

Beyond APOE: Dissecting the Genetic Drivers of Amyloid and Tau Pathology in Dementia with Lewy Bodies

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INTRODUCTION

Dementia with Lewy bodies (DLB) is frequently misdiagnosed as Alzheimer's disease (AD) due to overlapping clinical features. Unlike AD, DLB is primarily characterized by α -synuclein pathology, though amyloid and tau co-pathology is common. The genetic architecture of DLB remains poorly characterized, and post-mortem tissue — the gold standard for pathological assessment — is scarce. Alternative approaches leveraging in vivo biomarker data are needed to investigate how genetic variation shapes DLB biology and disentangle shared from disease-specific mechanisms across dementias.

METHODS

We analyzed 725 DLB cases and 2,533 cognitively healthy controls from ACE Alzheimer Center Barcelona, genotyped using the Axiom 815K Spanish Biobank Array. After standard quality control and TOPMed-based imputation, logistic regression was performed adjusting for age, sex, and four principal components. Variants with MAF ≥ 0.01 and $R^2 \geq 0.40$ were retained. Meta-analyses were conducted with published DLB GWAS datasets. Polygenic risk scores (PRS) were constructed using variants at $p < 10^{-5}$. Associations between DLB-PRS and CSF A β 42 and pTau181 were assessed by linear regression in two independent cohorts — DELCODE (Germany) and ACE Barcelona — adjusting for age, sex, diagnosis, and APOE genotype when the APOE region was excluded.

RESULTS

APOE (*TOMM40*) was the strongest genome-wide significant risk locus for DLB, followed up with signals at *GBA*, *SNCA-AS1*, and *TMEM175* (**Fig 1.**). Meta-analyses reinforced known loci and refined effect estimates. Full DLB-PRS associated significantly with CSF A β 42 and pTau181 both at DELCODE and ACE cohorts. After APOE exclusion, only CSF A β 42 remained nominally significant at DELCODE with a modified effect direction, while tau associations were fully attenuated (**Fig. 2**).

DISCUSSION

These findings confirm *APOE* as the dominant genetic driver of DLB and reveal a dissociation between APOE-dependent and independent contributions to AD-type biomarker profiles. APOE primarily mediates the link between DLB genetic risk and tau pathology, while non-APOE variants relate to amyloid biology through partially distinct mechanisms, consistent with known roles of *GBA* and *SNCA* in amyloid processing. The signal at *TMEM175* further implicates lysosomal dysfunction as a shared neurodegenerative mechanism. This study demonstrates the value of PRS paired with in vivo CSF biomarkers as a novel strategy to probe DLB pathological consequences, circumventing post-mortem tissue scarcity. Validation in neuropathologically confirmed and larger cohorts remains essential.

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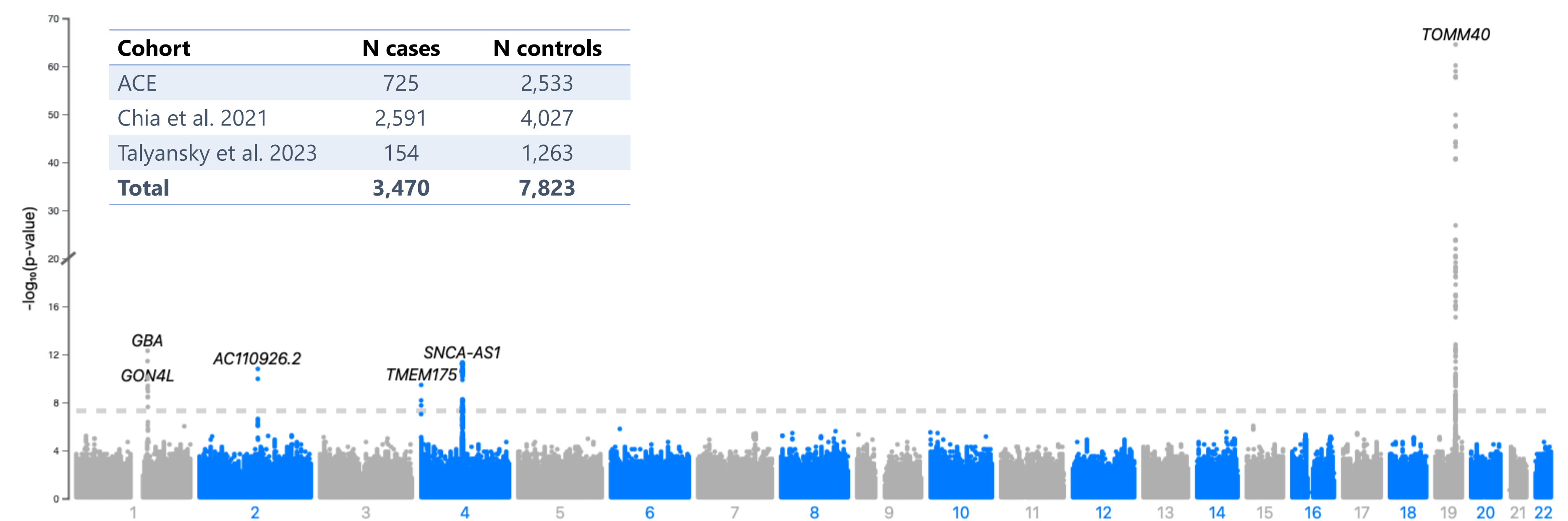


