



HAL
open science

Common variants in Alzheimer's disease and risk stratification by polygenic risk scores

Itziar de Rojas, Sonia Moreno-Grau, Niccolo Tesi, Benjamin Grenier-Boley, Victor Andrade, Iris E. Jansen, Nancy L. Pedersen, Najada Stringa, Anna Zettergren, Isabel Hernandez, et al.

► To cite this version:

Itziar de Rojas, Sonia Moreno-Grau, Niccolo Tesi, Benjamin Grenier-Boley, Victor Andrade, et al.. Common variants in Alzheimer's disease and risk stratification by polygenic risk scores. *Nature Communications*, 2021, 12 (1), pp.3417. 10.1038/s41467-021-22491-8. hal-03287265

HAL Id: hal-03287265

<https://hal.science/hal-03287265>

Submitted on 15 Jul 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

ARTICLE



<https://doi.org/10.1038/s41467-021-22491-8>

OPEN

Common variants in Alzheimer's disease and risk stratification by polygenic risk scores

Genetic discoveries of Alzheimer's disease are the drivers of our understanding, and together with polygenic risk stratification can contribute towards planning of feasible and efficient preventive and curative clinical trials. We first perform a large genetic association study by merging all available case-control datasets and by-proxy study results (discovery $n = 409,435$ and validation size $n = 58,190$). Here, we add six variants associated with Alzheimer's disease risk (near *APP*, *CHRNE*, *PRKD3/NDUFAF7*, *PLCG2* and two exonic variants in the *SHARPIN* gene). Assessment of the polygenic risk score and stratifying by *APOE* reveal a 4 to 5.5 years difference in median age at onset of Alzheimer's disease patients in *APOE* $\epsilon 4$ carriers. Because of this study, the underlying mechanisms of *APP* can be studied to refine the amyloid cascade and the polygenic risk score provides a tool to select individuals at high risk of Alzheimer's disease.

A full list of authors and their affiliations appears at the end of the paper.

Thus far, multiple loci associated with Alzheimer's disease (AD) have been described next to causal mutations in two subunits of γ -secretases, membrane-embedded aspartyl complexes (*PSEN1*, *PSEN2* genes), and the gene encoding one target protein of these proteases, the amyloid precursor protein gene (*APP*). The most prominent locus, *APOE*, was detected almost 30 years ago using linkage techniques¹. In addition, genome-wide association studies (GWAS) of AD case-control datasets and by-proxy AD case-control studies have identified 30 genomic loci that modify the risk of AD^{2–7}. These signals account for ~31% of the genetic variance of AD, leaving most of the genetic risk as yet uncharacterized⁸. Further disentangling the genetic constellation of common genetic variations underlying AD can drive our biological insights of AD and can point toward novel drug targets.

There are over 50 million people living with dementia and the global cost of dementia is well above 1 trillion US\$⁹. This means there is a medical and economical urgency to efficiently test interventions that are under development. Therefore, to increase power and reduce duration of trials, pre-symptomatic patients that are at high genetic risk of disease are increasingly developed¹⁰. However, only carriers of causal mutations (*APP*, *PSEN1*, and *PSEN2*) and the *APOE* $\epsilon 4$ allele are considered high risk, while other common and rare genetic variants are ignored¹¹. Despite that, the combined effects of all currently known variants in a polygenic risk score (PRS) is associated with the conversion of mild cognitive impairment to AD^{12,13}, the neuropathological hallmarks of AD, age at onset (AAO) of disease^{14–17} and lifetime risk of AD¹⁸.

In this work we aim to comprehend and expand the knowledge of the genetic landscape underlying AD and provide additional evidence that a PRS of variants can be a robust tool to select high risk individuals with an earlier AAO. We first performed a meta-GWAS integrating all currently published GWAS case-control

data, by-proxy case-control data, and the data from the Genome Research at Fundació ACE (GR@ACE) study¹⁹. We confirm the observed associations in a large independent replication study. Then, we construct an update of the PRS and test whether the effects of the PRS are influenced by diagnostic certainty, sex and AAO groups. Lastly, we test whether the PRS could be used to identify individuals at the highest odds of having AD and we compared AAO of the AD cases. This study describes the identification of six variants associated with AD risk and provides an extended PRS tool to select individuals at high risk of AD.

Results

Meta-GWAS of AD. We combined data from three AD GWASs: the summary statistics calculated from the GR@ACE¹⁹ case-control study (6331 AD cases and 6055 controls), the IGAP²⁰ case-control study (up to 30,344 AD cases and 52,427 controls) and the UKB AD-by-proxy case-control study²¹ (27,696 cases of maternal AD with 260,980 controls, and 14,338 cases of paternal AD with 245,941 controls, Fig. 1, Supplementary Data 1). Although we observed inflation in the resulting summary statistics (λ median = 1.08; see Supplementary Fig. 1d), it was not driven by an un-modeled population structure (LD score regression intercept = 1.036). The full details of the studies are described in methods. After study-specific variant filtering and quality-control procedures, we performed a fixed effects inverse-variance-weighted meta-analysis²² on the summary statistics of the three studies. Using this strategy, we identified a genome-wide significant (GWS) association ($p < 5 \times 10^{-8}$) for 36 independent genetic variants in 35 genomic regions (the *APOE* region contains signals for $\epsilon 4$ and $\epsilon 2$). As a sensitivity analysis, we removed the AD-by-proxy study and compared the resulted effect estimates with and without this dataset. We found a high correlation between the effect estimates from the case-control and by-proxy

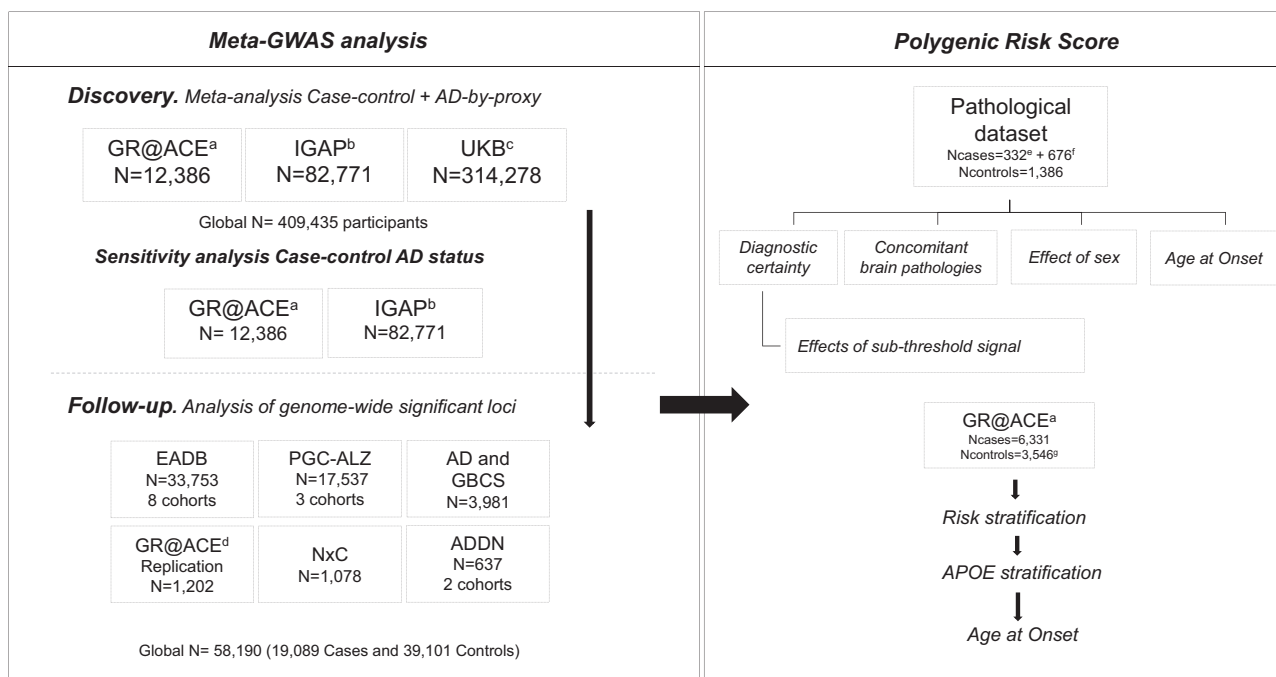


Fig. 1 Flow chart of analysis steps. Discovery meta-analysis in GR@ACE, IGAP stage 1 + 2 and UKBiobank followed by a replication in 16 independent cohorts. The genome-wide significant signals found in meta-GWAS were used to perform a Polygenic Risk Score in a clinical and pathological AD dataset. See Supplementary Methods for more information about the cohorts included and methods to the PRS generation. ^aExtended dataset (Moreno-Grau et al.¹⁹), ^bStagel + Stagel (Kunkle et al.²⁰), ^cBy proxy AD: Meta-analysis of maternal and paternal history of dementia (Marioni et al.²¹), ^dExtra and independent GR@ACE dataset incorporated only for replication purposes, ^ePathologically confirmed AD cases, ^fAD cases diagnosed based on clinical criteria, ^gControls participants aged 55 years and younger. *N* = Total of individuals within specified data.

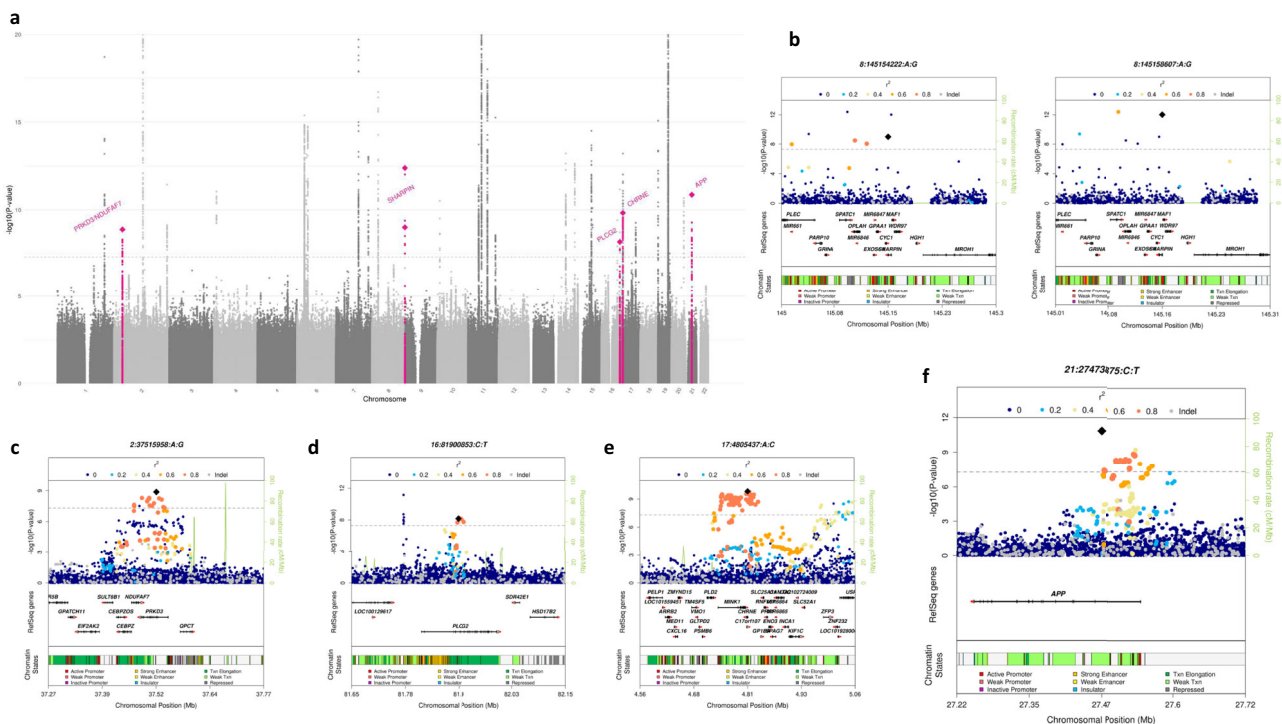


Fig. 2 GWAS meta-analysis for AD risk (N = 467,623). **a** Manhattan plot of overall meta-analysis for genome-wide association in Alzheimer’s disease highlighting in pink the loci associated with AD in this study (*PRKD3/NDUFAF7*, *SHARPIIN*, *CHRNE*, *PLCG2*, and *APP*). **b–f** Locus plots for the signals associated with AD in overall meta-analysis results.

approaches for the significant loci ($R^2 = 0.994$, $p = 8.1 \times 10^{-37}$; Supplementary Fig. 1e). Four genomic regions were not previously associated with AD (see Manhattan Plot, Fig. 2a).

