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RESEARCH

Linking genomic and proteomic signatures to brain amyloid burden: insights from GR@ACE/DEGESCO

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Abstract

Alzheimer's disease (AD) is a complex disease with a strong genetic component, yet many genetic risk factors remain unknown. We combined genome-wide association studies (GWAS) on amyloid endophenotypes measured in cerebrospinal fluid (CSF) and positron emission tomography (PET) as surrogates of amyloid pathology, which may provide insights into the underlying biology of the disease. We performed a meta-GWAS of CSF Aβ42 and PET measures combining six independent cohorts ($n = 2,076$). Given the opposite beta direction of Aβ phenotypes in CSF and PET measures, only genetic signals showing opposite directions were considered for analysis ($n = 376,599$). We explored the amyloidosis signature in the CSF proteome using SOMAscan proteomics (ACE cohort, $n = 1,008$), connected it with GWAS loci modulating amyloidosis and performed an enrichment analysis of overlapping hits. Finally, we compared our results with a large meta-analysis using publicly available datasets in CSF ($n = 13,409$) and PET ($n = 13,116$). After filtering the meta-GWAS, we observed genome-wide significance in the rs429358-*APOE* locus and annotated nine suggestive hits. We replicated the *APOE* loci using the large CSF-PET meta-GWAS, identifying multiple AD-associated genes including the novel *GADL1* locus. Additionally, we found 1,387 FDR-significant SOMAscan proteins associated with CSF Aβ42 levels. The overlap among GWAS loci and proteins associated with amyloid burden was minimal ($n = 35$). The enrichment analysis revealed mechanisms connecting amyloidosis with the plasma membrane's anchored component, synapse physiology and mental disorders that were replicated in the large CSF-PET meta-analysis. Combining CSF and PET amyloid GWAS with CSF proteome analyses may effectively elucidate causative molecular mechanisms behind amyloid mobilization and AD physiopathology.

Keywords Aβ42 · CSF biomarkers · PET tomography · GWAS · Proteome

Abbreviations

AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ASD	Autism spectrum disorder
Aβ	Amyloid
Aβ42	Amyloid beta 42
AV45	Florbetapir

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CADD	Combined Annotation Dependent Depletion
CDR	Clinical Dementia Rating
CI	Confidence interval
eQTL	Expression quantitative trait loci
FBB	Florbetaben
FDR	False discovery rate
FUMA	Functional Mapping and Annotation of Genome-Wide Association Studies
GPI	Glycosylphosphatidyl inositol
GWAS	Genome-wide association studies
HC	Healthy Control
LP	Lumbar puncture
MAC	Minor allele count
MAF	Minor allele frequency
MCI	Mild Cognitive impairment
MMSE	Mini-Mental State Exam
MRM	Multi Reaction Monitoring
n	Sample size
NIA-AA	National Institute on Aging and Alzheimer's Association
NINCDS/ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association
OR	Odds ratio
P	P-value
p-tau	Phosphorylated tau in Thr 181
PAD	Publicly available datasets
PET	Positron Emission Tomography
PCA	Principal component analysis
PCs	Principal components
pQTL	Protein quantitative trait loci
PRS	Polygenic risk scores
RFU	Relative fluorescent units
SCD	Subjective cognitive decline
SNP	Single nucleotide polymorphisms
t-tau	Total tau
λ	Genomic inflation factor

Background

Alzheimer's disease (AD) is the most common cause of dementia. AD is a growing epidemic with an expected doubling of annual new diagnosis in the next 20 years prevalence and a major socioeconomic impact with a projected direct economic cost of $2 trillion by 2030 (Alzheimer's Association 2022; El-Hayek et al. 2019; Nandi et al. 2022). In this sense, increasing the knowledge of AD aetiology and biomarker development would be an interesting approach to developing a clear understanding of the disease physiopathology and future drug developments. Genome wide association studies (GWAS) have permitted the discovery of more than 80 genetic variants associated with AD risk (Bellenguez et al. 2022; de Rojas et al. 2021). Despite the continued efforts led by international consortia, a large fraction of AD heritability remains to be elucidated since only 31% of AD genetic variance is explained by single-nucleotide polymorphisms (SNPs) (Ridge et al. 2016).

In this context, endophenotype analysis, which is based in the evaluation of highly heritable quantitative traits tightly linked to disease pathology, has emerged as a promising approach for studying AD physiopathology and genetic background (Glahn et al. 2004; Jansen et al. 2022; Q. Zhang et al. 2020). These intermediate phenotypes might be influenced by the same genetic factors that confer AD risk, and might have lower genetic complexity. Compared to disease phenotypes, endophenotypes are affected by fewer genes or environmental factors which facilitates the identification of genuine associations more effectively (Glahn et al. 2004; Gottesman et al. 2003; Q. Zhang et al. 2020). The most common endophenotypes for AD are amyloid beta 42 levels (Aβ42), total tau (t-tau) and phosphorylated tau in threonine 181 (p-tau) in cerebrospinal fluid (CSF) (Cruchaga et al. 2013; Gottesman et al. 2003; Hall & Smoller 2010). Moreover, positron emission tomography (PET) using various radiotracers for measuring amyloid and tau burden has been used as AD endophenotypes (Cruchaga et al. 2013; Deming et al. 2017; Kauwe et al. 2009). AD pathology in the brain is negatively correlated with CSF Aβ42 levels and positively correlated with PET radiotracer retention (Sunderland et al. 2003). These biomarkers are surrogates of AD brain pathology and understanding their biology might provide insights into novel mechanisms of AD (Hardy & Higgins 1992; Hardy & Selkoe 2002). To date, relatively few AD loci have been identified using the endophenotype approach (Deming et al. 2017; Jansen et al. 2022). Moreover, GWAS analyses of PET and CSF endophenotypes are commonly analysed separately and comparisons between them have been overlooked.

In this study, we combined GWAS of Aβ CSF levels from four different AD cohorts with two GWAS of Aβ-burden measured using PET radiotracers. We used this strategy of combining both Aβ endophenotypes (CSF and PET) to identify novel genetic variants associated with AD and to replicate known AD signals. We then tested polygenic risk scores (PRS) derived from large studies in our datasets, dissected the CSF proteome signature associated with brain amyloidosis in a sizable CSF collection, and compared the overlap of genomic meta-analyses and proteomic results.

Materials and methods

GWAS cohorts

This study comprised a total of 2,076 multi-ancestry individuals from the GR@ACE/DEGESCO cohorts, including Ace and Valdecilla, (White Europeans from Southwest Europe ethnicity), and ADNI cohorts (multi-ethnic) and had data for different Aβ CSF or PET endophenotypes (Fig. 1 and Table 1). To avoid overlap of subjects between the CSF and PET cohorts, we used only datasets with genotype-level information available and IBD analysis. If an individual was represented in both CSF and PET datasets, we prioritized the PET measures and removed that individual from the CSF dataset to ensure that each subject was only represented in either CSF or PET analyses.

Ace alzheimer center barcelona

The ACE cohort comprised 1,189 randomly selected individuals with available brain amyloidosis measurements obtained using CSF or PET imaging, divided into three independent and non-overlapping cohorts (corresponding to two CSF and one PET cohorts). We analysed two independent GWAS because we used different methods to quantify CSF Aβ42 (536 individuals tested using Innotest ELISA kits and 472 individuals tested using the Lumipulse automated platform (Orellana et al. 2022)). We included a third dataset of 181 individuals with subjective cognitive decline (SCD) tested using PET Florbetaben measures from the Fundació ACE Healthy Brain Initiative (FACEHBI) study (Rodriguez-Gomez et al. 2017). The clinical protocols of the ACE cohort have been previously published (Moreno-Grau et al. 2019; Orellana et al. 2022; Rodriguez-Gomez et al. 2017). Briefly, syndromic diagnosis of all subjects was established by a multidisciplinary group of neurologists, neuropsychologists, and social workers. We assigned a healthy control (HCs) or SCD diagnosis to individuals with a Clinical Dementia Rating (CDR) of 0. Conversely, the mild cognitive impairment (MCI) diagnosis was assigned to individuals with a CDR of 0.5. For MCI diagnosis, the classification of López et al. (2003), and Petersen's criteria were also used (Jessen et al. 2014; López et al. 2003; Petersen et al. 1999, 2014). We employed the 2011 National Institute on Aging and Alzheimer's Association (NIA-AA) guidelines for AD diagnosis (Jack et al. 2018). We performed a lumbar puncture (LP) to obtain CSF following consensus recommendations (Vanderstichele et al. 2012). The CSF obtained was centrifuged (2000 × g for 10 min at 4 °C) and stored at −80 °C. For Aβ42 analysis, CSF was defrosted at room temperature (20 °C), vortexed and protein levels measured using the commercial ELISA kit Innotest β-AMYLOID (1–42) in 536 individuals and the chemiluminescent enzyme-immunoassay LUMIPULSE G600II automated platform (Fujirebio Europe, Belgium) in 472 individuals (Orellana et al. 2022). FACEHBI patients were assessed for brain amyloid deposition by PET imaging using the florbetaben [^{18}F] radiotracer (FBB) (NeuraCeq©). A single slow intravenous bolus of 300 Mbq of FBB (6 s/mL) (> 10 mL during 20 min) was administered. After 90 min, PET images were acquired (Rodriguez-Gomez et al. 2017).

Case–control study of genome research at fundació ACE (GR@ACE) study

The GR@ACE study included AD dementia and control patients recruited from Ace Alzheimer Center Barcelona (Barcelona, Spain), Valme University Hospital (Seville, Spain), the Spanish National DNA bank Carlos III (University of Salamanca, Spain) and the Dementia Genetics Spanish Consortium (DEGESCO)(Ruiz et al. 2014). The AD dementia diagnosis was endorsed by a multidisciplinary working group based on the DSM-IV criteria and NIA-AA guidelines (Jack et al. 2018). The DNA samples were extracted from whole blood and genotyped following the established in-house protocol at ACE. Further information can be found elsewhere (de Rojas et al. 2021; Moreno-Grau et al. 2019).

