ALZHEIMER DISEASE

***APOE** ϵ 4-associated increase in AD risk linked to phospholipid dysregulation**

Apolipoprotein E ϵ 4 allele (*APOE** ϵ 4) is the strongest genetic risk factor for sporadic Alzheimer disease (AD), but little is known about its contribution to AD pathophysiology. Now, research has linked *APOE** ϵ 4 with phospholipid dysregulation. “Our findings reveal a novel molecular mechanism underlying the strong association between *APOE** ϵ 4 and sporadic AD,” says Dongming Cai, who led the study.

Cai and co-workers analysed the phospholipid compositions of human postmortem brain tissue from 23 *APOE** ϵ 4 carriers and 25 controls who carried the regular *APOE** ϵ 3 allele. The cognitive status of the individuals at death (at ages of 62–94 years) varied from no impairment to mild dementia.

The researchers identified a phospholipid pattern that correlated with progression from normal ageing to mild cognitive impairment and early AD. As the disease progressed, levels

of phosphoinositol biphosphate (PIP₂) and phosphoinositol (PI) decreased, whereas the level of phosphoinositol phosphate (PIP) increased. In *APOE** ϵ 4 carriers, PIP₂ levels were reduced before cognitive symptoms appeared, suggesting that *APOE** ϵ 4 disrupts phospholipid metabolism.

“Our findings reveal a novel ... mechanism ... between *APOE ϵ 4 and sporadic AD...”**

The findings were recapitulated in cultured hippocampal neurons and when tissue from transgenic mice carrying human *APOE** ϵ 4 was compared with that of mice carrying human *APOE** ϵ 3. Moreover, the researchers observed elevated levels of synaptojanin 1 (*synj1*) —a PIP₂-degrading enzyme—in *APOE** ϵ 4 mice. Genetic modification to reduce *synj1* levels in these mice restored PIP₂ levels

and alleviated deficits in novel-object and fear memory.

According to Cai, modification of phospholipid levels might provide a novel strategy for disrupting the pathophysiological processes in AD. “We are searching for potential pharmacological interventions to modulate PIP₂ levels with the goal to improve functional outcomes,” says Cai.

Moreover, the findings provide support for an earlier study which concluded that plasma phospholipid profiling could be used to detect preclinical AD and predict the development of memory impairment.

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Original article Zhu, L. *et al.* Phospholipid dysregulation contributes to ApoE4-associated cognitive deficits in Alzheimer's disease pathogenesis. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1510011112

Further reading Mapstone, M. *et al.* Plasma phospholipids identify antecedent memory impairment in older adults. *Nat. Med.* 20, 415–418 (2014).