Next, we aimed at replicating the associated loci in 16 cohorts (19,087 AD cases and 39,101 controls in total), many of them collected and analyzed by the European Alzheimer’s Disease Biobank (JPND-EADB) project. We tested all variants with suggestive association ($p < 10^{-5}$) located within a 200 kb region from the sentinel SNP. Overall, 384 variants were tested in the replication datasets (Supplementary Data 2). Discovery and replication were combined, and we identified associations in six variants comprising five genomic loci annotated using FUMA²³ (Table 1, Fig. 2b–f, Supplementary Fig. 2 and Supplementary Results). In *APP*, we identified a common (MAF = 0.46) intronic variant associated with a reduced risk of AD (rs2154481, OR = 0.95 [0.94–0.96], $p = 1.39 \times 10^{-11}$, Fig. 2f). In *SHARPIIN* (*SHANK* Associated RH Domain Interactor) gene, we found two missense mutations (rs34173062/p.Ser17Phe and rs34674752/p.Pro294Ser) that are in linkage equilibrium ($R^2 = 1.3 \times 10^{-6}$, $D' = 0.014$, $p = 0.96$). Both missense variants increased AD risk (p.Ser17Phe, MAF = 0.085, OR = 1.14 [1.10–1.18], $p = 9.6 \times 10^{-13}$ and p.Pro294Ser, MAF = 0.052, OR = 1.13 [1.09–1.18], $p = 1.0 \times 10^{-9}$, Fig. 2b). A variant close to the genes *PRKD3* and *NDUFAF7* (rs876461, MAF = 0.143) emerged as the most significant variant in the region after the combined analysis (OR = 1.07 [1.05–1.09], $p = 1.3 \times 10^{-9}$, Fig. 2c). In the 3’-UTR region of *CHRNE* (Cholinergic Receptor Nicotinic Epsilon Subunit), rs72835061 (MAF = 0.085) was associated with a 1.09-fold increased risk of AD (95% CI [1.06–1.11], $p = 1.5 \times 10^{-10}$, Fig. 2e). Our analysis also strengthened the evidence of association with AD for three additional genomic loci including an association with a variant in *PLCG2* (rs3935877, MAF = 0.13, OR = 0.92 [0.90–0.95], $p = 6.9 \times 10^{-9}$, Fig. 2d), and confirmed another common variant in *PLCG2*, a stop gain mutation in *IL-34* and a variant near *HS3ST1* (Table 1, Supplementary Fig. 3 and Supplementary Data 2, 3). We were not

able to replicate two loci (*ELK2AP* and *SPPL2A* regions) that showed suggestive association with AD ($p < 1 \times 10^{-7}$ in discovery).

Polygenic risk scores. In order to assess the robustness and combined effect of the genetic landscape of AD (Fig. 3, Supplementary Data 4), we constructed a weighted PRS based on the 39 genetic variants (excluding *APOE* genotypes) that showed GWS evidence of association with AD (see Methods, Fig. 4 and Supplementary Data 5). We tested if the association of the PRS with AD is independent of clinically important factors that are considered in the selection of individuals for clinical trials. First, we showed that the association of the PRS with clinically diagnosed AD cases is similar to the association with pathologically confirmed AD (OR = 1.30 vs. 1.38, per 1-SD increase in the PRS). In this setting, adding variants below the GWS threshold did not lead to a more significant association of the PRS with AD (Fig. 4a). Next, we tested whether the PRS was associated with AD in the presence of concomitant brain pathologies (besides AD). Among our autopsy-confirmed AD patients ($n = 332$), 84% had at least one concomitant pathology, and the PRS was associated with AD in the presence of all tested concomitant pathologies (Fig. 4b). Moreover, the patients often had more than one concomitant pathology (48.8%), but no difference was observed in the effect estimate of the PRS when more than one pathology was present (Fig. 4b). Last, we investigated the effect of sex and AAO (Fig. 4c). Our analysis revealed that the effect of the PRS was the same in both sexes (Fig. 4c) and was consistent with both early-onset (onset before 65 years; OR = 1.58, 95% CI [1.22–2.05], $p = 5.8 \times 10^{-4}$) as well as with late-onset AD (onset later than 85 years; OR = 1.29, 95% CI [1.10–1.51], $p = 1.5 \times 10^{-3}$).

PRSs has the potential to early identify subjects at risk of complex diseases²⁴. To identify people at the highest genetic risk of AD based on the PRS, we used the validated 39-variants

Table 1 Association for the AD loci selected for follow-up.

Chr	Closest gene	SNP	BP	A1	A2	Freq A1	Discovery meta-analysis			Follow-up datasets			Overall		
							OR [CI 95%]	P	OR [CI 95%]	P	OR [CI 95%]	P	OR [CI 95%]	P	
Variants showing novel genome-wide significant association with AD															
2	PRKD3/NDUFA7	rs876461	37515958	A	G	0.143	1.07 [1.04-1.09]	9.14 × 10 ⁻⁷	1.08 [1.04-1.13]	3.07 × 10 ⁻⁴	1.07 [1.05-1.09]	1.34 × 10 ⁻⁹			
8	SHARPIN	rs34674752	145154222	A	G	0.052	1.11 [1.06-1.16]	4.02 × 10 ⁻⁶	1.20 [1.10-1.31]	1.65 × 10 ⁻⁵	1.13 [1.09-1.18]	1.00 × 10 ⁻⁹			
8	SHARPIN	rs34173062	145158607	A	G	0.085	1.16 [1.11-1.21]	1.33 × 10 ⁻¹¹	1.09 [1.02-1.17]	7.35 × 10 ⁻³	1.14 [1.10-1.18]	9.62 × 10 ⁻¹³			
16	PLCG2	rs3935877	81900853	C	T	0.868	0.92 [0.90-0.95]	1.12 × 10 ⁻⁷	0.92 [0.85-0.99]	1.96 × 10 ⁻²	0.92 [0.90-0.95]	6.85 × 10 ⁻⁹			
17	CHRNE	rs72835061	4805437	A	C	0.085	1.09 [1.06-1.12]	3.92 × 10 ⁻⁹	1.07 [1.02-1.12]	7.83 × 10 ⁻³	1.09 [1.06-1.11]	1.51 × 10 ⁻¹⁰			
21	APP	rs2154481	27473875	C	T	0.483	0.95 [0.93-0.96]	9.26 × 10 ⁻¹⁰	0.96 [0.93-0.99]	3.31 × 10 ⁻³	0.95 [0.94-0.96]	1.39 × 10 ⁻¹¹			
Previously reported genome-wide significant hits replicating in the follow-up															
4	HS3S71	rs4351014	11027619	C	T	0.684	0.94 [0.92-0.96]	5.37 × 10 ⁻¹⁰	0.93 [0.88-0.98]	4.54 × 10 ⁻³	0.94 [0.92-0.95]	9.16 × 10 ⁻¹²			
16	IL34	rs4985556	70694000	A	C	0.111	1.08 [1.05-1.11]	2.28 × 10 ⁻⁸	1.09 [1.03-1.16]	4.59 × 10 ⁻³	1.08 [1.06-1.11]	3.91 × 10 ⁻¹⁰			
16	PLCG2	rs12444183	81773209	A	G	0.407	0.95 [0.93-0.97]	1.48 × 10 ⁻⁸	0.92 [0.88-0.96]	3.23 × 10 ⁻⁵	0.95 [0.93-0.96]	6.81 × 10 ⁻¹²			
Suggestive signals (not replicating)															
14	ELK2AP	rs7153315	106195719	C	G	0.750	0.94 [0.92-0.96]	9.80 × 10 ⁻⁸	1.16 [1.01-1.33]	0.0412	0.94 [0.92-0.97]	9.04 × 10 ⁻⁷			
15	SPLL2A	rs76523702	51002342	C	T	0.802	1.06 [1.04-1.08]	6.86 × 10 ⁻⁸	1.02 [0.97-1.07]	0.3501	1.05 [1.03-1.08]	1.08 × 10 ⁻⁷			

Results obtained with a fixed effects inverse-variance-weighted meta-analysis on the discovery and follow-up stages. Freq A1 is from GR@ACE discovery dataset. P value for significance <5 × 10⁻⁸. Effect allele: A1.

PRS in the large GR@ACE dataset. The PRS was associated with a 1.27-fold (95% CI [1.23–1.32]) increased risk for every standard deviation increase in the PRS ($p = 7.3 \times 10^{-39}$) and with a gradual risk increase when we stratified the dataset into 2% percentiles of the PRS (Fig. 5a, Supplementary Data 6). Next, we stratified the dataset in APOE genotype risk groups. The PRS percentiles were associated with AD within the APOE genotype groups (Fig. 5b, Supplementary Data 7). Finally, we compared the risk extremes and found a 16.2-fold (95% CI [8.84–29.5], $p = 1.5 \times 10^{-19}$) increased risk for the highest-PRS group (APOE ε4ε4) compared with the lowest-PRS group (APOE ε2ε2/ε2ε3; Supplementary Data 8). When we compared the median AAO in AD patients in these extreme risk groups we found a 9-year difference in the median age ($p_{Wilcoxon} = 1.7 \times 10^{-6}$) (Fig. 5c). Lastly, we studied the effects on AAO of the PRS in the APOE genotype groups. The PRS differentiated AAO only within APOE ε4 carriers. In APOE ε4 heterozygotes the PRS determined a 4-year difference in median AAO and in APOE ε4 homozygotes ($p_{Wilcoxon} = 6.9 \times 10^{-5}$), where the PRS determined a median AAO difference of 5.5 years ($p_{Wilcoxon} = 4.6 \times 10^{-5}$). For the selection of high-risk individuals, it is important to note that we found no difference in the odds and AAO for AD for APOE ε4 heterozygotes with the highest PRS compared to APOE ε4 homozygotes with the lowest PRS. The Cox regression also showed an impact of APOE on AAO, mainly on APOE ε4ε4 (significant APOE-PRS interaction ($p = 0.021$), Fig. 5d, Supplementary Data 9).