Valdecilla cohort for the study of memory and brain aging

The Valdecilla cohort comprised 97 individuals who were older than 55 years and extensively phenotyped with available CSF biomarker information. Biological samples were collected at baseline and several tests were performed to evaluate early signs of AD. Moreover, core biomarkers in CSF were analysed and a neuropsychological battery including The Free and Cued Selective Reminding Test (Buschke 1984), the Spanish version of the Face-Name Associative Memory Exam (Alegret et al. 2015), and the Logical Memory Test of the Wechsler Memory Scale-III (Wechsler 1945) and depression symptoms by the Geriatric Depression Scale (Sheikh & Yesavage 1986). HC (CDR = 0), MCI (CDR = 0.5) and dementia individuals (NIA-AA guidelines) were included in this analysis (Morris 1993). In the Valdecilla cohort, the Aβ42 biomarker was quantified by Lumipulse G600II which were interpreted according to previously established cut-off points (Alcolea et al. 2019). Further information about phenotype assessment was presented elsewhere (López-García et al. 2021).

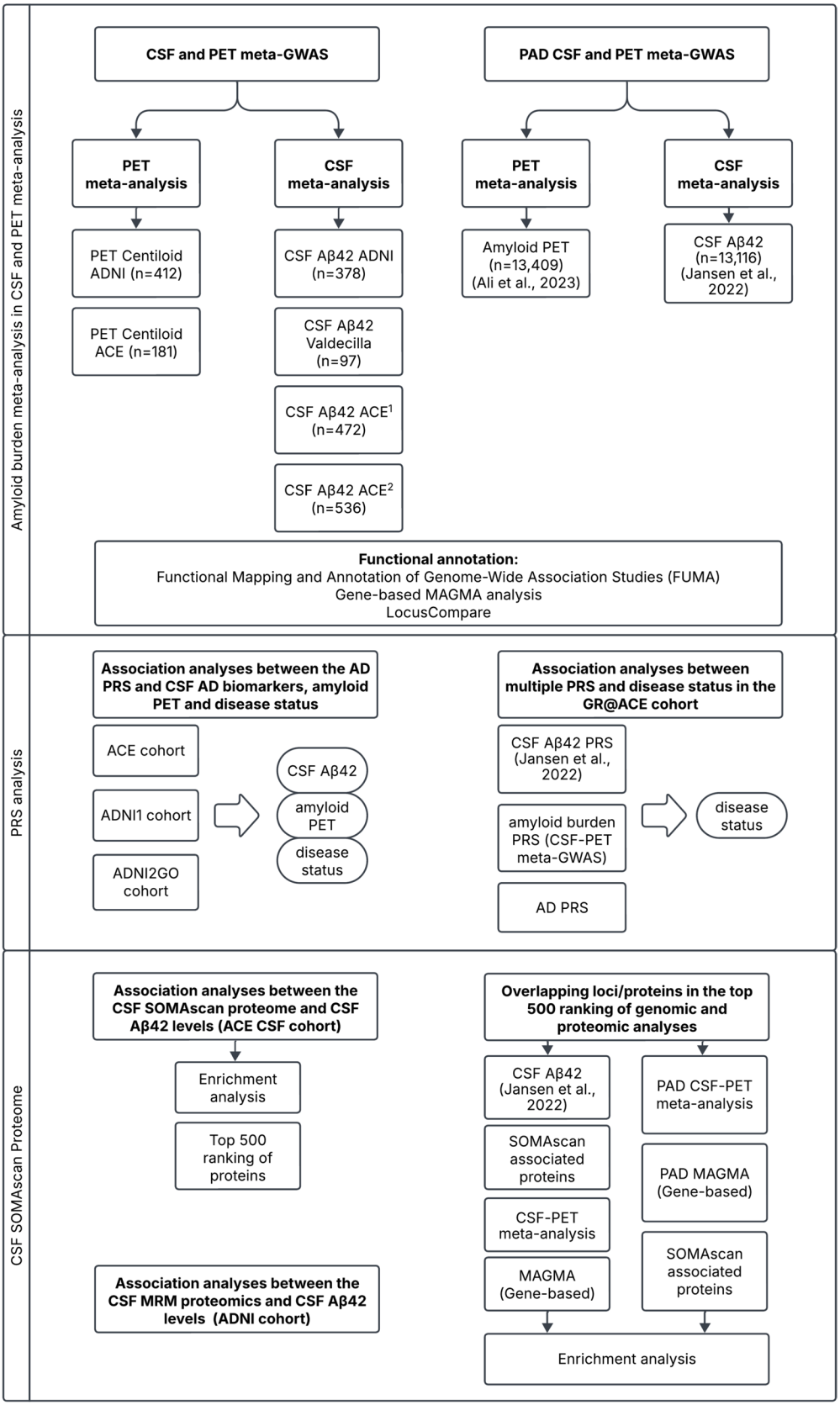

Fig. 1 Workflow of this study for each cohort and endophenotypes. ACE cohort used both Innotest ELISA kits (1) and CLEIA Lumipulse (2) for measuring CSF Aβ42 endophenotypes. This Flowchart was created using the Lucidchart online tool (https://www.lucidchart.com)

Table 1 Demographics information on each cohort

N	Phenotype	Cohort	Male (%)	Mean Age (sd)	HC (%)	MCI (%)	AD (%)	Centiloid PET (mean, sd)	Aβ42 CSF (mean, sd)	CSF Technique	*APOEε4* Carrier (%)
181	PET	ACE	69 (37.5)	66.3 (7.66)	100	0	0	5.80 (23.1)	-	-	26,7
412		ADNI2GO	225 (54.6)	72.5 (7.38)	29,13	64,32	6,55	37.8 (43.7)	-	-	40,5
536	CSF	ACE	231 (43.1)	73.8 (7.65)	5,41	59,33	35,26	-	757.06 (318.87)	Innotest ELISA	37,1
472			200 (42.4)	72.5 (8.13)	8,69	66,74	24,58	-	843.57 (441.40)	CLEIA LUMIPULSE	33,3
378		ADNI1	230 (60.8)	74.8 (7.04)	27,51	47,62	24,87	-	169 (56.7)	INNO-BIA AlzBio3	50,3
97		Valdecilla	39 (40.2)	67.0 (9.06)	44,33	38,14	17,53	-	895 (362)	CLEIA LUMIPULSE	28,9

HC Healthy Control, *MCI* Mild cognitive impairment, *AD* Alzheimer's disease, *N* sample size

Alzheimer's disease neuroimaging initiative (ADNI) cohort

Launched in 2003, ADNI is a longitudinal multicentre cohort for AD research based on United States and Canada (https://adni.loni.usc.edu/) (Mueller et al. 2005). The primary goal of ADNI has been to test whether biological markers, clinical and neuropsychological assessments can be combined to study the progression of MCI and early AD. We selected individuals from two separate ADNI databases: 1) the ADNI1 cohort with 378 individuals with available Aβ42 in CSF and 2) the ADNI2GO cohort with 412 individuals with available PET centiloid measures. In ADNI, syndromic diagnoses were based on a specific cut-off in the WMS-II LM test, education attainment, the Mini-Mental State Exam (MMSE) and CDR score. For HC and those with SCD, an MMSE score of 24–30 and a CDR of 0 were used. For those with MCI, a CDR of 0.5 and MMSE score of 24–30 were used. For those with AD, a CDR of 0.5–1 and an MMSE score of 20–26 were used. For the AD diagnosis, the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for *probable* AD were considered(Petersen et al. 2010). In ADNI individuals, Aβ42 CSF biomarker was measured using the Luminex xMAP platform (Luminex Corp, Austin, TX) for multiplexing with Innogenetics immunoassay reagents (INNO-BIA AlzBio3, Ghent, Belgium) (Landau et al. 2013; Shaw et al. 2009). ADNI2GO patients were screened for brain amyloid deposits using the Florbetapir [^{18}F] (AV45) radiotracer. After the injection of 370 MBq (10 mCi), four 5 min scans were acquired 50–70 min after the injection (Landau et al. 2013). Further information about PET data acquisition can be found elsewhere (https://adni.loni.usc.edu/data-samples/adni-data/neuroimaging/pet/).

PET imaging acquisition, harmonization and analysis

As FACEHBI and ADNI cohorts had different radiotracers, PET centiloid measures were used to perform a meta-analysis. Centiloids were calculated using Eq. (1), which was described for the conversion of FBB measures in the FACEHBI cohort (Rowe et al. 2017) and Eq. (2), which was described for the conversion of AV45 in ADNI (Klunk et al. 2015).

$$Centiloid_{FACEHBI} = (153.4 \times SUVR_{FBB}) - 154.9 \quad (1)$$

$$Centiloid_{ADNI} = (196.9 \times SUVR_{AV45}) - 196.03 \quad (2)$$

Genotyping, quality control and imputation

ACE and Valdecilla DNA samples were genotyped using the Axiom 815 K Spanish Biobank Array (Thermo Fisher). The

genotyping was performed by the Spanish National Center for Genotyping (CeGen, Santiago de Compostela, Spain). Genotyping procedures have been previously published elsewhere (de Rojas et al. 2021; Moreno-Grau et al. 2019). For the ADNI samples, the Illumina Human610-Quad BeadChip platform was used for genotyping in ADNI1, and the Illumina HumanOmniExpress BeadChip was used for ADNI2GO (Saykin et al. 2010).

Common quality control was applied to all GWAS datasets. Briefly, individuals with low-quality samples, excess of heterozygosity, sample call rate below 97%, sex discrepancies, variants call rate below 95% or a deviation from the Hardy–Weinberg equilibrium ($P > 1e\text{-}06$) were excluded from the analysis. In addition, familial relatedness (PI-HAT > 0.1875) or ancestry outliers based on principal component analysis (PCA) were also removed. The imputation was performed using the Haplotype Reference Consortium panel in the Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html#!). Only the common markers (MAF > 1%; MAC = 20) and high imputation quality ($R^2 > 0.3$) were selected for the subsequent analyses (GRCh37/hg19 reference assembly).

SOMAscan proteomic assay

We considered a subset of 1,008 CSF samples from the ACE CSF cohort that had available SOMAscan proteomic measures, including more than 7,000 proteins (SomaLogic, Boulder, Colorado), and clinical phenotypes for analysing the CSF proteome. Briefly, this multiplex proteomic assay uses a 50 µL CSF sample and modified DNA aptamers to measure protein abundance. First, proteins are bound to immobilized aptamers using streptavidin beads and tagged with fluorescent markers. After washing unbounded proteins, the streptavidin beads are released using ultraviolet light, and the protein–aptamer complex is re-captured by monomeric avidin. To select only specific complexes, the protein–aptamers are exposed to an anionic competitor and then, hybridized in a conventional DNA array for analysis as described elsewhere (Gold et al. 2010). Finally, the protein level measures expressed in relative fluorescent units (RFU) are normalized using the adaptive normalization by maximum likelihood method further described by Candia (Candia et al. 2017).

