eMethods

Study design and Participants

Diagnosis of late-onset AD was performed by neurologists after performing neurological clinical examination, blood tests, neuropsychological tests and brain imaging by magnetic resonance (70%) or computed tomography (30%) scans. Patients' inclusion also took into account levels of *core* biomarkers measured in cerebrospinal fluid (CSF) samples when available. Patients with behavioral disorders or other conditions that preclude neuroimaging acquisition were not included in the iBEAS study. All controls were subjected to an 3T MRI study that excluded the presence of structural neurological damage, including vascular-type lesions.

CSF samples collection and AD core biomarkers analysis

CSF samples from AD patients were obtained by lumbar puncture after ruling out contraindications and written informed consent. CSF samples were centrifuged at 2000 x g for 10 minutes, at 4°C, transferred to 1.5 mL polypropylene tubes in 0.5 mL aliquots, within next two hours and subsequently stored at -80°C. CSF levels of *core* AD biomarkers Aβ1–42, Aβ1–40, total Tau (tTau) and pTau181 were measured in the Lumipulse fully-automated platform using commercially available kits (Fujirebio Europe, Ghent, Belgium)[1] at the Sant Pau Hospital (Barcelona, Spain) (Supplementary Table 3).

APOE genotyping

Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) performed *APOE* genotyping. DNA was amplified by PCR using 10 µM oligonucleotide primers forward 5'-TAAGCTTGGCACGGCTGTCCAAGGA-3' and reverse 5' ACAGAATTCGCCCCCCGGCCTGGTACACAC-3'[2] in a Veriti™ Thermal Cycler (Applied Biosystems). Amplification reaction conditions are described in Supplementary Table 6. Amplified *APOE* sequences were incubated with 10 U

FastDigest HhaI restriction enzyme (New England BioLabs, Missisauga, ON, Canada) at 37ºC overnight and electrophoresed on a 4% agarose gel at 120 V for 50 minutes.

References

e1. Alcolea D, Delaby C, Muñoz L, et al. Use of plasma biomarkers for AT(N) classification of neurodegenerative dementias. J Neurol Neurosurg Psychiatry. Jun 08 2021;doi:10.1136/jnnp-2021-326603

e2. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res. Mar 1990;31(3):545-8.