Discussion

This work adds on the ongoing global effort to identify genetic variants associated with AD (Fig. 3). In the present work, we reported on the largest GWAS for AD risk to date, comprising genetic information of 467,623 individuals of European ancestry. We identified six variants that were not previously associated with the risk of AD and constructed a robust PRS for AD demonstrating its potential value for selecting subjects at risk of AD, especially within APOE ε4 carriers. This PRS was based on European ancestries and may or may not generalize to other ancestries. Validation in other populations will be required. We also acknowledge that controls included in GR@ACE are younger than cases and some of the controls might still develop AD later in life. This fact does not invalidate the analysis although reported estimates must be considered conservative. The differences in risk and AAO determined by the PRS of AD are relevant for design clinical trials that over-represent APOE ε4 carriers, as APOE ε4 heterozygous with highest-PRS values have a similar risk and AAO to APOE ε4 homozygotes (Fig. 5b). These represents ~1% of our control population, which is the same percentage as all APOE ε4 homozygotes. A trial that aims to include APOE ε4 homozygotes, could consider widening the selection criteria and in this way hasten the enrollment process. Also, our PRS could aid at the interpretation of the results of clinical trials, as it determines a relevant proportion of the AAO, which could either mimic or obscure a treatment effect.

The most interesting finding from our GWAS is the discovery of a common protective (MAF (C-allele) = 0.483) intronic variant in the APP gene. Our results directly support APP production or processing as a causal pathway not only in familial AD but in common sporadic AD. The SNP is in a DNase hypersensitive area of 295 bp (chr21:27473781-27474075) possibly involved in the transcriptional regulation of the APP gene. rs2154481 is an eQTL for the APP mRNA and an antisense transcript of the APP gene named AP001439.2 in public eQTL databases²⁵ (Supplementary Fig. 4). Functional evidence supports a modified APP transcription²⁶ as an LD block of 13 SNPs within the APP locus

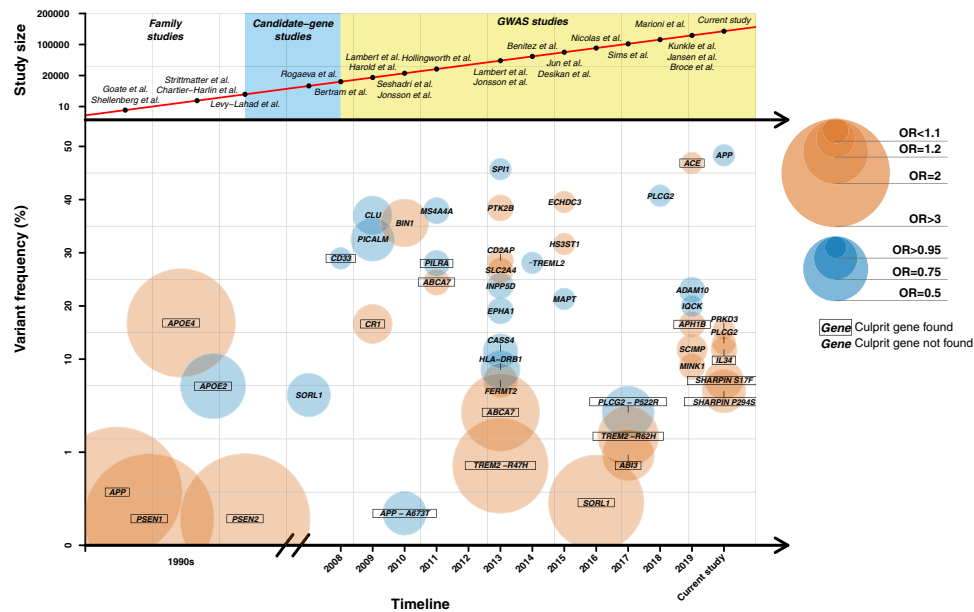


Fig. 3 Genetic landscape for Alzheimer's disease. This figure shows the history of genetic discoveries in AD research over the past 30 years. This figure was constructed to our best knowledge of literature, but is not a systematic review of literature. For common variants, we selected only signals firmly replicated in large meta-GWAS (Lambert et al.³, Kunkle et al.²⁰, Jun et al.⁴³, Sims et al.⁷, Jansen et al.³⁸ and present study). For rare variants, we only selected those variants widely replicated excluding those loci presenting conflicting results. Abbreviations and more information about the genes can be found in Supplementary Data 4. The risk alleles associated with AD were represented in orange and the protective alleles in blue. GWAS Genome-Wide Association Study, OR odds ratio.

(including rs2154481) increased the TFCEP2 transcription factor avidity to its binding site and increased the enhancer activity of this specific intronic region²⁶. Based on this evidence, we can postulate that a life-long slightly higher *APP* gene expression protects the brain from AD insults. Still, this seems counter-intuitive as duplications of the gene lead to early-onset AD²⁷. A U-shaped effect, or hormesis effect of *APP* might help explain our observations and it might also fit the accelerated cognitive deterioration observed in AD patients treated with beta-secretase inhibitors^{28,29} as these reduce beta-amyloid in their brain. An alternative hypothesis is that mechanisms underlying the variant are related to the overexpression of protective fragments of the APP protein³⁰. Disentangling the molecular mechanism of our finding will help refine and steer the amyloid hypothesis.

Additionally, other three variants identified are altering protein sequence or affecting regulatory motifs. Two independent missense mutations in *SHARPIN* increased the AD risk. *SHARPIN* was previously proposed as an AD candidate gene^{31,32}, and functional analysis of a rare missense variant (NM_030974.3:p.Gly186Arg) resulted in the aberrant cellular localization of the variant protein and attenuated the activation of NF- κ B, a central mediator of inflammatory and immune responses. Functional analysis of the two identified missense variants will show if the effect on immune reaction in AD is similar. The variant located in the *CHRNE* which encodes a subunit of the cholinergic receptor (AChR) is a strong modulator of *CHRNE* expression. The same allele that increases AD risk increases the expression in the brain and other tissues according to GTEx ($p = 2.1 \times 10^{-13}$) (Supplementary Fig. 5). The detection of a potential hypermorph allele linked to AD risk and affecting cholinergic function could reintroduce this neurotransmitter pathway into the search for preventative strategies. Further functional studies are needed to consolidate this hypothesis.

Altogether, we described six additional loci associated with sporadic AD. These signals reinforce that AD is a complex disease in which amyloid processing and immune response play key

roles. We add to the growing body of evidence that the polygenic scores of all genetic loci to date, in combination with *APOE* genotypes, are robust tools that are associated with AD and its AAO. These properties make PRS promising in selecting individuals at risk to apply preventative therapeutic strategies.

Methods

Data. Participants in this study were obtained from multiple sources, including raw data from case-control samples collected by GR@ACE/DEGESCO, summary statistics data from the case-control samples in the IGAP and the summary statistics of AD-by-proxy phenotype from the UK Biobank. An additional case-control samples from 16 independent cohorts (19,087 AD cases and 39,101 controls) was used for replication, largely collected and analyzed by the European Alzheimer's Disease Biobank (JPNDEADB) project. Full descriptions of the samples and their respective phenotyping and genotyping procedures are provided in the Supplementary Methods.

GR@ACE. The GR@ACE study¹⁹ recruited AD patients from Fundació ACE, Institut Català de Neurociències Aplicades (Catalonia, Spain), and control individuals from three centers: Fundació ACE (Barcelona, Spain), Valme University Hospital (Seville, Spain), and the Spanish National DNA Bank-Carlos III (University of Salamanca, Spain) (<http://www.bancoadn.org>). Additional cases and controls were obtained from dementia cohorts included in the Dementia Genetics Spanish Consortium (DEGESCO)³³. At all sites, AD diagnosis was established by a multidisciplinary working group—including neurologists, neuropsychologists, and social workers—according to the DSM-IV criteria for dementia and the National Institute on Aging and Alzheimer's Association's (NIA-AA) 2011 guidelines for diagnosing AD. In our study, we considered as AD cases any individuals with dementia diagnosed with probable or possible AD at any point in their clinical course. For further details on the contribution of the sites, see Supplementary Data 10. Written informed consent was obtained from all the participants. The ethics and scientific committees have approved this research protocol (Acta 25/2016, Ethics Committee H., Clinic I Provincial, Barcelona, Spain).

Genotyping, quality control, and imputation. DNA was extracted from peripheral blood according to standard procedures using the Chemagic system (Perkin Elmer). Samples reaching DNA concentrations of >10 ng/μl and presenting high integrity were included for genotyping. Cases and controls were randomized across sample plates to avoid batch effects.

Genotyping was conducted using the Axiom 815K Spanish biobank array (Thermo Fisher) at the Spanish National Center for Genotyping (CeGEN, Santiago de Compostela, Spain). The genotyping array not only is an adaptation of the Axiom biobank genotyping array but also contains rare population-specific

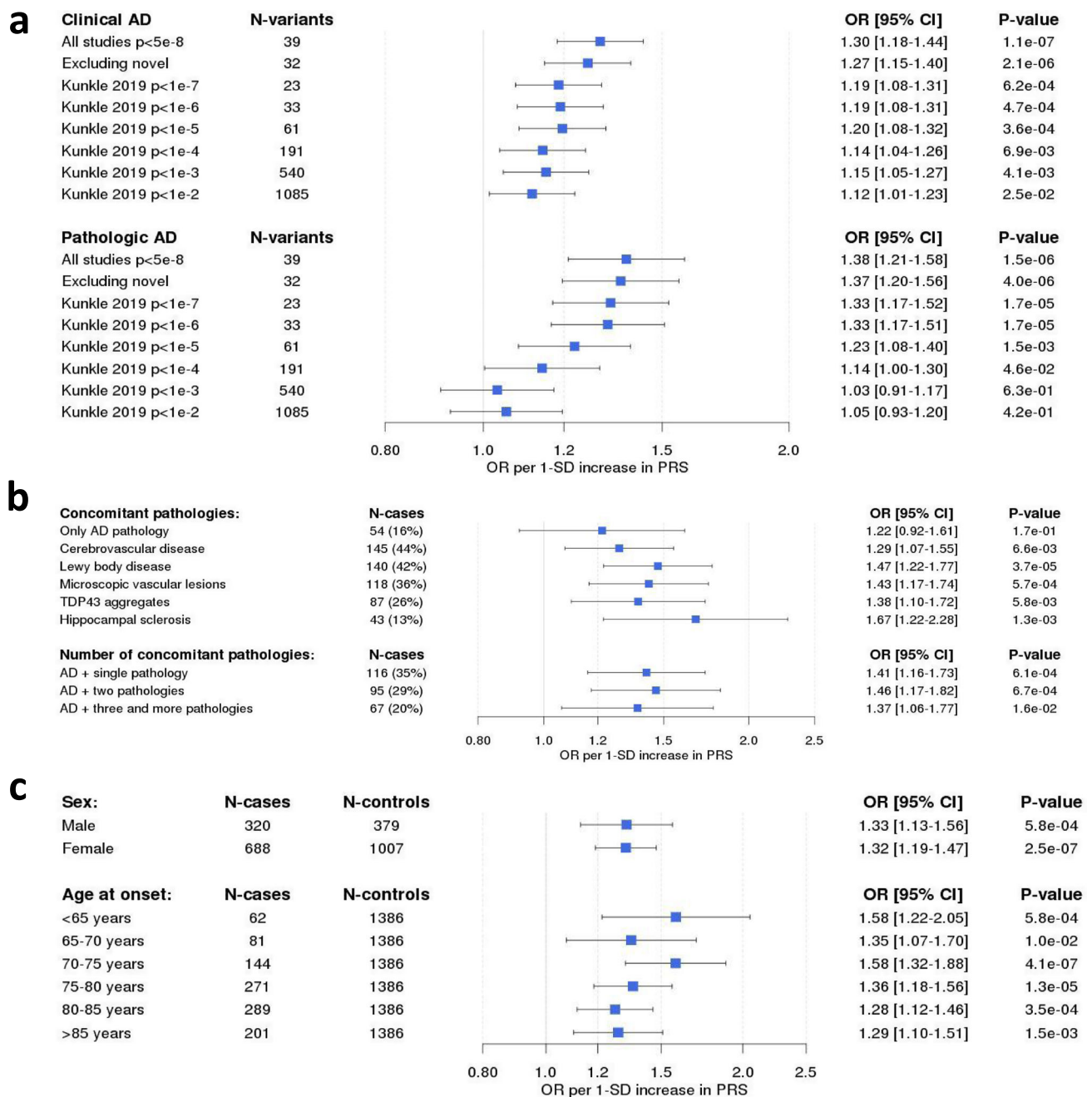


Fig. 4 Polygenic risk scores for AD. **a** The 39-SNP PRS association with clinical (OR = 1.30, 95% CI [1.18-1.44], $p = 1.1 \times 10^{-7}$) and pathologically confirmed AD cases (OR = 1.38, per 1-SD increase in the PRS, 95% CI [1.21-1.58], $p = 1.5 \times 10^{-6}$) from EADB-F.ACE/BBB dataset. **b** PRS association with AD in the presence of concomitant brain pathologies (besides AD). **c** PRS association with AD stratified by sex and AAO. A similar association of the PRS with AD was found in both sexes (OR_{males} = 1.33, [1.13-1.56], $p = 5.8 \times 10^{-4}$ vs. OR_{females} = 1.32, [1.19-1.47], $p = 2.5 \times 10^{-7}$). In (a-c) data are presented as Odds Ratio per 1-SD increase in PRS (95% CI). The generated PRS was validated using logistic regression adjusted by four principal components.