Statistical analysis

GWAS and meta-GWAS

We harmonized CSF and PET endophenotypes measures performing a log10 transformation to adjust to a normal distribution, and Z-score values were determined using the *scale* R function (*center* = TRUE, *scale* = TRUE) (Supplementary Fig. 1). We used R software version 4.1.1.

The GWAS on each dataset was run using a generalized linear model in the software PLINK2 (Chang et al. 2015). All individuals with available amyloid burden information were analysed using the statistical model considering population microstratification (four PCs), sex, age, and dementia status for the association analysis. The genome-wide significance threshold was set to $P < 5e\text{-}08$ and the suggestive threshold was set to $P < 1e\text{-}05$. We then performed an inverse-variance weighted meta-analysis on each amyloid burden endophenotype separately, Aβ42 ($n = 1{,}483$) in CSF and amyloid PET imaging ($n = 593$).

Thereafter, both Aβ endophenotypes were further combined into a single meta-analysis ($n = 2{,}076$) using the sample size weighted method in METAL software. This approach integrates p-values from different studies, weighting them by the sample size of each cohort, which provides a way to combine evidence across studies without relying on the beta direction (Willer et al. 2010). This is particularly useful when dealing with datasets where the beta coefficients are not directly comparable or when different methods are used to measure the same biological outcome, as is the case with PET and CSF amyloid measurements.

We chose this meta-analysis of p-values approach because the beta directions and methods applied to measure amyloid burden differ between PET and CSF assessments. Specifically, in AD, the two measurements exhibit opposite biological directions: decreased levels of CSF Aβ42 are associated with increased amyloid plaque deposition in the brain, as observed through PET imaging. The PET amyloid burden is measured through radiotracer retention, while CSF measures account for soluble Aβ42 levels, which decrease as amyloid plaques accumulate in the brain. Thus, directly comparing beta coefficients across these methods could be misleading (Stouffer et al. 1949; Willer et al. 2010). In this sense, we studied genetic markers with opposite beta direction of these amyloid CSF and PET endophenotypes in relation with AD.

By combining p-values, we focused on the statistical significance and opposite beta direction, this strategy accounted for the AD opposite biological contexts and different measurement techniques, enabling a more robust and generalized analysis of amyloid burden across different datasets. The genetic markers evaluated in the meta-analysis were filtered considering a opposite beta direction in each CSF and PET endophenotype-independent GWAS and its presence in at least half of the datasets to select SNPs for further analysis. The code for this filtering is available on the Supplementary Material, and additional code will be shared upon reasonable request (Supplementary Material 1).

Additionally, we performed another CSF-PET meta-analysis considering the largest publicly available datasets for CSF Aβ42 ($n = 13{,}116$) (Jansen et al. 2022) and

amyloid PET ($n = 13{,}409$) (Ali et al. 2023) (publicly available datasets; PAD analysis). To homogenize the results with our primary analysis, these datasets were converted to the GRCh37 assembly using the UCSC LiftOver software (https://genome.ucsc.edu/cgi-bin/hgLiftOver). Because we did not have access to genotype-level information for all cohorts included in these studies, we were unable to prune potential overlapping subjects between both meta-analyses. Therefore, the results of combining these large meta-GWAS (PAD) should be interpreted cautiously and are considered primarily for generating additional evidence about the pathways observed in our main analysis, where subject overlap was checked at the genotype level and removed to create two genuinely independent datasets (CSF and PET).

Finally, we attempted to replicate previously published genes for 1) AD described in Bellenguez (Bellenguez et al. 2022), 2) CSF Aβ42 genes reported by Jansen and the EADB consortium (Jansen et al. 2022), and 3) neuropathological features described in Beecham (Beecham et al. 2014) (Supplementary Table 1, Supplementary Table 2, Supplementary Table 3, and Supplementary Material 2).

Functional examination of identified sentinel snps and linked genomic regions

Clumping and annotation of suggestive signals ($P < 1e\text{-}05$) were performed using the software PLINK1.9 (Purcell et al. 2007). Additional annotations of biological function and gene-mapping were performed using meta-analysis summary statistics using the online tool Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA) (Watanabe et al. 2017). We set the threshold for independent significant SNPs at $P < 1e\text{-}05$, $R^2 < 0.05$, separated by over 250 kb, and we used the 1000G Phase3 reference panel to analyse suggestive signals in European population. For functional annotation, SNPs were matched to available databases such as ANNOVAR, Combined Annotation Dependent Depletion (CADD) scores, RegulomeDB and chromatin states based on a hidden Markov model from the Roadmap Epigenomics Project. Significant hits were mapped to genes according to 3 methods: 1) Physical distance with a maximum of 10 kb from nearby genes in the reference assembly, 2) expression quantitative trait loci (eQTL) associations assigned to SNP in blood, vascular, heart, brain tissues and embryonic stem cell derived cells, and 3) three-dimensional DNA interactions with SNPs and other gene regions where promoters were considered to be 250 bp upstream and 500 bp downstream of the transcription starting site for chromatin interaction. Moreover, a gene-based analysis was performed using MAGMA v1.08 that assigned exclusively protein-coding genes (Ensembl build 85) to the top SNPs found. Only 11,807 genes were mapped, and the gene-wide significance was defined at $P = 0.05/11{,}807 = 4.235e\text{-}06$. We also conducted FUMA annotations in the amyloid burden meta-analysis considering the largest meta-GWAS for amyloid PET and CSF reported to date (Ali et al. 2023; Jansen et al. 2022). Additionally, we conducted a colocalization analysis using the LocusCompare tool (http://locuscompare.com/) (B. Liu et al. 2019) to investigate the functional relevance of the obtained GWAS results. The colocalization analysis was performed considering the latest available AD summary statistics (Lambert et al. 2013) and QTL results that were searched in the GTEx Portal version 7 focusing on brain and whole blood tissues (https://gtexportal.org/home/).

Polygenic Risk Scores (PRS)

We computed the AD PRS described in Bellenguez et al. (2022) that considered 83 loci. However, some SNPs were not imputed or had a low imputation quality ($R^2 < 0.3$), and we decided to calculate the AD PRS including genetic variants found in all imputed datasets ($n = 76$; Supplementary Table 4). Because some control samples were included in the first stage of the AD GWAS, we considered the independent effects reported in the second stage for the PRS calculation. We added the gene dosages of these SNPs weighting by their beta coefficients (effect size); the allele analysed was matched to the reported allele (A1) by Bellenguez (Bellenguez et al. 2022). Additionally, due to the large effect on AD risk and its well-established association with most AD endophenotypes, the *APOE* locus was excluded from all these PRS. These analyses were performed separately for the ACE, ADNI1 and ADNI2GO cohorts. In contrast, the Valdecilla cohort was excluded due to reduced sample size, and ACE PET cohort was excluded in the case–control analysis because all individuals were cognitively unimpaired. We analysed the AD PRS association with the case–control status, CSF Aβ42, and PET amyloid burden measurements. We considered as a covariate the age, sex, and disease status only in associations with biomarkers. Additionally, we considered the fixed effect meta-analysis model considering the heterogeneity threshold (I^2) of 75% as high (Higgins et al. 2003). Furthermore, we performed a sensitivity analysis on AD PRS association with the disease status in individuals with available CSF biomarkers. We classified according the ATN (amyloid, tau, neurodegeneration) status (Jack et al. 2018), the A-T-N- individuals as controls, A + as cases and we excluded MCI individuals with T- or N- classification.

Additionally, considering the GR@ACE cohort individuals, including 7,437 cases and 8,999 controls, we also calculated another PRS for A) AD (Bellenguez et al. 2022) ($n = 76$ SNPs; Supplementary Table 4), B) CSF Aβ42 levels ($n = 30$ SNPs; Supplementary Table 5) considering the genetic variants with a $P < 1e\text{-}05$ described in Jansen (Jansen et al. 2022), and C) an amyloid burden PRS considering suggestive variants found in our meta-analysis (combining

endophenotypes filtering according to opposite beta direction; $n=9$ SNPs; Supplementary Table 6) the same way as described above. Further information about the cohort has been previously published (de Rojas et al. 2021; Moreno-Grau et al. 2019). For PRS computation, the beta coefficients and standard errors were estimated using the equations described by Zhu (Zhu et al. 2016). Again, we associated these scaled PRS with case–control data in non-overlapping individuals to assess if Aβ genetic determinants are also related to disease risk. We also conducted a sensitivity analysis for the association of these PRS with the disease status excluding individuals with MCI diagnosis.

Association between biomarker levels and SOMAscan proteomics

We assessed the association between SOMAscan 7 k proteomic panel and CSF Aβ42 levels ($n=1{,}008$) in the ACE CSF cohort. Briefly, SOMAscan proteomic measures were log10 transformed, outliers were removed at ± 3 standard deviations from the mean and standardized using the scale R function with centring and scaling. For further analysis, we selected 2,682 proteins based on correlations between: 1) two independent SOMAscan assay analysing the same samples, and 2) comparing aptamer- and antibody-based proteomic platforms (Frick et al. 2024; Puerta et al. 2024). To identify proteins associated to CSF Aβ42, a linear regression model was performed on scaled CSF Aβ42 levels and proteomic measures. We considered disease status, sex, age, and the CSF biomarker technique as covariates. Subsequently, the top 500 ranking of significant proteins associated with CSF Aβ42 (False discovery rate; FDR < 1.864e-05) was analysed in the WEB-based GEne SeT AnaLysis Toolkit (WebGestalt)(Liao et al. 2019) to perform an over-representation analysis (ORA) considering several functional databases and the whole genome as built-in reference gene list following the idea of investigating the complete genome (GWAS and gene-based analyses) (Supplementary Table 7). We also performed an enrichment analysis on the complete subset of valid SOMAscan proteins ($n=2{,}682$) to evaluate the impact of platform analyte preselection and quality control process on the results obtained.

To explore the biological significance of the GWAS results, we displayed the overlap between loci controlling amyloidosis and the proteins significantly associated with CSF Aβ42 in the ACE CSF cohort using Venn diagrams. The top 500 proteome and genome hits selected from the CSF Aβ42 meta-GWAS described by Jansen et al. (2022), the meta-analysis of CSF-PET endophenotypes filtered by opposite beta size direction, and the gene-based MAGMA analysis performed by FUMA were identified and annotated (Supplementary Table 8, Supplementary Table 9, Supplementary Table 10, Supplementary Table 11 and Supplementary Table 12). The top rankings were compared and the overlap between genomic and proteomic analysis was identified and evaluated using WebGestalt tool as described above.