Fig 1. Meta-analysis of ACE and publicly available datasets (Chia et al. 2021, Talyanski et al. 2023).

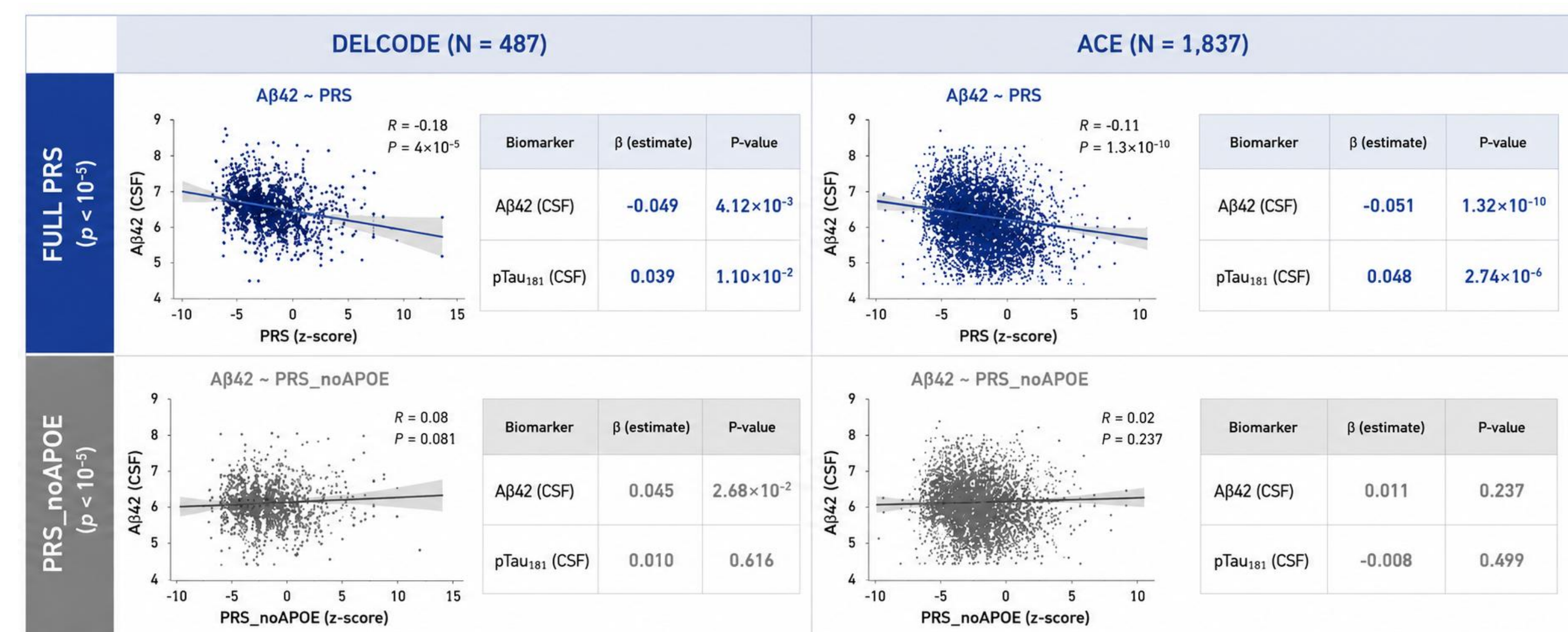


Fig 2. Association of DLB PRS with CSF AD biomarkers (A β 42 and ptau181) in two independent cohorts. PRS computed with variants with p-value $< 10^{-5}$

TAKE HOME MESSAGE

- ✓ Largest DLB meta-analysis to date
- ✓ APOE (*TOMM40*) is the strongest risk locus for DLB
- ✓ Replication of previous signals in *GBA*, *SNCA*, *TMEM175*
- ✓ DLB PRS associates with AD biomarkers
- ✓ APOE drives the association with AD pathology

NEXT STEPS

- ✓ Expand biomarker examination
- ✓ Fine-locus mapping
- ✓ Increase samples size via E-DLB consortia

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