Identifying endophenotypes of *APOE*-ε4 to unravel clinicopathological heterogeneity and mixed neuropathologies across the Lewy body disease spectrum: current advances and emerging opportunities

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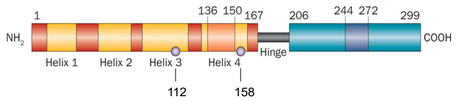
BACKGROUND

Genome-wide association studies and pathology-proven investigations have consistently highlighted the ε4-allele of apolipoprotein E (*APOE*-ε4) as a major genetic risk factor (figure below), **not only for Alzheimer's disease but also for Lewy body dementias**, highlighting *APOE*-ε4's important role in modulating the pathogenesis of amyloid-β, tau, and α-synuclein proteins.

(Guerreiro et al, 2018; Kunkle et al, 2019)

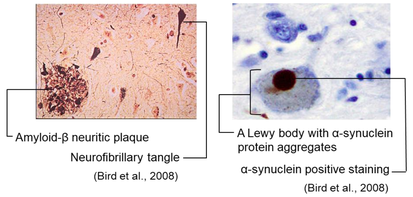


APOE-ε2
Cys-112, Cys-158
Protective

APOE-ε3
Cys-112, Arg-158
Neutral

APOE-ε4
Arg-112, Arg-158
Risk Factor

APOE-ε4 may also **independently** increase the risk for **mixed pathologies** in Alzheimer's disease and Lewy body dementias (Robinson et al, 2018).

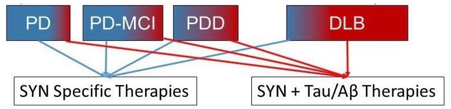


However, the precise phenotypic associations of *APOE*-ε4 in α-synucleinopathies (endophenotypes) are **variable**.

OBJECTIVE

The **primary objective** of this comprehensive review was to identify endophenotypes of *APOE*-ε4 across the Lewy body disease spectrum (LBDS) [which include Parkinson's disease (PD), PD with mild cognitive impairment (PD-MCI), PD dementia (PDD), and dementia with Lewy bodies (DLB), Figure below].

Our review will highlight current advances, opportunities to test novel hypotheses and may also uncover shared neurobiological dysfunctions across these α-synucleinopathies.



METHODS

Scientific databases were systematically searched from January 1st, 1995, to December 31st, 2023, following PRISMA guidelines. Studies exploring the relationship of *APOE*-ε4 with multimodal and/or diverse phenotypes (e.g., neuroimaging, cognitive, fluid-based) in PD, PD-MCI, PDD, and DLB were reviewed.

RESULTS

A total of 152 studies were included.

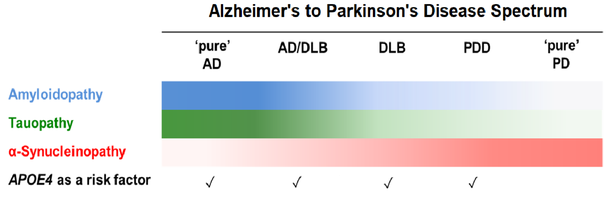
APOE-ε4 was **consistently** associated with:

↓ amyloid-β 42 cerebrospinal fluid levels in PDD and DLB,
↓ performance in the memory domain across the LBDS,
↑ mediotemporal atrophy especially in DLB,
↑ cerebral amyloid angiopathy in DLB,
↓ survival and ↑ cognitive decline in DLB,
↑ AD-type neuropathological features.

APOE-ε4 **may** additionally be linked to:

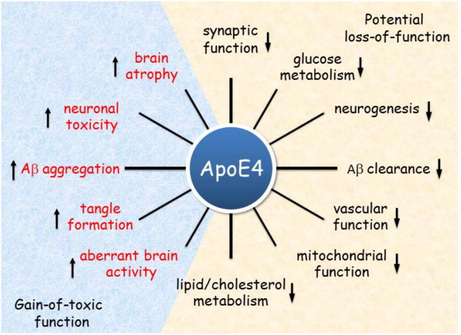
↑ diffuse cortical Lewy body pathology in LBDS,
↑ tracer retention on amyloid positron emission tomography in LBDS,
↑ odds of dementia in PD and PD-MCI,
↑ interaction with other genetic factors to elevate the cumulative risk for DLB.

Studies also highlighted possible interactions of *APOE*-ε4 with neuropsychiatric, epigenetic (DNA methylation), lifestyle, and biochemical (dysfunctional proteolytic processing) factors across LBDS.



CONCLUSIONS

APOE-ε4 contributes to clinicopathological heterogeneity across the Lewy body disease spectrum. Further research to elucidate reliable endophenotypes of *APOE*-ε4 will provide mechanistic insights as well as opportunities to target shared mechanisms across the neurodegenerative dementia spectrums.



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