Additionally, we used available proteomic data of ADNI to evaluate in an independent cohort the association between CSF proteomic measures and CSF Aβ42 levels. The ADNI proteomic measures were obtain using the Multi Reaction Monitoring (MRM) targeted mass spectroscopy technique ($n=288$). Further information on the quality control can be found online at adni.loni.ucla.edu under the "Biomarkers Consortium CSF Proteomics MRM data set" in the "Data Primer" document (Spellman et al. 2015). Proteomic measures were transformed to Z-score and outliers were removed as described above for the ACE cohort. We averaged MRM protein fragments of the same protein that correlated with a Pearson $r>0.5$, and non-correlating fragments were not considered for analysis (Tijms et al. 2020). There were 138 candidate proteomic measures for further analysis. We also conducted a linear model association analysis using age, sex, disease status, and site as covariates to evaluate CSF proteomic changes related with CSF Aβ42.

Results

Meta-analysis of Aβ endophenotypes

The genome-wide meta-analysis of CSF endophenotypes involved 4 independent AD cohorts with Aβ42 measures ($n=1{,}483$; $\lambda=1.009$). The genomic inflation factor (λ) suggested no gross bias or stratification. As it was expected, we observed a consistent genome-wide significant association with rs429358-*APOE* locus as a sentinel variant (Beta = −0.58 [−0.658, −0.503]; $P=8.36\text{e-}49$). We detected 19 additional suggestive pQTL signals for Aβ42 levels in CSF (Supplementary Table 13). Similarly, the meta-analysis of amyloid PET endophenotype involved 2 independent cohorts ($n=593$; $\lambda=1.013$), revealed a genome-wide significant association in the same sentinel variant in the opposite direction (rs429358-*APOE* locus; Beta = 0.684 [0.555, 0.813]; $P=2.00\text{e-}25$). An additional novel hit at rs72737013 close to the *ANXA1* gene (Beta = 0.813 [0.528, 1.099]; $P=2.39\text{e-}08$) was detected. Additionally, there were 43 additional independent suggestive signals annotated for amyloid burden measured using PET (Supplementary Table 14).

We combined the summary statistics from both CSF and PET Aβ meta-analyses without considering the beta direction ($n=2{,}076$). Again, we confirmed the sentinel variant rs429358 to be the most significant locus in the *APOE* region. Other genetic variants emerged as GWAS-significant in this new meta-analysis. However, none of them were inversely associated with CSF and PET endophenotypes in

all studies except for the rs429358-*APOE* marker. We considered these hits as false positive signals (Supplementary Table 15).

In looking for new suggestive signals beyond *APOE*, we extracted the subset of 376,599 SNPs with opposite beta direction in CSF and PET endophenotype analyses. After the SNP selection in the combined Aβ meta-analysis, the rs429358-*APOE* variant ($P = 9.50e-67$) remained as the only GWAS-significant hit (Fig. 2A, upper) but nine additional suggestive consistent variants were identified in genes such as *NPY5R, TIAM2* or *MAGI2,* among others (Table 2). Additionally, the combination of Aβ endophenotypes and the selection of SNPs with opposite beta direction in CSF and PET enhanced the significant replication of several genetic markers previously described for AD (Bellenguez et al. 2022), CSF Aβ42 levels (Jansen et al. 2022) and neuropathological features (Beecham et al. 2014) (Supplementary Material 2, Supplementary Table 1, Supplementary Table 2, Supplementary Table 3).

However, the PAD CSF-PET meta-analysis (Ali et al. 2023; Jansen et al. 2022) (effective sample size $n = 23,532$) identified several markers previously associated with AD and its endophenotypes. These significant markers were identified on chromosome 19 including the rs429358-*APOE* ($P = 5.94e-601$), as well as, the rs4844610-*CR1* ($P = 5.76e-18$), rs7982-*CLU* ($P = 7.81e-11$), rs12151021-*ABCA7* ($P = 3.92e-10$), rs6733839-*BIN1* ($P = 1.02e-08$), rs117834516-*FERMT2* ($P = 4.82e-08$) and the novel

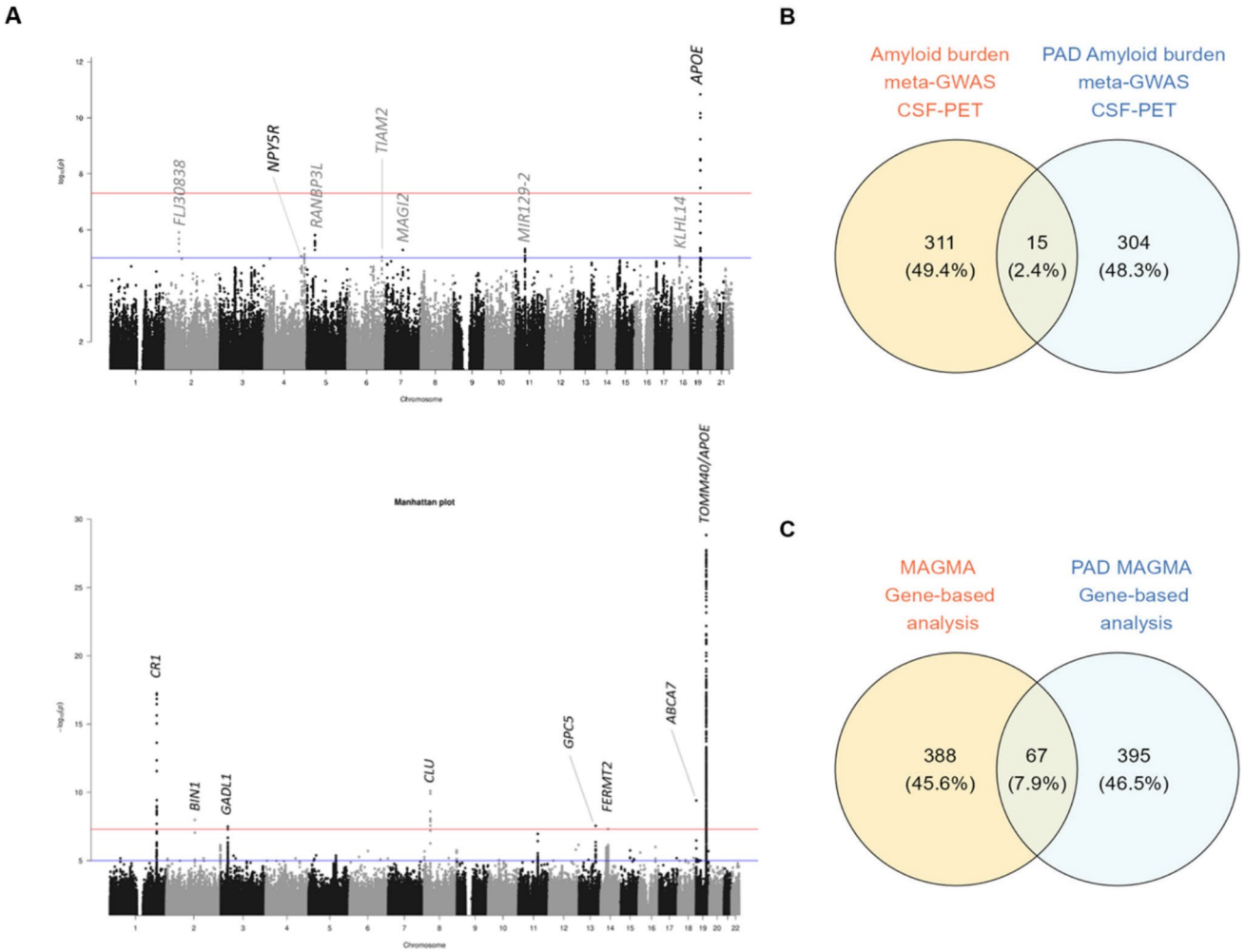

Fig. 2 Plots of the Aβ burden meta-analysis combining data of CSF-PET endophenotypes. **A** (upper) Manhattan plot of our CSF-PET meta-analysis ($n = 2,076$). Results were filtered according to beta direction and dataset missingness. Suggestive independent markers were annotated with the nearest gene name. Mapped genes coloured in grey represent those that were not replicated in the PAD CSF-PET meta-GWAS. (lower) Manhattan plot of the PAD CSF-PET meta-analysis filtered ($n = 23,532$). Genome-wide significant independent markers were annotated with the nearest gene name. The Y-axis was restricted to visualize suggestive signals. The genome-wide significance threshold was set to $P < 5e-08$ (red line) and the suggestive threshold was set to $P < 1e-05$ (blue line). **B** Venn diagram representing the overlap between the top 500 ranking of independent genetic markers comparing the PAD and our amyloid burden meta-analysis. **C** Venn diagram representing the overlap between the top 500 ranking of independent genes in the PAD and our gene-based analysis

Table 2 Results of the genome wide meta-analysis filtered combining CSF and PET endophenotypes (4.9% of total SNPs)

rsID	SNP	Nearest Gene	REF	ALT	A1	FreqA1	Call Rate	n	Zscore	P-value	Direction
rs429358	**19:45,411,941**	**APOE (0 kb)**	**T**	**C**	**C**	**0.211**	1.000	**2076**	**−17.259**	**9.50E-67**	**—++**
rs78402940	2:59,125,664	FLJ30838 (0 kb)	A	G	G	0.089	0.999	1979	−4.849	1.24E-06	–?-++
rs62354504	5:36,361,976	RANBP3L (59.96 kb)	G	A	A	0.027	0.999	1262	−4.807	1.53E-06	?-?-+?
rs62340552	4:180,023,617	NA	C	T	T	0.041	0.993	1798	−4.582	4.61E-06	–?-+?
rs2902373	11:43,637,563	MIR129-2 (34.53 kb)	C	T	T	0.222	0.993	2076	−4.571	4.84E-06	—++
rs73141455	7:78,648,931	MAGI2 (0 kb)	G	T	T	0.038	0.995	1798	−4.555	5.24E-06	–?-+?
rs115822934	4:164,308,011	NPY5R (34.92 kb)	G	T	T	0.032	0.998	1798	−4.448	8.65E-06	++?+-?
rs1523589	18:30,242,590	KLHL14 (−10.04 kb)	C	A	A	0.201	0.996	2076	−4.440	8.99E-06	++++−
rs4395536	4:168,504,316	NA	A	G	G	0.914	0.987	1979	−4.435	9.23E-06	++?+−
rs11963901	6:155,436,138	TIAM2 (0 kb)	C	T	T	0.106	0.999	1979	−4.434	9.23E-06	–?-++

Meta-analysis was performed using a sample size weighted method without considering beta direction, and filtered by beta and data availability in at least half of each endophenotypes cohorts. Reference SNP (rs) code for the SNP: rsID, Genetic markers in GRCh37/hg19 genomic assembly: SNP, Reference allele: REF, Alternative allele: ALT, Effect allele: A1, Sample size: n

Bold: significant results $P < 5e\text{-}08$ with opposite beta direction

rs4955351-*GADL1* ($P = 3.19e-08$) which was not previously associated to AD or amyloid levels (Fig. 2A lower, Supplementary Table 16). However, we observed no significant GTEx QTL near *GADL1* in brain and whole blood tissues, and the colocalization analysis reveal no overlap between GWAS and eQTL results in this region (Supplementary Table 17). Additionally, the PAD analysis replicated the rs115822934-*NPY5R* variant ($P = 3.21e-04$) originally found suggestive in our CSF-PET meta-analysis (Supplementary Table 18). Importantly, we also observe concordances between our local effort (amyloid burden CSF-PET meta-GWAS) and the PAD. Specifically, we detected 15 overlapping sentinel markers in the top 500 ranking of the amyloid burden meta-GWAS from both the PAD and our current meta-analysis (Fig. 2B), as well as 67 overlapping genes in the PAD and our gene-based top 500 ranking (Fig. 2C).