variations observed in the Spanish population. The DNA samples were genotyped according to the manufacturer's instructions (Axiom™ 2.0 Assay Manual Workflow). The Axiom 2.0 assay interrogates biallelic SNPs and simple indels in a single-assay workflow. Starting with 200 ng of genomic DNA, the samples were processed through a manual target preparation protocol, followed by automated processing of the array plates in the GeneTitan Multi-Channel (MC) instrument. Target preparation involved DNA amplification, fragmentation, purification, and resuspension of the target in a hybridization cocktail. The hybrid-ready targets were then transferred to the GeneTitan MC instrument for automated, hands-free processing, including hybridization, staining, washing, and imaging. The CEL files were generated using the GeneTitan MC instrument. Quality control (QC) was performed for samples and plates using the Affymetrix power tool (APT) 1.15.0 software following the Axiom data analysis workflow. The sample quality

was determined based on the resolution of AT and GC channels in a group of non-polymorphic SNPs (resolution > 0.82). Samples with a call rate greater than 97% and plates with an average call rate above 98.5% were included for final SNP calling. The samples were jointly called. Markers passing all the QC tests were used in downstream analysis ($N_{\text{SNPs}} = 729,868$; 95.4%) using the SNPfisher R package (Thermo Fisher). To assess the sample genotyping concordance, we intentionally resampled 200 samples and determined a concordance rate of 99.5%.

We also conducted previously described standard QC prior to imputation¹⁹. In brief, individual QC includes genotype call rates >97%, sex checks, and no excess heterozygosity; we removed population outliers as well (European cluster of 1000 Genomes). We included variants with a call rate of >95%, with a minor allele frequency (MAF) of >0.01, in Hardy-Weinberg equilibrium ($p < 1 \times 10^{-4}$ in controls) and without differential missingness between cases and controls

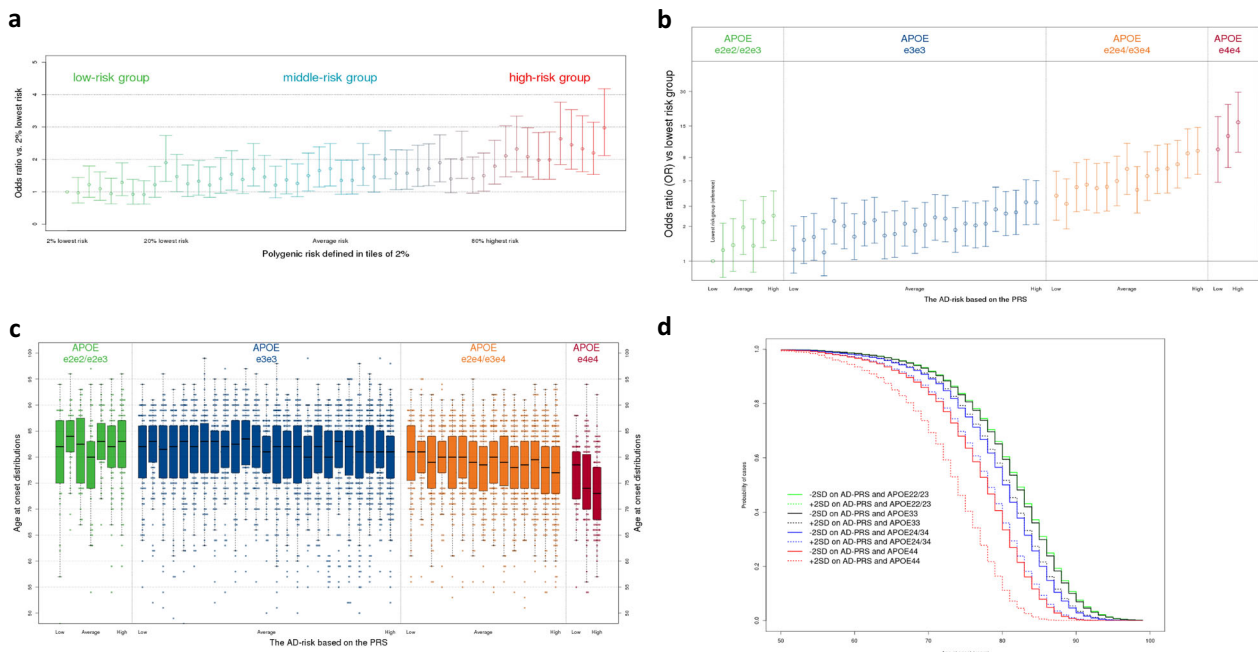


Fig. 5 Polygenic Risk Scores APOE stratification for AD in $n = 12,386$ biologically independent samples from GR@ACE/DEGESCO. a The AD risk of PRS groups compared to those with the 2% lowest risk. The 2% highest risk had a 3.0-fold (95% CI [2.12–4.18], $p = 3.2 \times 10^{-10}$) increased risk compared with those with the 2% lowest risk. No interaction was found between the PRS and APOE genotypes (p value = 0.76). **b** The AD risk stratified by PRS and APOE risk groups compared to the lowest risk group (OR 95% CI). Association was found between highest and lowest-PRS percentiles within the APOE genotype groups: $\epsilon 2\epsilon 2/\epsilon 2\epsilon 3$ carriers (OR = 2.48 [1.51–4.08], $p = 3.4 \times 10^{-4}$), $\epsilon 3\epsilon 3$ carriers (OR = 2.67 [1.93–3.69], $p = 3.5 \times 10^{-9}$), $\epsilon 2\epsilon 4/\epsilon 3\epsilon 4$ carriers (OR = 2.47 [1.67–3.66], $p = 6.8 \times 10^{-6}$), and $\epsilon 4\epsilon 4$ carriers (OR = 2.02 [1.05–3.85], $p = 3.4 \times 10^{-2}$). Comparisons of the highest and lowest-PRS percentiles with respect to the APOE genotype groups: a difference was found between highest $\epsilon 2\epsilon 2/\epsilon 2\epsilon 3$ carriers vs. lowest $\epsilon 3\epsilon 3$ carriers (OR = 0.51 [0.34–0.75], $p = 7.8 \times 10^{-4}$), but not between highest $\epsilon 3\epsilon 3$ carriers vs. lowest $\epsilon 2\epsilon 4/\epsilon 3\epsilon 4$ carriers (OR = 1.17 [0.82–1.66], $p = 0.40$) and highest $\epsilon 2\epsilon 4/\epsilon 3\epsilon 4$ carriers vs. lowest $\epsilon 4\epsilon 4$ carriers (OR = 0.89 [0.52–1.53], $p = 0.68$). **c** The AAO of AD stratified by PRS and APOE risk groups. No difference in odds for AD was found between the PRS percentiles with AAO in APOE $\epsilon 2\epsilon 2/\epsilon 2\epsilon 3$ (lowest = 82 years, highest = 83 years, $p_{Wilcoxon} = 0.39$) and APOE $\epsilon 3\epsilon 3$ (lowest = 82 years, highest = 81 years, $p = 0.16$). However, a 4-year difference was found between APOE $\epsilon 4$ heterozygotes ($p_{Wilcoxon} = 6.9 \times 10^{-5}$, 81 years compared with 77 years) and 5.5 years difference ($p_{Wilcoxon} = 4.6 \times 10^{-5}$, 78.5 years compared with 73 years) in APOE $\epsilon 4$ homozygotes. Data are represented as boxplots as described in the manual of ggplot2 package in R. **a–c** Logistic regression models adjusted for four population ancestry components were used as statistical test. **d** Cox regression model on AAO. The determinants are the PRS and the APOE categories, a PRS*APOE interaction term and population substructure as covariates. The curve shows the probability a case in one of the eight groups has developed AD by a certain age (x -axis).

(Supplementary Data 11, Supplementary Fig. 1). Imputation was carried out using the Haplotype reference consortium³⁴ (HRC, full panel) and the 1000 Genomes reference panel³⁵ (for indels only) on the Michigan Imputation Server (<https://imputationserver.sph.umich.edu>). Rare variants (MAF < 0.001) and variants with low imputation quality ($R^2 < 0.30$) were excluded. Logistic regression models, adjusted for the first four ancestry principal components¹⁹, were fitted using Plink (v2.00a). Population-based controls were used; therefore, age was not included as a covariate. Age and gender statistically behave like phenotype proxies (for AD status in this case). Therefore, adjusting for co-variation with age and gender could result in an over-adjustment of GWAS results. After QC steps, we included 6,331 AD cases and 6,055 control individuals and tested 14,542,816 genetic variants for association with AD.

IGAP summary statistics. The GWAS summary results from the IGAP were downloaded from the National Institute on Aging Genetics of Alzheimer’s Disease Data Storage Site (NIAGADS, <https://www.niagads.org/>)²⁰. Details on data generation and analyses by the IGAP have been previously described²⁰. In brief, the IGAP is a large study based upon genome-wide association using individuals of European ancestry. Stage 1 of the IGAP comprises 21,982 AD cases and 41,944 cognitively normal controls from four consortia: the Alzheimer Disease Genetics Consortium (ADGC), the European Alzheimer’s Disease Initiative (EADI), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, and the Genetic and Environmental Risk in AD/Defining Genetic, Polygenic, and Environmental Risk for Alzheimer’s Disease (GERAD/PERADES) Consortium. Summary statistics are available for 11,480,632 variants, both genotyped and imputed (1000 Genomes phase 1, v3). In Stage 2, 11,632 SNPs were genotyped in an independent set of 8362 AD cases and 10,483 controls.

UK Biobank summary statistics. UK Biobank data—including health, cognitive, and genetic data—was collected on over 500,000 individuals aged 37–73 years from across Great Britain (England, Wales, and Scotland) at the study baseline

(2006–2010) (<http://www.ukbiobank.ac.uk>)³⁶. Several groups have demonstrated the utility of self-report of parental history of AD for case ascertainment in GWAS (proxy-AD approach)^{21,37,38}. For this study, we used the published summary statistics of Marioni et al.²¹. They included, after stringent QC, 314,278 unrelated individuals for whom AD information was available on at least one parent in the UK Biobank (<https://datashare.is.ed.ac.uk/handle/10283/3364>). In brief, the 27,696 participants whose mothers had dementia (maternal cases) were compared with the 260,980 participants whose mothers did not have dementia. Likewise, the 14,338 participants whose fathers had dementia (paternal cases) were compared with the 245,941 participants whose fathers did not have dementia²¹. The phenotype of the parents is independent, and therefore, the estimates could be meta-analyzed. After analysis, the effect estimates were made comparable to a case-control setting. Further information on the transformation of the effect sizes can be found elsewhere^{21,39}. The data available comprises summary statistics of 7,794,553 SNPs imputed to the HRC reference panel (full panel).

