data from a large cohort of patients diagnosed with DLB. These data allowed for a careful exploration of the genetic effects on co-pathology. Despite this, the absolute number of our patient collection was relatively small compared to the larger-scale GWASs that are standard in the field today. Although interesting, our results must be confirmed in more extensive studies that longitudinally collect clinical, cognitive and neuropathological information, such as quantifications of TDP-43 co-pathology and microangiopathic changes. Analysis of such clinical information would provide additional insights into the genetic factors driving cognitive decline across DLB subtypes and across males and females. More extensive studies are also required to determine the relative importance of common variation and rare mutations in *GBA*, a locus where the risk is known to be pleomorphic.[5] Another limitation of our study is that all participants were individuals of European ancestry. It will be essential to include diverse populations in future efforts to obtain a comprehensive understanding of the genetic drivers underlying DLB.

In conclusion, our data show that *APOE ε4* is not an independent driver of α-synuclein pathology in DLB. Instead, the severity of Alzheimer's disease co-pathology influences the association of *APOE ε4*. Based on this, it is clear that the severity of Alzheimer's disease co-pathology should be considered in future genetic studies, as missing neuropathological subgroups may obscure association signals. Moreover, considering the severity of Alzheimer's disease co-pathology may make it easier to determine the manner in which α-synuclein and Alzheimer's disease pathology interact in DLB. The severity of Alzheimer's disease co-pathology, and the corresponding underlying genetics, may be used to assign patients to subgroups, each with different symptoms and each requiring specific targeted treatments.

Acknowledgements

We thank the patients and families whose help and participation made this work possible. We thank the members of the International LBD Genomics Consortium (a complete list of site investigators who contributed samples for genome sequencing can be found in the Appendix). We thank Dr Bryan Traynor and the Laboratory of Neurogenetics (NIH) for their collegial support and technical assistance. This work utilized the computational resources of the NIH HPC Biowulf cluster (http://hpc.nih.gov).

Funding

This study was supported in part by the Intramural Research Program of the National Institutes of Health (National Institute on Aging, National Institute of Neurological Disorders and Stroke; project numbers: 1ZIAAG000935, 1ZIANS003154). K.K. was funded by the Finnish Cultural Foundation, The Finnish Parkinson Foundation, The Päivikki and Sakari Sohlberg Foundation and The Finnish Brain Foundation.

Competing interests

S.W.S. serves on the Scientific Advisory Council of the Lewy Body Dementia Association. S.W.S. is an editorial board member for the *Journal of Parkinson's Disease* and *JAMA Neurology*. All other authors have no conflicts of interest to declare that are relevant to the content of this article.

Supplementary material

Supplementary material is available at *Brain* online.

Appendix I

International LBD Genomics Consortium

Full details are provided in the Supplementary material.

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