To link the variants of interest to specific genes and obtain relevant functional information about these loci, we applied FUMA to the suggestive signals from the Aβ meta-analysis that were filtered based on opposite direction in CSF and PET (Table 2). There were 125 prioritized genes mapped using at least two strategies (positional mapping, eQTL or chromatin interactions) and 45 genes were selected based on the three strategies described in methods. As expected, the majority of the prioritized genes were related to the rs429358-*APOE*. Excluding chromosome 19, we prioritized 23 genes mapped (6 SNPs) with a CADD score > 12.37 suggesting a potential deleterious effect (Supplementary Table 19)(Kircher et al. 2014). In contrast to the univariate SNP analysis, the gene-based analysis performed using MAGMA revealed 15 study-wise significant loci ($P < 4.235e-06$) excluding the *APOE* region (Table 3, Supplementary Fig. 2). Interestingly, the identified genetic variants in some of these genes (*TENM3*, *TMEM132D*, *PTPRD*, *CNTN5*, *RBFOX1*, *CSMD1*, *TIAM2*, *RORA* and *WWOX)* have been previously related to neuroimaging endophenotypes (Brouwer et al. 2022; Furney et al. 2010; Homann et al. 2022), extreme AD PRS measures (Gouveia et al. 2022), AD endophenotypes (CSF Aβ42 or p-tau levels (Chibnik et al. 2018; Deming et al. 2017; Hong et al. 2020a; Kunkle et al. 2019; Raghavan et al. 2020)), mental disorders (Bigdeli et al. 2021; Luciano et al. 2018) and cognitive decline in AD (Homann et al. 2022; Lee et al. 2017; Sherva et al. 2020). Additionally, the gene-based analysis of the PAD amyloid burden meta-GWAS revealed genes previously associated to AD such as *APOE* ($P = 2.09e-13$), *CLU* ($P = 2.13e-07$), *FERMT2* ($P = 3.49e-07$) and the *CR1* locus ($P = 3.64e-06$), which reached borderline gene-wide significance threshold at $P < 2.717e-06$ (Supplementary Table 20).

Table 3 Gene-based MAGMA results from FUMA analysis considering genome-wide significant results $P < 4.235e-06$

Gene	EntrezID	UniProtID	CHR	Start	Stop	n SNPS	Zscore	*P*-value
NECTIN2	5819	Q92692	19	45,349,432	45,392,485	37	7.787	3.442E-15
APOE	348	P02649	19	45,409,011	45,412,650	4	7.282	1.648E-13
APOC1	341	P02654	19	45,417,504	45,422,606	5	6.774	6.278E-12
CSMD1	64,478	Q96PZ7	8	2,792,875	4,852,494	929	6.437	6.076E-11
TOMM40	10,452	O96008	19	45,393,826	45,406,946	24	6.109	5.000E-10
WWOX	51,741	Q9NZC7	16	78,133,310	79,246,564	323	5.566	1.307E-08
LHPP	64,077	Q9H008	10	126,150,403	126,306,457	153	5.507	1.822E-08
BCL3	602	P20749	19	45,250,962	45,263,301	6	5.449	2.540E-08
CNTN5	53,942	O94779	11	98,891,683	100,229,616	556	5.358	4.217E-08
TENM3	55,714	Q9P273	4	183,065,140	183,724,177	114	5.312	5.432E-08
PTPRD	5789	P23468	9	8,314,246	10,612,723	332	5.258	7.272E-08
TIAM2	26,230	Q8IVF5	6	155,153,831	155,578,857	60	5.243	7.904E-08
RBFOX1	54,715	Q9NWB1	16	6,069,095	7,763,340	382	5.079	1.900E-07
GPC5	2262	P78333	13	92,050,929	93,519,490	275	4.956	3.604E-07
RORA	6095	P35398	15	60,780,483	61,521,518	185	4.827	6.948E-07
MACROD2	140,733	A1Z1Q3	20	13,976,015	16,033,842	354	4.787	8.471E-07
TMEM132D	121,256	Q14C87	12	129,556,270	130,388,211	205	4.759	9.717E-07
CDH13	1012	P55290	16	82,660,408	83,830,204	315	4.592	2.201E-06
LRP1B	53,353	Q9NZR2	2	140,988,992	142,889,270	318	4.549	2.696E-06
KIR3DX1	90,011	Q9H7L2	19	55,043,909	55,057,053	9	4.487	3.616E-06
FAM53B	9679	Q14153	10	126,307,861	126,432,838	42	4.479	3.751E-06

CHR Chromosome, *NSNP* Number of SNPs, *n* Sample size, *EntrezID* Entrez Gene Identifier, *UniProtID* UniProt Swiss Protein Identifier

Association between AD PRS with AD endophenotypes and other clinical features

We observed a significant result in the meta-analysed associations between the AD PRS and Aβ levels (CSF Beta = −0.05 [−0.10, −0.00]; $P = 3.43e\text{-}02$ and PET Beta = 0.10 [0.02, 0.17]; $P = 1.30e\text{-}02$). These results might suggest that genes involved in AD risk could potentially modulate amyloid levels (Fig. 3A, B).

As expected, we observed a significant result in the association meta-analysis of the AD PRS with case–control dementia status including all individuals with available information of the 3 endophenotype datasets (OR = 1.18 [1.05, 1.32]; $P = 5.29e\text{-}03$). These results suggest that these genes modulate the disease status as previously reported (Bellenguez et al. 2022) (Fig. 4). Even though ADNI2GO did not reach statistical significance, it had a similar beta coefficients and direction, possibly due to the low proportion of AD cases in this cohort (6.55%). Moreover, we also observed a significant result in the sensitivity analysis excluding MCI individuals with non-amyloid pathology (Supplementary Fig. 3A).

Association between genetic variants of amyloid endophenotypes with case–control status

To assess whether CSF Aβ42 genetic modulators are also related to AD risk, we constructed different PRS including variants detected in our study and previous meta-GWAS (Bellenguez et al. 2022). We then checked the association

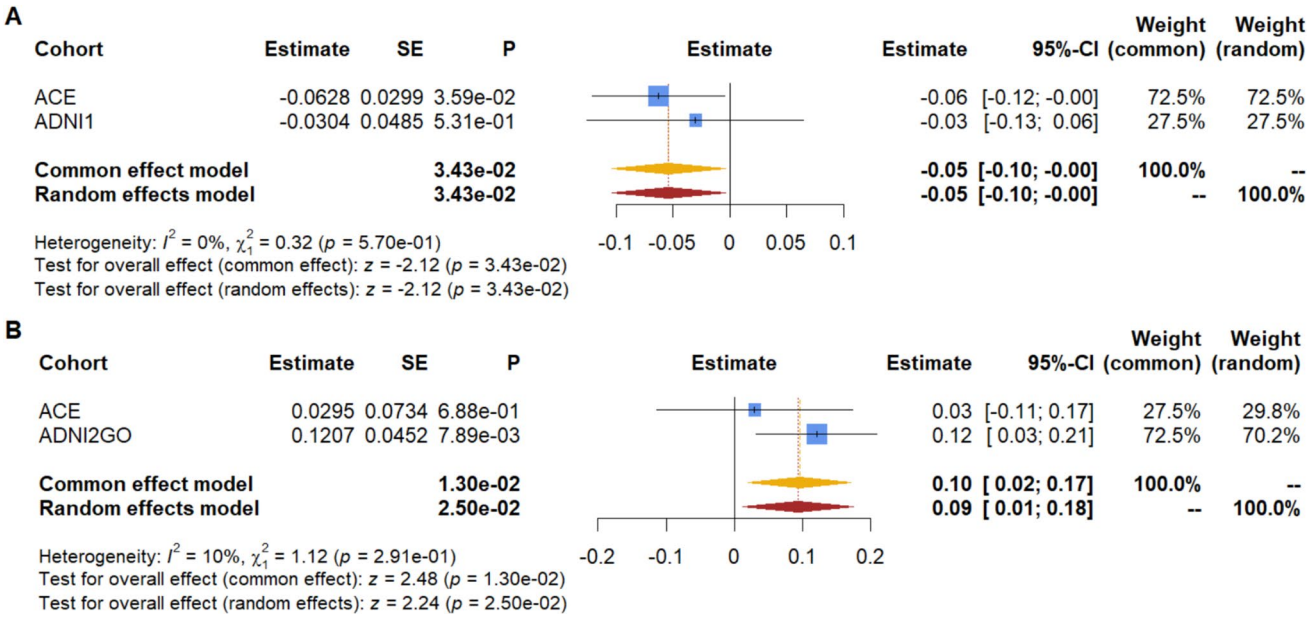

Fig. 3 Forest plot of the meta-analysis association between the AD PRS. **A** CSF Aβ42, and (**B**) Aβ PET endophenotypes. The significance threshold was set to 0.05