Meta-GWAS of AD. After study-specific variant filtering and quality-control procedures, we performed a fixed effects inverse-variance-weighted meta-analysis²² on the discovery and follow-up stages (Supplementary Data 1 and Supplementary Data 12). To determine the lead SNPs (those with the strongest association per genomic region), we performed clumping on SNPs with a GWS p value ($p < 5 \times 10^{-8}$) (Plink v1.90, maximal linkage disequilibrium (LD) with $R^2 < 0.001$ and physical distance 250 Kb). In the APOE region, we only considered the APOE $\epsilon 4$ (rs429358) and APOE $\epsilon 2$ (rs7412) SNPs⁴⁰. LD information was calculated using the GR@ACE imputed genotypes as a reference. Polygenicity and confounding biases, such as cryptic relatedness and population stratification, can yield an inflated distribution of test statistics in GWAS. To distinguish between inflation from a true polygenic signal and bias we quantified the contribution of each by examining the relationship between test statistics and linkage disequilibrium (LD) using the LD Score regression intercept (LDSC software⁴¹). Chromosomal regions associated with AD in previous studies were excluded from follow-up (Lambert

et al.³, Kunkle et al.⁴², and Jansen et al.³⁸). We tested all variants with suggestive association ($p < 10^{-5}$) located in proximity (200 kb) of genomic regions selected for follow-up to allow for the potential refinement of the top associated variant.

Conditional analyses were performed in regions where multiple variants were associated with AD using logistic regression models, adjusting for the genetic variants in the region (Supplementary Data 13, 14).

Regional plots were generated with a mixture of homemade Python (v2.7) and R (v3.6.0) scripts. Briefly, given an input variant, we calculated the LD between the input variant and all the surrounding variants within a window of length defined by the user. The LD was calculated in the 1000 Genomes samples of European ancestry. We used gene positions from RefSeq (release 93); in the case of multiple gene models for a given gene, we reported the model with the largest number of exons. We used recombination rates from HapMap II and chromatin states from ENCODE/Broad (15 states were grouped to highlight the predicted functional elements). As a reference genome, we used GRCh37. Quantile–quantile plots, Manhattan plots, and the exploration of genomic inflation factors were performed using the R package qqman.

Polygenic risk scores. We calculated a weighted individual PRS based on the 39 genetic variants that showed GWS evidence of association with AD in the present study, excluding *APOE* to check the impact of PRS modulating *APOE* risk (Table 1 and Supplementary Data 3). The selected variants were directly genotyped or imputed with high quality (median imputation score $R^2 = 0.93$). The PRSs were generated by multiplying the genotype dosage of each risk allele for each variant by its respective weight and then summing across all variants. We weighted this by the effect size from previous IGAP studies [Kunkle et al.⁴² (36 variants), Sims et al.⁷ (2 variants), Jun et al.⁴³ (*MAPT* locus), Supplementary Data 5]. The generated PRS was validated using logistic regression adjusted by four principal components in a sample of 676 AD cases diagnosed based on clinical criteria and 332 pathologically confirmed AD cases from the European Alzheimer's Disease Biobank–Fundació ACE/Barcelona Brain Bank dataset (EADB–FACE/BBB, Supplementary Information). This dataset was not used in prior genetic studies. In this dataset, all pathologically confirmed cases were scored for the presence or absence of concomitant pathologies. In all analyses, we compared the AD patients to the same control dataset ($n = 1386$). We performed analyses to test the robustness of the PRS. We tested the effect of adding variants below the genome-wide significance threshold using a pruning and thresholding approach. For this, we used the summary statistics of the IGAP⁴² study, and we selected independent variants using the `clump_data()` function from the `TwoSampleMR` package (v0.4.25). We used strict settings for clumping ($R^2 = 0.001$ and window = 1 MB) and increasing p value thresholds ($>1 \times 10^{-7}$, $>1 \times 10^{-6}$, $>1 \times 10^{-5}$, $>1 \times 10^{-4}$, $>1 \times 10^{-3}$, and $>1 \times 10^{-2}$). We tested the association of the results with clinically diagnosed and pathologically confirmed AD patients. To evaluate the effect of diagnostic certainty, we tested whether the PRS was different between the two patient groups. For the PRS with 39 GWS variants, we tested whether the PRS had sex-specific effects, whether it resulted in different age-of-onset groups of AD, and the effect of the PRS in the presence of concomitant brain pathologies.

Risk stratification of the validated PRSs. We searched for the groups at the highest risk of AD in the GR@ACE dataset (6331 AD cases and 6055 controls). We stratified the population into PRS percentiles, taking into account survival bias anticipated at old age¹⁸. To eliminate selection bias, we calculated the boundaries of the percentiles in the control participants aged 55 years and younger ($n = 3546$). Based on the boundaries from this population, the rest of the controls and all AD cases were then assigned into their appropriate percentiles. We first explored risk stratification using only the PRSs. For this, we split the PRSs into 50 groups (2 percentiles) and compared all groups with that which had the lowest PRS. Second, we explored risk stratification considering both the *APOE* genotypes and the PRSs. The *APOE* genotypes were pooled in the analyses as *APOE* $\epsilon 2\epsilon 2/\epsilon 2\epsilon 3$ ($n = 998$, split into 7 PRS groups), *APOE* $\epsilon 3\epsilon 3$ ($n = 7611$, split into 25 PRS groups), *APOE* $\epsilon 2\epsilon 4/\epsilon 3\epsilon 4$ ($n = 3399$, split into 15 PRS groups), and *APOE* $\epsilon 4\epsilon 4$ ($n = 382$, split into 3 PRS groups). We studied the effect of PRS across groups of individuals stratified by the *APOE* genotypes with the lowest-PRS group (*APOE* as the reference group using logistic regression models adjusted for four population ancestry components). Finally, we compared the median AAO using a Wilcoxon test.

We implemented a Cox regression model on AAO in the GR@ACE/DEGESCO dataset case-only adjusted for covariates as *APOE* group, the interaction between the PRS and *APOE* and four population ancestry components. All analyses were done in R (v3.4.2).

Functional annotation. We used Functional Mapping and Annotation of Genome-Wide Association Studies²³ (FUMA, v1.3.4c) to interpret SNP–trait associations (see Supplementary Methods and Supplementary Data 15–18). FUMA is an online platform that annotates GWAS findings and prioritizes the most likely causal SNPs and genes using information from 18 biological data repositories and tools. As input, we used the summary statistics of our meta-GWAS. Gene prioritization is based on a combination of positional mapping, expression quantitative trait loci (eQTL) mapping, and chromatin interaction mapping. Functional annotation was performed by applying a methodology similar to that described by Jansen et al.³⁸. We referred to the original publication for details on the methods and repositories of FUMA²³.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The discovery summary statistics of this study are publicly available in Fundació ACE server [https://fundacioace-my.sharepoint.com/:u/g/personal/iderojas_fundacioace_org/EaTwpPg9cRjHn7Kos4h39OUbaxajsJHL_C110fC89bc8w?e=ZdcEUy].

Received: 17 July 2020; Accepted: 17 March 2021;

Published online: 07 June 2021

References

- Pericak-Vance, M. A. et al. Linkage studies in familial Alzheimer disease: evidence for chromosome 19 linkage. *Am. J. Hum. Genet.* **48**, 1034–1050 (1991).
- Seshadri, S. et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA J. Am. Med. Assoc.* **303**, 1832–1840 (2010).
- Lambert, J. C. et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat. Genet.* **45**, 1452–1458 (2013).
- Jonsson, T. et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *N. Engl. J. Med.* **368**, 107–116 (2013).
- Guerreiro, R. et al. TREM2 variants in Alzheimer's disease. *N. Engl. J. Med.* **368**, 117–127 (2013).
- Jonsson, T. et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. *Nature* **488**, 96–99 (2012).
- Sims, R. et al. Rare coding variants in *PLCG2*, *ABI3*, and *TREM2* implicate microglial-mediated innate immunity in Alzheimer's disease. *Nat. Genet.* **49**, 1373–1384 (2017).
- Ridge, P. G. et al. Assessment of the genetic variance of late-onset Alzheimer's disease. *Neurobiol. Aging* **41**, 200.e13–200.e20 (2016).
- 2020 Alzheimer's disease facts and figures. *Alzheimer's Dement.* **16** 391–460 (2020).
- Reiman, E. M. et al. Alzheimer's prevention initiative: a plan to accelerate the evaluation of presymptomatic treatments. *J. Alzheimer's Dis* **26**, 321–329 (2011).
- Huang, L.-K., Chao, S.-P. & Hu, C.-J. Clinical trials of new drugs for Alzheimer disease. *J. Biomed. Sci.* **27**, 18 (2020).
- Rodríguez-Rodríguez, E. et al. Genetic risk score predicting accelerated progression from mild cognitive impairment to Alzheimer's disease. *J. Neural Transm.* **120**, 807–812 (2013).
- Adams, H. H. H. et al. Genetic risk of neurodegenerative diseases is associated with mild cognitive impairment and conversion to dementia. *Alzheimer's Dement.* <https://doi.org/10.1016/j.jalz.2014.12.008> (2015).
- Desikan, R. S. et al. Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. *PLoS Med.* <https://doi.org/10.1371/journal.pmed.1002258> (2017).
- Lacour, A. et al. Genome-wide significant risk factors for Alzheimer's disease: role in progression to dementia due to Alzheimer's disease among subjects with mild cognitive impairment. *Mol. Psychiatry* **22**, 153–160 (2016).
- Sleegers, K. et al. A 22-single nucleotide polymorphism Alzheimer's disease risk score correlates with family history, onset age, and cerebrospinal fluid A β 42. *Alzheimer's Dement* **11**, 1452–1460 (2015).
- Zhang, Q. et al. Risk prediction of late-onset Alzheimer's disease implies an oligogenic architecture. *Nat. Commun.* <https://doi.org/10.1038/s41467-020-18534-1> (2020).
- van der Lee, S. J. et al. The effect of *APOE* and other common genetic variants on the onset of Alzheimer's disease and dementia: a community-based cohort study. *Lancet Neurol.* [https://doi.org/10.1016/S1474-4422\(18\)30053-X](https://doi.org/10.1016/S1474-4422(18)30053-X) (2018).
- Moreno-Grau, S. et al. Genome-wide association analysis of dementia and its clinical endophenotypes reveal novel loci associated with Alzheimer's disease and three causality networks: The GR@ACE project. *Alzheimer's Dement.* **0**, 1333–1347 (2019).
- Kunkle, B. W. et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Amyloid β , tau, immunity and lipid processing. *Nat. Genet.* **51**, 414–430 (2019).
- Marioni, R. E. et al. GWAS on family history of Alzheimer's disease. *Transl. Psychiatry* <https://doi.org/10.1038/s41398-018-0150-6> (2018).
- Willer, C. J., Li, Y. & Abecasis, G. R. METAL: Fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* <https://doi.org/10.1093/bioinformatics/btq340> (2010).
- Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. *Nat. Commun.* <https://doi.org/10.1038/s41467-017-01261-5> (2017).
- Khera, A. V. et al. Genome-wide Polygenic Scores for Common Diseases Identify Individuals With Risk Equivalent to Monogenic Mutations. *Nat. Genet.* **50**, 1219–1224 (2018).