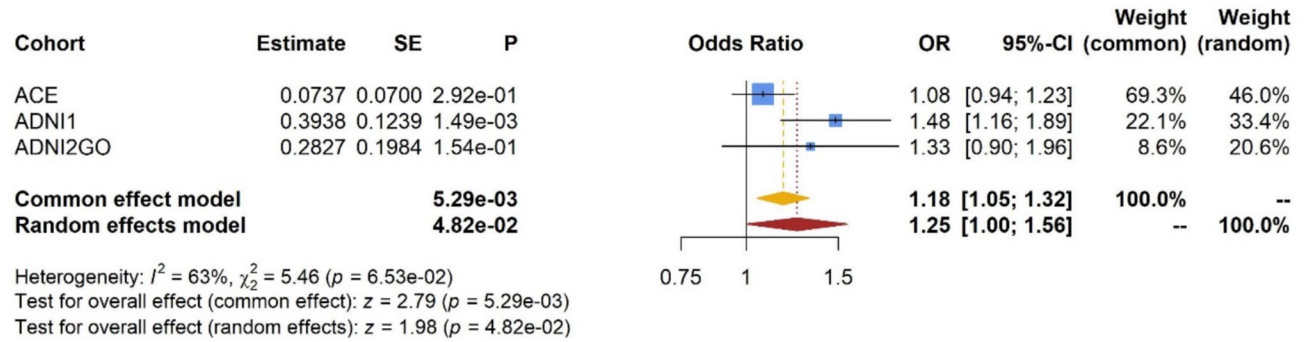

Fig. 4 Forest plot of the meta-analysis association between the AD PRS and dementia status as case–control. In ACE (305 cases and 703 controls, 30.25%), ADNI1 (94 cases and 285 controls, 24.80%) and ADNI2GO cohorts (27 cases and 385 controls, 6.55%)

of calculated PRS in the GR@ACE case–control study (de Rojas et al. 2021) including all individuals with available phenotype information. We did not observe any significant association for any calculated PRS for amyloid (Fig. 5) which could be due to the reduced set of independent markers reported for these phenotypes ($P < 1e\text{-}05$) or not having an impact on AD pathology. As expected, the AD PRS was highly associated with the case–control (OR = 1.34 [1.28, 1.39]; $P = 4.89e\text{-}43$), thus supporting that the AD genes previously described by us and the EADB consortium (Bellenguez et al. 2022; de Rojas et al. 2021) might be modulating the disease risk in the GR@ACE/DEGESCO cohort. We obtained similar results in the sensitivity analysis excluding MCI individuals (Supplementary Fig. 3B).

CSF proteome signatures associated with the Aβ42 CSF levels

We regressed the CSF Aβ42 peptide levels on CSF SOMAscan aptamer levels to identify the proteomic signature associated with amyloid burden (Fig. 6A). We identified 1,387 study-wide significant proteins in the linear model of CSF Aβ42 (FDR < 1.864e-05) (Supplementary Table 21). Notably, we observed a marked asymmetry in the beta coefficients of SOMAmers on CSF Aβ42 levels, with the majority showing positive beta estimates, suggesting a positive correlation contributing to increased CSF Aβ42 levels (Fig. 6A). Thus, the top 100 ranks of significant associations have an estimate range between 0.449 and 0.317, which contributes to an increase of this magnitude in CSF Aβ42 levels,

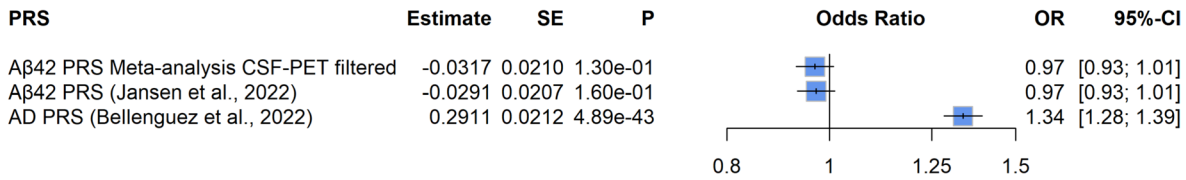

Fig. 5 Forest plot of the association between the AD, Aβ PRS and case–control status. PRS for AD (76 SNPs from Bellenguez et al. 2022) and Aβ42 (30 SNPs from Jansen et al. 2022, 9 SNPs from our meta-analysis). The GR@ACE cohort included 7,437 cases and 8,999 controls

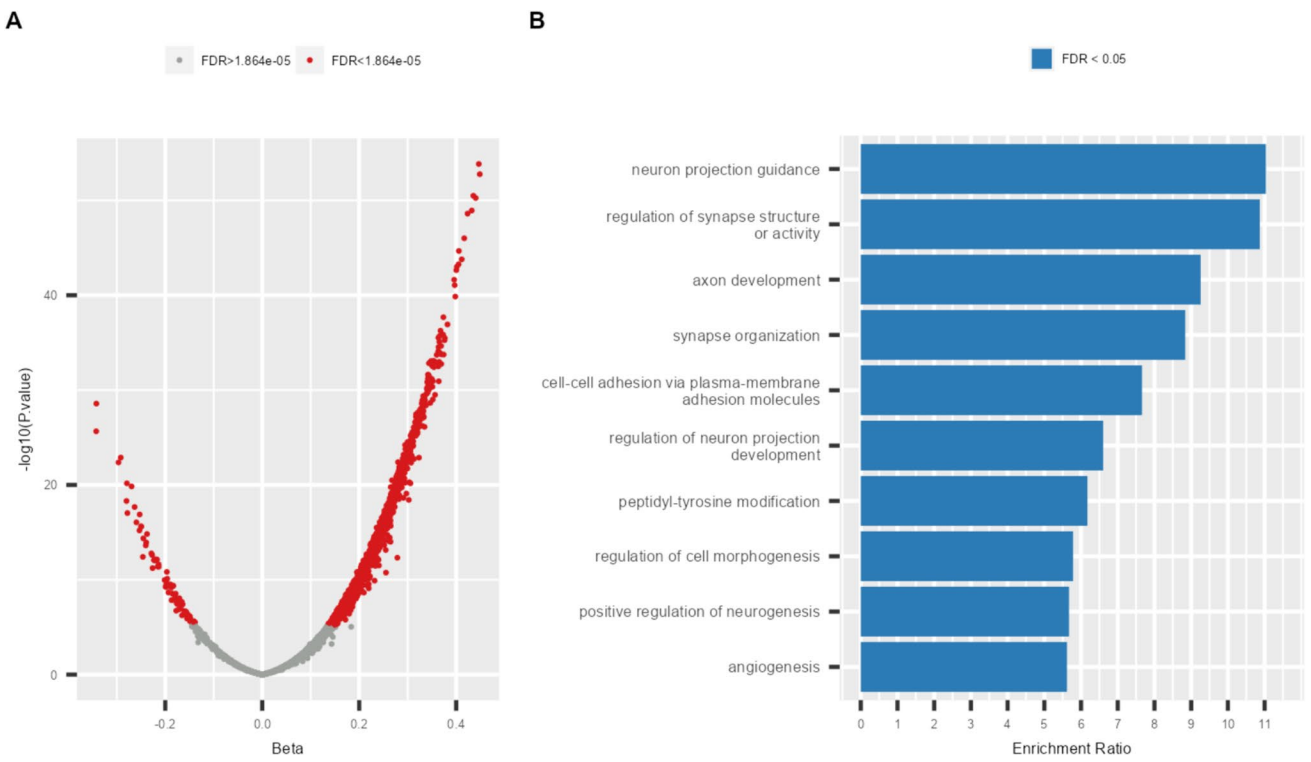

Fig. 6 Associations between CSF SOMAscan and CSF Aβ42 levels. **A** Volcano plot only considering proteins with good inter-assay correlation (n = 2,682), significant proteins (FDR < 1.864e-05) were highlighted in red (n = 1,387). B) Top 10 results of the enrichment analysis of significant protein associations with CSF Aβ42 levels using the WebGestalt tool

and the variance explained by these highly associated proteins ranges of between 0.202 and 0.297. Importantly, we observed multiple proteins that have been associated with the CSF levels of Aβ species or its mechanisms in previous studies, such as MTMR7, LMOD4, GD3S, SERA/PHGDH, SELS, ATE1, NPTXR, and the 14–3-3 eta protein, among others (Bernardo et al. 2009; Do et al. 2024; Galiano et al. 2016; Hamano et al. 2023; Leuba et al. 2004; Ramanan et al. 2021; Wesenhagen et al. 2022). Furthermore, we observed no significant associations with CSF Aβ42 considering the ADNI MRM proteomic data. We could observe that the majority of proteins had a positive beta coefficient as well ($n = 104$, 75.362%) (Supplementary Fig. 4A, Supplementary Table 22). There were 93 proteomic measures that were also represented in the CSF SOMAscan association analysis in the ACE cohort (Supplementary Fig. 4B). Additionally, we found that there were 12 significant aptamer measures, corresponding to 9 unique UniProt codes, with opposite beta direction in the top 100 ranking of the amyloid-associated proteins in the CSF SOMAscan platform that were also represented in the ADNI proteomic analysis (Supplementary Fig. 4C, Supplementary Table 23).

An enrichment analysis performed for significant proteins associated with CSF Aβ42 levels revealed genes involved in *neuronal projection guidance* (enrichment ratio = 11.034; FDR < 2.2e-16), *synaptic structure and activity* (enrichment ratio = 10.868; FDR < 2.2e-16), *cell–cell adhesion by plasma membrane molecules* (enrichment ratio = 7.660; FDR < 2.2e-16), *peptidyl-tyrosine modifications* (enrichment ratio = 6.174; FDR < 2.2e-16), *regulation of cell morphogenesis* (enrichment ratio = 5.786; FDR < 2.2e-16) and *angiogenesis* (enrichment ratio = 5.617; FDR < 2.2e-16) which are mainly driven by the large proportion of proteins with a positive betas ($n = 1{,}300$; 93.73%) (Fig. 6B; Supplementary Table 24, Supplementary Table 25). Furthermore, when comparing the enrichment results from the ORA analysis between the entire set of valid SOMAscan proteins and the proteins significantly associated with Aβ42 levels, we observed a complete lack of overlap, reinforcing the validity of our findings (Supplementary Fig. 5).

To identify those genes that were commonly associated with CSF Aβ42 levels in genomic and proteomic analyses, we compared the top 500 common list of signals in the following four analyses: CSF Aβ42 meta-GWAS by EADB (Jansen et al. 2022), our meta-analysis of CSF-PET, gene-based MAGMA, and SOMAscan protein analysis. The top 500 rankings were reduced to 339, 326, 455, 319 and 462 loci for the meta-GWAS by Jansen et al. (2022), our current CSF-PET meta-analysis and its gene-based MAGMA analysis, the PAD CSF-PET meta-GWAS and its gene-based MAGMA analysis (Ali et al. 2023; Jansen et al. 2022), respectively. The top 500 of the SOMAscan associations was reduced to 462 proteins. These reductions were due to the presence of SNPs that were not annotated and could not be matched to UniProt or the presence of duplicated UniProt codes (Supplementary Table 8, Supplementary Table 9, Supplementary Table 10, Supplementary Table 11 and Supplementary Table 12).

We found three genes/proteins (*CHST1*, *PTPRD* and *TMEM132D*) present in all four analyses, representing only 0.2% of the total loci/proteins analysed (full overlap). In addition, 32 other proteins overlapped between the SOMAscan proteomics and any genomic analysis, including four proteins represented in 3 different analyses (Fig. 7A, Supplementary Table 26). Similar results were obtained in investigating the top rankings of the SOMAscan analysis, the PAD CSF-PET meta-GWAS and its gene-based analysis; only the *TMEM132D* was represented in all analyses (Fig. 7B). Interestingly, we found that 10 of the 23 loci/proteins observed were also overlapping with the ranking considering our main CSF-PET meta-GWAS results. This overlapping with PAD CSF-PET meta-GWAS support the validity of our approach (Supplementary Fig. 6, Supplementary Table 27). However, there was a reduced consistency between the top 500 SOMAscan proteins associated with CSF Aβ42 and any genomic results with less than 2.5% of overlapping proteins. These results suggest that the Aβ42-related protein signature in CSF might not be closely linked to amyloid genetic modulators, indicating that the proteome signature associated with Aβ42 burden in the brain primarily reflects general disease processes largely unrelated to the genetic elements controlling amyloid production.

Finally, to gain insight into the few commonalities identified by comparing genetic and proteome signatures associated to the amyloid burden in the brain, we conducted a new enrichment analysis. Despite the reduced overlapping hits among proteome and genome studies, several significant mechanisms related to the *synthesis of glycosylphosphatidyl inositol (GPI)-anchored proteins by post-translational modifications* were identified (enrichment ratio = 48.070; FDR = 1.86e-04) and the *anchored component of the membrane* (enrichment ratio = 31.778; FDR = 1.32e-04), *cell–cell adhesion* via *plasma membrane molecules* (enrichment ratio = 26.207; FDR = 3.42e-06), *mental disorders* (enrichment ratio = 12.853; FDR = 3.42e-06) such as *autism* (enrichment ratio = 18.556; FDR = 0.002) and *anxiety* (enrichment ratio = 23.524; FDR = 0.004), and *regulation and development of neuron projections* (enrichment ratio = 13.035; FDR = 0.002) among others (FDR < 0.05). Interestingly, six of these mechanisms were also represented in the enrichment analysis of the PAD CSF-PET meta-analysis, which confirms our main results (Fig. 7C, Supplementary Table 28, Supplementary Table 29, Fig. 7D, Supplementary Table 30, Supplementary Table 31).

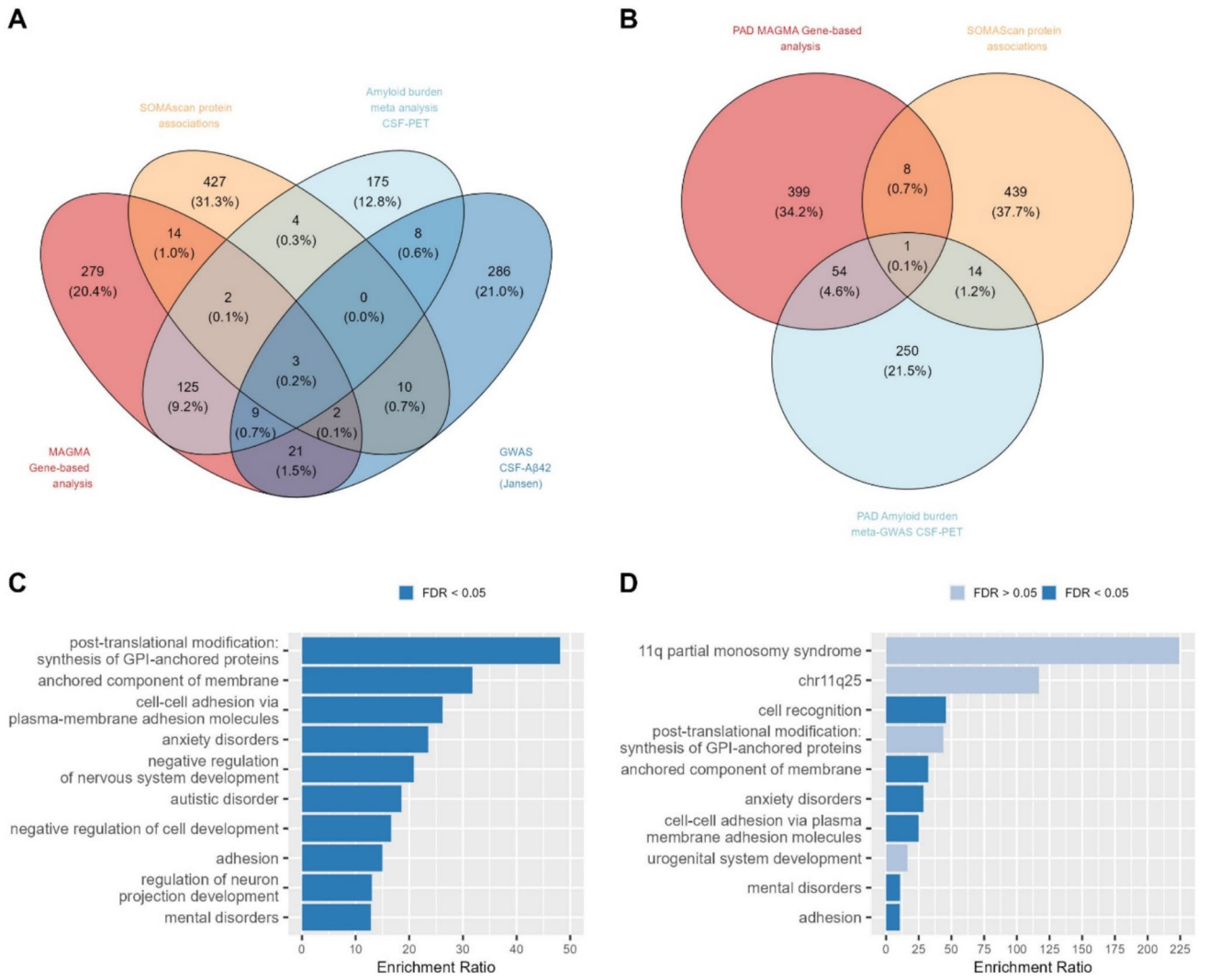

Fig. 7 Overlapping loci/proteins in genomic and proteomic analysis. **A** Venn diagram of the top 500 ranking of CSF Aβ42-associated proteins in the SOMAscan panel (orange), our gene-based MAGMA analysis (red), GWAS of CSF Aβ42 (Jansen et al. 2022) (dark blue) and our amyloid burden meta-analysis of filtered CSF-PET endophenotypes (light blue). B) Venn diagram of the top 500 ranking of CSF Aβ42-associated proteins in the SOMAscan panel (orange), PAD gene-based MAGMA meta-analysis (red) and PAD amyloid burden meta-analysis of filtered CSF-PET endophenotypes (light blue). **C** Top 10 enrichment analysis results of the overlapping proteins between our genomic and proteomic analyses. **C** Top 10 enrichment analysis results of the overlapping proteins between proteomic and PAD genomic analyses. The analysis was done using the WebGestalt tool

Discussion

Amyloid burden CSF-PET meta-analysis reveals significant genetic markers

For the first time, we have combined meta-GWAS results obtained from analysing amyloid PET and CSF Aβ42 levels. Our innovative experimental approach identified novel genetic variants associated with amyloid burden endophenotypes. This meta-analytic approach benefited from combining endophenotypic information from six cohorts thereby increasing our statistical power. As expected, we identified a genome-wide significant hit at the rs429358-*APOE* loci. Although this locus has been extensively associated with AD, the finding of this genome-wide significant supports the validity of our meta-analytic approach. We also observed a novel genome-wide significant hit near the *ANXA1* locus exclusively associated with PET amyloid. Genetic markers in this locus have been linked to psychiatric disorders (Huang et al. 2010; Suhre et al. 2017), and brain volume measurements (Zhao et al. 2019). Additionally, this gene has been related to anti-inflammatory processes (Shen et al. 2020), and may play a potential role in the degradation of Aβ species in cell lines (Ries et al.

2016). However, neither the large PET meta-GWAS available nor the PAD meta-analysis conducted by us replicated this finding. For these reasons, we believe that this signal could be a false positive. We attribute the lack of additional hits to the relatively small sample size of our CSF-PET meta-GWAS. By repeating this strategy with a larger sample size, we expect to identify more genetic modulators of Aβ42 peptide expression in the brain. Indeed, using a similar approach with currently available summary statistics (PAD study), we were able to detect several sentinel markers surpassing the GWAS significance threshold. Specifically, the PAD CSF-PET meta-analysis identified several significant genes that have been previously related to AD (*CR1*, *BIN1*, *CLU*, *ABCA7*, *FERMT2* and *APOE* (Bellenguez et al. 2022; Corder et al. 1993; Harold et al. 2009; Lambert et al. 2009, 2013)) or amyloid proteins (*CR1*, *CLU*, *APOE* and *FERMT2* (Calero et al. 2000; Chapuis et al. 2017; Jansen et al. 2022)), as well as *PICALM* and *GPC5* suggestive genes (Harold et al. 2009; Harper et al. 2022). Notably, we also identified the novel *GADL1* locus in the PAD study, which encodes for a protein from the glutamate decarboxylase family, suggesting that it might have a glutamate decarboxylase activity in the CNS (Chen et al. 2014; Goudet et al. 2009). However, the QTL and colocalization analysis indicated limited functional relevance of this genetic marker in altering gene expression in tissues of interest, and no significant association AD was observed. Further research is needed to elucidate the role of the *GADL1* gene in amyloid burden, although this genetic marker might be a false positive finding with spurious association with amyloid burden not supported by other analyses.