25. Lonsdale, J. et al. The genotype-tissue expression (GTEx) project. *Nat. Genet.* **45**, 580–585 (2013).
26. Myrum, C., Nikolaienko, O., Bramham, C. R., Haavik, J. & Zayats, T. Implication of the APP gene in intellectual abilities. *J. Alzheimer's Dis* **59**, 723–735 (2017).
27. Cenini, G. et al. Wild type but not mutant APP is involved in protective adaptive responses against oxidants. *Amino Acids* **39**, 271–283 (2010).
28. Egan, M. F. et al. Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* **378**, 1691–1703 (2018).
29. Panza, F., Lozupone, M. & Watling, M. & Imbimbo, B. P. Do BACE inhibitor failures in Alzheimer patients challenge the amyloid hypothesis of the disease? *Expert Rev. Neurother.* **19**, 599–602 (2019).
30. Hefter, D. & Draguhn, A. APP as a protective factor in acute neuronal insults. *Front. Mol. Neurosci.* **10**, 22 (2017).
31. Lancour, D. et al. One for all and all for One: Improving replication of genetic studies through network diffusion. *PLoS Genet* **14**, e1007306 (2018).
32. Asanomi, Y. et al. A rare functional variant of SHARPIN attenuates the inflammatory response and associates with increased risk of late-onset Alzheimer's disease. *Mol. Med.* **25**, 20 (2019).
33. Ruiz, A. et al. Assessing the role of the TREM2 p.R47H variant as a risk factor for Alzheimer's disease and frontotemporal dementia. *Neurobiol. Aging* **35**, 444.e1–444.e4 (2014).
34. McCarthy, S. et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–1283 (2016).
35. 1000 Genomes Project Consortium. et al. A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).
36. Sudlow, C. et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old Age. *PLOS Med.* **12**, e1001779 (2015).
37. Liu, J. Z., Erlich, Y. & Pickrell, J. K. Case-control association mapping by proxy using family history of disease. *Nat. Genet.* **49**, 325–331 (2017).
38. Jansen, I. E. et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat. Genet.* **51**, 404–413 (2019).
39. Lloyd-Jones, L. R., Robinson, M. R., Yang, J. & Visscher, P. M. Transformation of summary statistics from linear mixed model association on all-or-none traits to odds ratio. *Genetics* **208**, 1397–1408 (2018).
40. Jun, G. et al. Comprehensive search for Alzheimer disease susceptibility loci in the APOE region. *Arch. Neurol.* **69**, 1270–1279 (2012).
41. Bulik-Sullivan, B. et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* <https://doi.org/10.1038/ng.3211> (2015).
42. Kunkle, B. W. et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates A β , tau, immunity and lipid processing. *Nat. Genet.* **51**, 414–430 (2019).
43. Jun, G. et al. A novel Alzheimer disease locus located near the gene encoding tau protein. *Mol. Psychiatry* **21**, 108–117 (2016).

Acknowledgements

We would like to thank patients and controls who participated in this project. The present work has been performed as part of the doctoral program of I. de Rojas at the Universitat de Barcelona (Barcelona, Spain) supported by national grant from the Instituto de Salud Carlos III FI20/00215. The Genome Research @ Fundació ACE project (GR@ACE) is supported by Grifols SA, Fundació bancaria “La Caixa”, Fundació ACE, and CIBERNED. A.R. and M.B. receive support from the European Union/EFPIA Innovative Medicines Initiative Joint undertaking ADAPTED and MOPEAD projects (grant numbers 115975 and 115985, respectively). M.B. and A.R. are also supported by national grants PI13/02434, PI16/01861, PI17/01474, PI19/01240 and PI19/01301. Acción Estratégica en Salud is integrated into the Spanish National R + D + I Plan and funded by ISCIII (Instituto de Salud Carlos III)—Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER—“Una manera de hacer Europa”). Some control samples and data from patients included in this study were provided in part by the National DNA Bank Carlos III (www.bancoadn.org), University of Salamanca, (Spain) and Hospital Universitario Virgen de Valme (Sevilla, Spain); they were processed following standard operating procedures with the appropriate approval of the Ethical and Scientific Committee. Amsterdam dementia Cohort (ADC): Research of the Alzheimer center Amsterdam is part of the neurodegeneration research program of Amsterdam Neuroscience. The Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting VUmc funds. The clinical database structure was developed with funding from Stichting Dioraphte. Genotyping of the Dutch case-control samples was performed in the context of EADB (European Alzheimer DNA biobank) funded by the JPco-fuND FP-829-029 (ZonMW project number 733051061). 100-Plus study: We are grateful for the collaborative efforts of all participating centenarians and their family members and/or relations. This work was supported by Stichting Alzheimer Nederland (WE09.2014-03), Stichting Dioraphte, horstingstuit foundation, Memorabel (ZonMW project number 733050814, 733050512) and Stichting VUmc Fonds. Genotyping of the 100-Plus Study was performed in the context of EADB (European Alzheimer DNA biobank) funded by the JPco-fuND FP-829-029 (ZonMW project number

733051061). Longitudinal Aging Study Amsterdam (LASA) is largely supported by a grant from the Netherlands Ministry of Health, Welfare and Sports, Directorate of Long-Term Care. The authors are grateful to all LASA participants, the fieldwork team and all researchers for their ongoing commitment to the study. This work was supported by a grant (European Alzheimer DNA BioBank, EADB) from the EU Joint Program—Neurodegenerative Disease Research (JPND) and also funded by Inserm, Institut Pasteur de Lille, the Lille Métropole Communauté Urbaine, the French government's LABEX DISTALZ program (development of innovative strategies for a transdisciplinary approach to AD). Genotyping of the German case-control samples was performed in the context of EADB (European Alzheimer DNA biobank) funded by the JPco-fuND (German Federal Ministry of Education and Research, BMBF: 01ED1619A). Full acknowledgments for the studies that contributed data can be found in the Supplementary Note. We thank the numerous participants, researchers, and staff from many studies who collected and contributed to the data. We thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results data for these analyses. The investigators within IGAP contributed to the design and implementation of IGAP and/or provided data but did not participate in analysis or writing of this report. IGAP was made possible by the generous participation of the control subjects, the patients, and their families. The i-Select chips was funded by the French National Foundation on AD and related disorders. EADI was supported by the LABEX (laboratory of excellence program investment for the future) DISTALZ grant, Inserm, Institut Pasteur de Lille, Université de Lille 2 and the Lille University Hospital. GERAD was supported by the Medical Research Council (Grant n° 503480), Alzheimer's Research UK (Grant n° 503176), the Wellcome Trust (Grant n° 082604/2/07/Z) and German Federal Ministry of Education and Research (BMBF): Competence Network Dementia (CND) grant n° 01GI0102, 01GI0711, 01GI0420. CHARGE was partly supported by the NIA/NHLBI grants AG049505, AG058589, HL105756 and AGES contract N01-AG-12100, the Icelandic Heart Association, and the Erasmus Medical Center and Erasmus University. ADGC was supported by the NIH/NIA grants: U01 AG032984, U24 AG021886, U01 AG016976, and the Alzheimer's Association grant ADGC-10-196728. This research has been conducted using the UK Biobank public resource obtained through the University of Edinburgh Data Share (<https://datashare.is.ed.ac.uk/handle/10283/3364>).

Author contributions

A.Ru and S.v.d.L. designed and conceptualized the study, interpreted the data and drafted the paper. I.d.R. contributed to data acquisition, the analysis, interpreted the data, and co-wrote the paper. S.M.G. and N.T. contributed to the analysis and interpreted the data. S.J.v.d.L. and I.d.R. performed polygenic score analyses. L.C.C. and J.C. conducted the functional analysis of APP. H.Ho, W.v.d.F., S.J.v.d.L., and A.Ru supervised the study. All authors critically revised the paper for important intellectual content and approved the final paper. **GR@ACE/DEGESCO: Study design or conception:** M.Me, J.C., and A.Ru. **Data generation:** L.M., L.C.C., A.G.P., M.E.S., S.M.G., I.d.R., I.Q., and A.C. **Sample contribution:** M.Bo, J.M.G.A., M.Me, M.Ma, M.C., T.S., S.G.M., G.G.R., A.L.M., J.M., L.M.R., G.P.R., M.M.G., C.M.R., I.R.A., V.A.I., C.L., E.R.R., P.S.J., D.A.I., P.P., M.D.F., I.A.I., J.P.T., A.C., L.Ta, A.M.M., M.J.B., A.F.G., I.Q., I.H., L.M., P.G.G., E.A.M., S.V., O.S.G., A.Bena, A.P.C., A.E., A.Sa, C.Ab, G.O., M.R.R., M.A.I., N.R., S.G., A.O., A.Rab, A.Bel, F.Mo, M.Z., A.C.G., J.A.P., M.F.F., E.F.M., D.B.R., M.B.S.A., P.M., R.H.V., A.A.P., A.A., L.M.P., R.S.V., E.Ge, A.L., R.B., J.F., J.L.R., S.Men, M.Ba, I.d.R., and S.M.G. **Analysis:** S.M.G. and I.d.R. **Study supervision/management:** A.C., L.Ta, M.Bo, M.Me, J.C., and A.Ru. **IGAP: Critical revision:** A.C.N., B.W.K., L.A.F., J.L.H., L.S.W., M.A.P.V., R.May, M.A.I., J.C.B., A.L.D.S., C.L.S., E.B., M.F., Q.Y., X.J., R.S., C.H., K.M., S.Mea, V.E.P., A.Meg, P.A.H., R.Mar, P.A., G.Sc, J.Will, and S.Se. **EADB: Sample contribution:** N.T., I.E.J., N.T., K.A.M., C.D., G.N., G.C., G.Sp, K.S., M.I., M.K., R.F.S., J.C.L., A.Ra, D.G., J.S.V., D.R., E.Gr, H.Ha, I.G., J.K., L.Fa, L.Fr, A.M.H., J.V., L.H., G.H., N.Sca, M.H.K., M.Y., H.Ho, W.M.v.d.F., M.Hu.l., N.M.v.S., A.T.H., B.G.N., C.V.B., E.S., R.V., S.E., T.N., F.K., J.V.D., V.G., A.U., A.Benu, A.K.S., B.B., C.Mas, C.F., E.C., F.Ma, G.B., I.Ap, J.Q.T., L.Ki, L.K.l., L.P., L.Tr, L.B., M.L., M.Ar, R.G., S.F., F.J., J.D.S., O.G., T.G., M.J.H., T.P., K.Bu, M.E.si, S.R.H., E.Dur, A.Ru, I.H., S.M.G., I.d.R., Y.A.L.P., A.d.M., C.C.I., J.P., S.J.v.d.L., C.G., N.B., O.H., P.B., A.H., T.K., M.E.w., O.A.S., R.N.K., J.Wilf, P.F., P.R., P.Sc, P.Sa, N.Sch, D.W., E.R., G.R., H.S., I.R., A.Sc, A.Sp, A.Sq, C.Cha, C.Chi, C.P., A.P., B.A., B.N., C.M.F., D.S., E.Da, E.dü.z, E.F., F.T., F.P., F.S.G., G.Gi, G.Gra, G.P., H.B., J.H., J.L., M.C.D., M.T., M.T.H., M.Schm, M.W., M.S., O.Q., O.L., P.C., P.D., R.C., S.So, S.He, S.A., S.B., S.C., T.L., V.B., V.D., P.G.K., M.M.N., M.C.D.N., O.P., W.M., A.W.L., I.Ap, C.B.F., A.A.L.K., G.B., M.Sca, M.Sp, M.V., M.Hi, K.F., L.W., M.D., P.H., and A.Ra. **Analysis:** N.J.A., R.M.T., V.An, N.T., I.E.J., N.St, S.J.v.d.L., I.d.R., S.M.G., B.G.B., and C.B. **Studies supervision/management:** S.H.H., K.A.M., C.D., G.N., G.C., G.S., K.S., M.I., M.K., R.F.S., D.G., J.S.V., D.R., E.Gr, H.Ha, I.G., J.K., L.Fr, A.M.H., J.V., L.H., G.H., N.Sca, M.H.K., M.Y., H.Ho, W.M.v.d.F., M.Hui, N.M.v.S., N.J.A., J.D., M.Sche, A.K.S., C.G., N.B., O.H., P.B., A.H., T.K., J.Wilf, P.F., P.R., P.Sa, P.Sc, M.Hul, N.T., I.E.J., A.T.H., B.G.N., C.V.B., E.S., R.V., S.E., P.A., A.Ru, and J.C.L. **PGC-ALZ: Sample contribution:** I.E.J., A.Ro, I.Sa, D.Aa, G.Se, S.B.S., S.D., D.P., S.H., I.K.K., N.L.P., C.A.R., and O.A.A. **Analysis:** S.Ha, I.K.K., and I.E.J. **Study supervision/management:** O.A.A., C.M.v.d., and D.P. **AD and GBCS: Sample contribution:** H.Z., S.K., I.S., and K.B. **Analysis:** N.M.S. and A.Z. **Study supervision/management:** I.S.k., A.Z., and K.B.l. **NxC: Sample contribution:** A.C.A., M.T.M., M.S.R., and C.An.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41467-021-22491-8>.