Importantly, these results should be interpreted with extreme caution because PAD analysis is not entirely independent as various cohorts were represented in both summary statistics of the PAD analysis, which violated the independence assumption of the meta-analysis approaches (Supplementary Table 32). This overlapping samples (11.284%) could lead to overestimated effects and increased proportion of false positive findings. Compared to our local effort, where we eliminated any potential overlap between CSF and PET cohorts, we remain very cautious about the PAD results due to the potential overlap of subjects among studies. Future efforts are necessary to confirm the findings from the PAD analysis. Nevertheless, the PAD analysis replicated the rs115822934-*NPY5R* marker, alongside the rs429358-*APOE*, originally identified in our CSF-PET meta-analysis. These results might suggest that *NPY5R* could be genuinely involved in amyloid pathology (Otowa et al. 2012). Again, further studies considering completely independent cohorts and expanding the sample size of these analysis, are needed to validate our observation and working hypothesis.

Associations between the CSF proteome, CSF Aβ42 levels, and genomic overlap

In spite of these limitations, our experimental strategy permitted us to evaluate common pathways potentially associated to CSF-soluble Aβ42 (circulating amyloid)(Strozyk et al. 2003), brain amyloid species detected by PET (insoluble species such as amyloid plaques or cerebral amyloid angiopathy)(Sabri et al. 2015) and proteome signature associated to CSF Aβ42 peptide levels. To assess the relationship between genetic modulators and protein levels, we analysed the overlap between loci-controlling amyloid levels and significant proteins associated with CSF Aβ42 levels. Importantly, three genes/proteins (*CHST1*, *PTPRD* and *TMEM132D*) were identified and prioritized in all analyses, thus suggesting that these modulators might be key drivers controlling amyloid pathology. Lower *TMEM132D* levels have been observed in patients with frontotemporal dementia (Remnestål et al. 2020), and genetic markers in this gene have been related to anxiety, panic disorders and the rate of cognitive decline (Erhardt et al. 2012; Haaker et al. 2014; Sherva et al. 2020). This locus was the only that also overlapped with all PAD rankings, suggesting that might be a potential modulator of amyloid pathology. The *PTPRD* gene, which was also represented in the large PAD meta-GWAS gene-based ranking, has been significantly associated to synaptic process in schizophrenia (Trubetskoy et al. 2022), AD susceptibility, neurofibrillary tangle and neuritic plaques (Chibnik et al. 2018). We consider these two loci excellent candidates for further translational research due to their consistent statistical significance and previous literature findings. Nevertheless, there is a possibility that we are not capturing pathological mechanisms occurring similarly in both CSF and PET due to the opposite direction filtering, which could be contributing to the accumulation or reduction in both CSF and PET amyloid levels. These discordances have been described in previous articles (Blennow et al. 2015; Mattsson et al. 2015; Reimand et al. 2020), suggesting that they might be caused due to the differential sensitivity to amyloid species across the AD continuum. Further research is needed to elucidate the role of these common and discordant amyloid mechanisms occurring in brain and their contribution to the disease.

In this study, we found a limited overlap between genetic modulators of amyloid burden and the proteins associated with the CSF levels of Aβ42. This could be interpreted as a result of the inherent statistical noise in these multiomic analyses, the lack of power in our main analysis, or it could indicate that the observed discordance is genuine. The poor heritability reported for CSF traits in previous studies (Jansen et al. 2022) supports that common SNPs might not strongly modulate the CSF amyloid burden. Moreover, no amyloid PRS showed a significant association with the risk

of developing AD, whereas the AD PRS showed a strong association with the AD case–control status and amyloid levels, which is fully consistent with previous studies (Hong et al. 2020b; Jansen et al. 2019; Kumar et al. 2022; Kunkle et al. 2019). These results suggest either a lack of statistical power to detect genuine hits associated with amyloid burden or a limited causal role of common genetic modulators of amyloid deposits in the aetiology of clinical AD. Further studies are needed to clarify these discrepancies. Interestingly, we observed a higher number of loci/proteins overlapped with the SOMAscan protein associations with CSF Aβ42 levels and the gene-based analysis than in the sentinel SNP-based GWAS analyses (our meta-analysis $n = 21$). The gene-based approach could be particularly powerful because the genetic markers summarised at (protein-coding) gene level might reduce the statistical noise on a full GWAS dataset (Watanabe et al. 2017).

We also noted a large number of significant CSF SOMAscan proteins associated with CSF Aβ42 levels. Notably, most of the observed associations were predominantly positive in our study. Similar results were also found in the ADNI CSF proteomic associations with CSF Aβ42. Interestingly, Bader reported a correlation map illustrating high correlations between CSF proteomic measures suggesting that these measures might lead to multiple significant associations (Bader et al. 2020). The massive abundance of significant proteins might simply reflect a general neurodegenerative signature that occurs as a result of widespread neuronal cell death or reactive gliosis. These changes are likely to be epiphenomenal rather than specific to the AD process. The potential implication of these findings is important for interpreting CSF proteome results. Indeed, only a minority of proteomic markers associated to Aβ42 might be genuine mediators modulating the AD-related amyloid endophenotype. Overall, the lack of overlap between Aβ42 and AD risk GWAS studies suggests that genetic factors modulating amyloid production may represent only a relatively small component of overall AD causality. These findings are also in line with several clinical trials targeting amyloid, that have observed a reduced association between Aβ reduction and AD progression, as well as only modest control of AD progression with these monotherapies. This also suggests that both amyloid-dependent and amyloid-independent mechanisms must be addressed simultaneously to effectively control disease progression (Hyman 2011; Leonenko et al. 2019).

Despite the poor overlap, we detected 35 overlapping genes and proteins pointing to a few enriched mechanisms in our CSF-PET meta-GWAS. We consider these overlapping signals of special importance because they could point to genuine amyloid-related mechanisms involved in AD causality and development. We found Aβ burden significantly associated with pathways controlling the anchored proteins in the membrane, which had also been represented in the PAD enriched analysis ($n = 23$ loci/proteins). Interestingly, six enriched mechanisms were represented in both overlapping loci/protein rankings of the PAD and our CSF-PET meta-analysis. These results validate our findings and suggest that the enrichment analysis is more powerful in detecting genuine associations than analysing individual genes, particularly in the context of reduced statistical power.

Additionally, the enrichment analysis pointed to synapse molecules and cell adhesion mechanisms such as *cell–cell adhesion* via *plasma membrane molecules, adhesion, synapse organization*, among others. Neuronal cadherins and integrins have been linked to the synaptic process, plasticity and long-term potentiation and modulation of Aβ levels (Asada-Utsugi et al. 2011), while their loss has been correlated to cognitive decline (Terry et al. 1991; Uemura 1998; Wu & Reddy 2012). Furthermore, we detected a link between amyloid levels and mental disorders, such as anxiety which has been associated with high Aβ deposition across the AD continuum (Bensamoun et al. 2016; Cai et al. 2021; Kuo et al. 2014). On the contrary, autism spectrum disorder (ASD) has been associated with Aβ processing via the non-amyloidogenic pathway leading to reduced Aβ levels in ASD patients (Lahiri et al. 2020). Other overlapping loci and proteins such as *ROBO2*, *CNTN5*, *OPCML*, *NRG3, NGFR* or *CACNA2D3*, have been associated with cognitive performance (F. Liu et al. 2007; Li et al. 2020), age at onset (Hollingworth et al. 2011; Wang et al. 2014), schizophrenia (Morar et al. 2010; Potkin et al. 2009; T. Zhang et al. 2018) or ASD (Suda et al. 2011; Zuko et al. 2013), AD (Dauar et al. 2022; Tosto et al. 2015) and its endophenotypes (Cano et al. 2023; Van Der Meer et al. 2021).

Limitations

Considering all these observations, it is difficult to conceive that all of them can be explained by pure random chance. However, our analysis had important limitations. First, we use a suboptimal p-value-based meta-analysis method, however, this strategy becomes highly valuable for integrating diverse studies reporting different estimate metrics and combining endophenotypes measured by various techniques (Borenstein et al. 2009; Yoon et al. 2021). Also, the CSF-PET meta-analysis did not report beta coefficients which were estimated. The restrictive SNP filtering allowed the evaluation of only 4.9% of genomic markers, likely due to meta-analysing multiple datasets and reducing marker identification involved in common mechanisms between soluble-CSF and insoluble-PET amyloid species. Moreover, as mentioned earlier, the PAD analysis was not completely independent, with an 8.272% and 3.073% of overlapping samples between our main meta-analysis, the CSF (Jansen et al. 2022) and PET (Ali et al. 2023) summary statistics,

respectively. The PAD CSF-PET meta-analysis should be interpreted with extreme caution due to these overlapping samples among summary statistics that could lead inflated estimates and biased results. Because we used publicly available results, we could not confirm the presence of additional overlapping samples, potentially leading to overfitting. The publicly available amyloid PET meta-GWAS conducted a different data harmonisation process, potentially introducing variability (Ali et al. 2023). Although, the GWAS is a powerful tool for identifying genetic risk factors, further functional and mechanistic validations are needed to interpret causality, including fine-mapping analysis to pinpoint causal variant, eQTL analysis to evaluate the effects on gene expression, mendelian randomization strategies to infer causality and functional studies for validating biological effects. Furthermore, neuropathological information was not available for these samples, leaving us unaware of other concomitant pathological changes. The ADNI proteomic analysis had a limited statistical power due to a reduced sample size and the limited number of proteomic analytes evaluated in the mass spectrometry assay. Finally, the lack of significant findings for several PRS associations may suggest that there is insufficient statistical power to find genetic variants that affect the amyloid endophenotype. These concerns should be addressed in future research.

Conclusions

In summary, our results demonstrate the feasibility of combining Aβ endophenotypes in CSF and PET, along with proteome analysis, to gain novel insights into the fundamental biology of AD. The strong proteomic associations with Aβ endophenotypes could help identify signalling pathways and molecular mechanisms involved in Aβ and AD pathology, as well as the overlapping pathways that control the amyloidotic process. Further studies are needed to refine these observed associations, connecting AD loci and proposed causal pathways with brain amyloidogenesis.

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Data availability The data that support the findings of this study are publicly available from the corresponding authors upon reasonable request. Additionally, the raw SOMAscan proteomic data is publicly accessible through the Alzheimer's Disease Data Initiative (ADDI) community.

Declarations

Ethics approval and consent to participate In accordance with Spanish regulations for the biomedical research field, all the protocols of this study were approved by the Clinical Research Ethics Commission of the Hospital Clinic (Barcelona, Spain) for ACE cohort and the Clinical Research Ethics Commission of Cantabria (Spain) for Valdecilla cohort. This research followed the Declaration of Helsinki. All participants were informed about the procedures and objectives of this study by a neurologist before signing an informed consent. Moreover, data confidentiality and privacy of patients were protected as specified in applicable laws.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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