Correspondence and requests for materials should be addressed to S.J.v.d.L. or A.R.

Peer review information *Nature Communications* thanks the anonymous reviewers for their contribution to the peer review of this work. Peer reviewer reports are available.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2021

Itziar de Rojas ^{1,2,306}, Sonia Moreno-Grau^{1,2,306}, Niccolo Tesi^{3,4,5,306}, Benjamin Grenier-Boley^{6,306}, Victor Andrade^{7,8,306}, Iris E. Jansen^{3,9,306}, Nancy L. Pedersen¹⁰, Najada Stringa ¹¹, Anna Zettergren ¹², Isabel Hernández^{1,2}, Laura Montreal¹, Carmen Antúnez¹³, Anna Antonelli¹⁴, Rick M. Tankard ¹⁵, Joshua C. Bis¹⁶, Rebecca Sims ¹⁷, Céline Bellenguez ⁶, Inés Quintela¹⁸, Antonio González-Perez¹⁹, Miguel Calero ^{2,20,21}, Emilio Franco-Macías²², Juan Macías²³, Rafael Blesa^{2,24}, Laura Cervera-Carles ^{2,24}, Manuel Menéndez-González ^{25,26,27}, Ana Frank-García^{2,28,29,30}, Jose Luís Royo³¹, Fermin Moreno^{2,32,33}, Raquel Huerto Vilas^{34,35}, Miquel Baquero³⁶, Mónica Díez-Fairen ^{37,38}, Carmen Lage ^{2,39}, Sebastián García-Madrona⁴⁰, Pablo García-González ¹, Emilio Alarcón-Martín^{1,31}, Sergi Valero^{1,2}, Oscar Sotolongo-Grau¹, Abbe Ullgren^{41,42}, Adam C. Naj^{43,44}, Afina W. Lemstra³, Alba Benaque¹, Alba Pérez-Cordón ¹, Alberto Benussi ⁴⁵, Alberto Rábano^{2,21,46}, Alessandro Padovani⁴⁵, Alessio Squassina ⁴⁷, Alexandre de Mendonça⁴⁸, Alfonso Arias Pastor^{34,35}, Almar A. L. Kok^{11,49}, Alun Meggy⁵⁰, Ana Belén Pastor ^{21,46}, Ana Espinosa^{1,2}, Anaïs Corma-Gómez²³, Angel Martín Montes ^{2,29,51}, Ángela Sanabria^{1,2}, Anita L. DeStefano^{52,53}, Anja Schneider^{8,54}, Annakaisa Haapasalo ⁵⁵, Anne Kinhult Ståhlbom^{41,42}, Anne Tybjærg-Hansen^{56,57}, Annette M. Hartmann⁵⁸, Annika Spottke^{54,59}, Arturo Corbatón-Anchuelo^{60,61}, Arvid Rongve ^{62,63}, Barbara Borroni⁴⁵, Beatrice Arosio^{64,65}, Benedetta Nacmias ^{66,67}, Børge G. Nordestgaard ^{57,68}, Brian W. Kunkle^{69,70}, Camille Charbonnier⁷¹, Carla Abdelnour^{1,2}, Carlo Masullo⁷², Carmen Martínez Rodríguez^{26,73}, Carmen Muñoz-Fernandez⁷⁴, Carole Dufouil^{75,76}, Caroline Graff^{41,42}, Catarina B. Ferreira⁷⁷, Caterina Chillotti⁷⁸, Chandra A. Reynolds ⁷⁹, Chiara Fenoglio⁸⁰, Christine Van Broeckhoven ^{81,82,83}, Christopher Clark ⁸⁴, Claudia Pisanu ⁴⁷, Claudia L. Satizabal ^{52,85,86}, Clive Holmes⁸⁷, Dolores Buiza-Rueda^{2,88}, Dag Aarsland ^{89,90}, Dan Rujescu⁵⁸, Daniel Alcolea ^{2,24}, Daniela Galimberti ^{80,91}, David Wallon ⁹², Davide Seripa⁹³, Edna Grünblatt ^{94,95,96}, Efthimios Dardiotis⁹⁷, Emrah Düzel^{98,99}, Elio Scarpini^{80,91}, Elisa Conti¹⁰⁰, Elisa Rubino¹⁰¹, Ellen Gelpi^{102,103}, Eloy Rodríguez-Rodríguez ^{2,39}, Emmanuelle Duron^{104,105,106}, Eric Boerwinkle^{107,108}, Evelyn Ferri⁶⁵, Fabrizio Tagliavini¹⁰⁹, Fahri Küçükali ^{81,82,83}, Florence Pasquier ^{110,111}, Florentino Sanchez-Garcia¹¹², Francesca Mangialasche¹¹³, Frank Jessen^{54,114,115}, Gaël Nicolas ⁷³, Geir Selbæk ^{116,117,118}, Gemma Ortega^{1,2}, Geneviève Chêne^{75,76}, Georgios Hadjigeorgiou¹¹⁹, Giacomina Rossi¹⁰⁹, Gianfranco Spalletta^{120,121}, Giorgio Giaccone¹⁰⁹, Giulia Grande¹²², Giuliano Binetti^{123,124}, Goran Papenberg¹²², Harald Hampel¹²⁵, Henri Bailly^{106,126}, Henrik Zetterberg ^{127,128,129,130}, Hilikka Soininen ^{131,132}, Ida K. Karlsson^{10,133}, Ignacio Alvarez ^{37,38}, Ildebrando Appollonio^{100,134}, Ina Giegling⁵⁸, Ingmar Skoog¹², Ingvild Saltvedt ^{135,136}, Innocenzo Rainero¹³⁷, Irene Rosas Allende^{26,138}, Jakub Hort^{139,140}, Janine Diehl-Schmid¹⁴¹, Jasper Van Dongen ^{81,82}, Jean-Sebastien Vidal ^{106,126}, Jenni Lehtisalo^{131,142}, Jens Wiltfang^{143,144,145}

Jesper Qvist Thomassen⁵⁶, Johannes Kornhuber¹⁴⁶, Jonathan L. Haines^{147,148}, Jonathan Vogelgsang^{143,149}, Juan A. Pineda²³, Juan Fortea^{2,24}, Julius Popp^{150,151,152}, Jürgen Deckert¹⁵³, Katharina Buerger^{154,155}, Kevin Morgan¹⁵⁶, Klaus Fließbach⁸, Kristel Slegers^{81,82,83}, Laura Molina-Porcel^{14,102}, Lena Kilander¹⁵⁷, Leonie Weinhold¹⁵⁸, Lindsay A. Farrer¹⁵⁹, Li-San Wang⁴⁴, Luca Kleineidam^{7,8}, Lucia Farotti¹⁶⁰, Lucilla Parnetti¹⁶⁰, Lucio Tremolizzo^{100,134}, Lucrezia Hausner¹⁶¹, Luisa Benussi¹²⁴, Lutz Froelich¹⁶¹, M. Arfan Ikram¹⁶², M. Candida Deniz-Naranjo¹¹², Magda Tsolaki¹⁶³, Maitée Rosende-Roca^{1,2}, Malin Löwenmark¹⁵⁷, Marc Hulsman^{3,4}, Marco Spallazzi¹⁶⁴, Margaret A. Pericak-Vance⁷⁰, Margaret Esiri¹⁶⁵, María Bernal Sánchez-Arjona²², Maria Carolina Dalmaso⁷, María Teresa Martínez-Larrad^{60,61}, Marina Arcaro⁹¹, Markus M. Nöthen¹⁶⁶, Marta Fernández-Fuertes²³, Martin Dichgans^{154,155,167}, Martin Ingelsson¹⁵⁷, Martin J. Herrmann¹⁵³, Martin Scherer¹⁶⁸, Martin Vyhnaek^{139,140}, Mary H. Kosmidis¹⁶⁹, Mary Yannakoulia¹⁷⁰, Matthias Schmid^{54,158}, Michael Ewers^{154,155}, Michael T. Heneka^{8,54}, Michael Wagner^{8,54}, Michela Scamosci¹⁷¹, Miia Kivipelto^{113,172,173,174}, Mikko Hiltunen¹⁷⁵, Miren Zulaica^{2,33}, Montserrat Alegret^{1,2}, Myriam Fornage¹⁷⁶, Natalia Roberto¹, Natasja M. van Schoor¹¹, Nazib M. Seidu¹², Nerisa Banaj¹²⁰, Nicola J. Armstrong¹⁵, Nikolaos Scarmeas^{177,178}, Norbert Scherbaum¹⁷⁹, Oliver Goldhardt¹⁴¹, Oliver Hanon^{106,126}, Oliver Peters^{180,181}, Olivia Anna Skrobot¹⁸², Olivier Quenez⁷¹, Ondrej Lerch^{139,140}, Paola Bossù¹⁸³, Paolo Caffarra¹⁸⁴, Paolo Dionigi Rossi⁶⁵, Paraskevi Sakka¹⁸⁵, Per Hoffmann^{166,186}, Peter A. Holmans¹⁷, Peter Fischer¹⁸⁷, Peter Riederer¹⁸⁸, Qiong Yang⁵³, Rachel Marshall¹⁷, Rajesh N. Kalara^{189,190}, Richard Mayeux^{191,192,193}, Rik Vandenberghe^{194,195}, Roberta Cecchetti¹⁷¹, Roberta Ghidoni¹²⁴, Ruth Frikke-Schmidt^{56,57}, Sandro Sorbi^{66,67}, Sara Hägg¹⁰, Sebastiaan Engelborghs^{196,197,198,199}, Seppo Helisalmi²⁰⁰, Sigrid Botne Sando^{201,202}, Silke Kern¹², Silvana Archetti²⁰³, Silvia Boschi¹³⁷, Silvia Fostinelli¹²⁴, Silvia Gil¹, Silvia Mendoza²⁰⁴, Simon Mead²⁰⁵, Simona Ciccone⁶⁵, Srdjan Djurovic^{206,207}, Stefanie Heilmann-Heimbach¹⁶⁶, Steffi Riedel-Heller²⁰⁸, Teemu Kuulasmaa¹⁷⁵, Teodoro del Ser²⁰⁹, Thibaud Lebouvier^{110,111}, Thomas Polak¹⁵³, Tiia Ngandu^{113,142}, Timo Grimmer¹⁴¹, Valentina Bessi^{66,210}, Valentina Escott-Price^{17,211}, Vilmantas Giedraitis¹⁵⁷, Vincent Deramecourt^{110,111}, Wolfgang Maier^{8,54}, Xueqiu Jian⁸⁵, Yolande A. L. Pijnenburg³, EADB contributors*, The GR@ACE study group*, DEGESCO consortium*, IGAP (ADGC, CHARGE, EADI, GERAD)*, PGC-ALZ consortia*, Patrick Gavin Kehoe¹⁸¹, Guillermo Garcia-Ribas⁴⁰, Pascual Sánchez-Juan^{2,39}, Pau Pastor^{37,38}, Jordi Pérez-Tur^{2,212,213}, Gerard Piñol-Ripoll^{34,35}, Adolfo Lopez de Munain^{2,32,33,214}, Jose María García-Alberca^{2,204}, María J. Bullido^{2,30,215,216}, Victoria Álvarez^{26,138}, Alberto Lleó^{2,24}, Luis M. Real^{23,217}, Pablo Mir^{2,88}, Miguel Medina^{2,21}, Philip Scheltens³, Henne Holstege^{3,4}, Marta Marquie^{1,2}, María Eugenia Sáez¹⁹, Ángel Carracedo^{18,218}, Philippe Amouyel⁶, Gerard D. Schellenberg⁴⁴, Julie Williams^{17,50}, Sudha Seshadri^{52,85,219}, Cornelia M. van Duijn^{162,220}, Karen A. Mather^{221,222}, Raquel Sánchez-Valle¹⁴, Manuel Serrano-Ríos^{60,61}, Adelina Orellana^{1,2}, Lluís Tàrraga^{1,2}, Kaj Blennow^{127,128}, Martijn Huisman^{11,223}, Ole A. Andreassen^{224,225}, Danielle Posthuma⁹, Jordi Clarimón^{2,24,307}, Mercè Boada^{1,2,307}, Wiesje M. van der Flier^{3,307}, Alfredo Ramirez^{7,8,54,226,307}, Jean-Charles Lambert^{6,307}, Sven J. van der Lee^{3,4,307} & Agustín Ruiz^{1,2,307}✉

¹Research Center and Memory clinic Fundació ACE, Institut Català de Neurociències Aplicades, Universitat Internacional de Catalunya, Barcelona, Spain. ²CIBERNED, Network Center for Biomedical Research in Neurodegenerative Diseases, National Institute of Health Carlos III, Madrid, Spain. ³Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands. ⁴Section Genomics of Neurodegenerative Diseases and Aging, Department of Clinical Genetics, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands. ⁵Delft Bioinformatics Lab, Delft University of Technology, Delft, The Netherlands. ⁶Univ. Lille, Inserm, Institut Pasteur de Lille, CHU Lille, U1167-Labex DISTALZ-RID-AGE-Risk Factors and Molecular Determinants of Aging-Related Diseases, Lille, France. ⁷Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, University of Cologne, Medical Faculty, Cologne, Germany. ⁸Department of Neurodegenerative diseases and Geriatric Psychiatry, University Clinic Bonn, Bonn, Germany. ⁹Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, VU University, Amsterdam, The Netherlands. ¹⁰Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ¹¹Amsterdam

UMC-Vrije Universiteit Amsterdam, Department of Epidemiology and Data Science, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands. ¹²Neuropsychiatric Epidemiology Unit, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, Centre for Ageing and Health (AgeCap), University of Gothenburg, Gothenburg, Sweden. ¹³Unidad de Demencias, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain. ¹⁴Alzheimer's disease and other cognitive disorders unit. Service of Neurology, Hospital Clínic de Barcelona. Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain. ¹⁵Mathematics and Statistics, Murdoch University, Perth, WA, Australia. ¹⁶Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA. ¹⁷Division of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK. ¹⁸Grupo de Medicina Xenómica, Centro Nacional de Genotipado (CEGEN-PRB3-ISCIII), Universidade de Santiago de Compostela, Santiago de Compostela, Spain. ¹⁹CAEBI, Centro Andaluz de Estudios Bioinformáticos, Sevilla, Spain. ²⁰UFIEC, Instituto de Salud Carlos III, Madrid, Spain. ²¹CIEN Foundation/Queen Sofia Foundation Alzheimer Center, Madrid, Spain. ²²Unidad de Demencias, Servicio de Neurología y Neurofisiología, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain. ²³Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario de Valme, Sevilla, Spain. ²⁴Department of Neurology, II B Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain. ²⁵Servicio de Neurología, Hospital Universitario Central de Asturias, Oviedo, Spain. ²⁶Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain. ²⁷Departamento de Medicina, Universidad de Oviedo, Oviedo, Spain. ²⁸Department of Neurology, La Paz University Hospital, Instituto de Investigación Sanitaria del Hospital Universitario La Paz, IdiPAZ, Madrid, Spain. ²⁹Hospital La Paz Institute for Health Research, IdiPAZ, Madrid, Spain. ³⁰Universidad Autónoma de Madrid, Madrid, Spain. ³¹Departamento de Especialidades Quirúrgicas, Bioquímicas e Inmunología, School of Medicine, University of Málaga, Málaga, Spain. ³²Department of Neurology, Hospital Universitario Donostia, San Sebastian, Spain. ³³Neurosciences Area, Instituto Biodonostia, San Sebastian, Spain. ³⁴Unitat Trastorns Cognitius, Hospital Universitari Santa Maria de Lleida, Lleida, Spain. ³⁵Institut de Recerca Biomedica de Lleida (IRBLleida), Lleida, Spain. ³⁶Servei de Neurologia, Hospital Universitari i Politècnic La Fe, Valencia, Spain. ³⁷Fundació Docència i Recerca MútuaTerrassa, Terrassa, Barcelona, Spain. ³⁸Memory Disorders Unit, Department of Neurology, Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain. ³⁹Neurology Service, Marqués de Valdecilla University Hospital (University of Cantabria and IDIVAL), Santander, Spain. ⁴⁰Hospital Universitario Ramon y Cajal, IRYCIS, Madrid, Spain. ⁴¹Karolinska Institutet, Center for Alzheimer Research, Department NVS, Division of Neurogeriatrics, Stockholm, Sweden. ⁴²Unit for Hereditary Dementias, Theme Aging, Karolinska University Hospital-Solna, Stockholm, Sweden. ⁴³Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. ⁴⁴Penn Neurodegeneration Genomics Center, Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. ⁴⁵Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. ⁴⁶BT-CIEN, Madrid, Spain. ⁴⁷Department of Biomedical Sciences, Section of Neuroscience and Clinical Pharmacology, University of Cagliari, Cagliari, Italy. ⁴⁸Faculty of Medicine, University of Lisbon, Lisbon, Portugal. ⁴⁹Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Psychiatry, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands. ⁵⁰UK Dementia Research Institute at Cardiff, Cardiff University, Cardiff, UK. ⁵¹Department of Neurology, La Paz University Hospital, Madrid, Spain. ⁵²Department of Neurology, Boston University School of Medicine, Boston, MA, USA. ⁵³Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA. ⁵⁴German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany. ⁵⁵A.I Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland. ⁵⁶Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark. ⁵⁷Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. ⁵⁸Martin-Luther-University Halle-Wittenberg, University Clinic and Outpatient Clinic for Psychiatry, Psychotherapy and Psychosomatics, Halle (Saale), Germany. ⁵⁹Department of Neurology, University of Bonn, Bonn, Germany. ⁶⁰Instituto de Investigación Sanitaria, Hospital Clínico San Carlos (IdISSC), Madrid, Spain. ⁶¹Spanish Biomedical Research Centre in Diabetes and Associated Metabolic Disorders (CIBERDEM), Madrid, Spain. ⁶²Haugesund Hospital, Helse Fonna, Department of Research and Innovation, Haugesund, Norway. ⁶³University of Bergen, Institute of Clinical Medicine (KI), Bergen, Norway. ⁶⁴Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy. ⁶⁵Geriatric Unit, Fondazione Cà Granda, IRCCS Ospedale Maggiore Policlinico, Milan, Italy. ⁶⁶Department of Neuroscience, Psychology, Drug Research and Child Health University of Florence, Florence, Italy. ⁶⁷IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy. ⁶⁸Department of Clinical Biochemistry, Herlev Gentofte Hospital, Herlev, Denmark. ⁶⁹Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, FL, USA. ⁷⁰John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA. ⁷¹Normandie Univ, UNIROUEN, Inserm U1245, CHU Rouen, Department of Genetics and CNR-MAJ, FHU G4 Génomique, F-76000 Rouen, France. ⁷²Institute of Neurology, Catholic University of the Sacred Heart, School of Medicine, Milan, Italy. ⁷³Hospital de Cabueñes, Gijón, Spain. ⁷⁴Servicio de Neurología, Hospital Universitario de Gran Canaria Dr.Negrín, Las Palmas, Spain. ⁷⁵Inserm, Bordeaux Population Health Research Center, UMR 1219, Univ. Bordeaux, ISPED, CIC 1401-EC, Univ Bordeaux, Bordeaux, France. ⁷⁶CHU de Bordeaux, Pole de Santé Publique, Bordeaux, France. ⁷⁷Instituto de Medicina Molecular João lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal. ⁷⁸Unit of Clinical Pharmacology, University Hospital of Cagliari, Cagliari, Italy. ⁷⁹Department of Psychology, University of California—Riverside, Riverside, CA, USA. ⁸⁰University of Milan, Dino Ferrari Center, Milan, Italy. ⁸¹VIB Center for Molecular Neurology, Antwerp, Belgium. ⁸²Laboratory of Neurogenetics, Institute Born-Bunge, Antwerp, Belgium. ⁸³Department of Biomedical Sciences, University of Antwerp., Antwerp, Belgium. ⁸⁴Institute for Regenerative Medicine, University of Zürich, Zürich, Switzerland. ⁸⁵Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, San Antonio, TX, USA. ⁸⁶Department of Population Health Sciences, UT Health San Antonio, San Antonio, TX, USA. ⁸⁷Division of Clinical Neurosciences, School of Medicine, University of Southampton, Southampton, UK. ⁸⁸Unidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain. ⁸⁹Department of Old Age Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK. ⁹⁰Centre of Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway. ⁹¹Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy. ⁹²Normandie Univ, UNIROUEN, Inserm U1245, CHU Rouen, Department of Neurology and CNR-MAJ, FHU G4 Génomique, F-76000 Rouen, France. ⁹³Complex Structure of Geriatrics, Department of Medical Sciences Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy. ⁹⁴Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric University Hospital Zurich (PUK), University of Zurich, Zurich, Switzerland. ⁹⁵Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland. ⁹⁶Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland. ⁹⁷School of Medicine, University of Thessaly, Larissa, Greece. ⁹⁸German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany. ⁹⁹Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany. ¹⁰⁰School of Medicine and Surgery, University of Milano-Bicocca and Milan Center for Neuroscience, Milan, Italy. ¹⁰¹Department of Neuroscience and Mental Health, AOU Città della Salute e della Scienza di Torino, Torino, Italy. ¹⁰²Neurological Tissue Bank of the Biobanc-Hospital Clinic-IDIBAPS, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain. ¹⁰³Division of Neuropathology and Neurochemistry, Department of Neurology, Medical University of Vienna, Vienna, Austria. ¹⁰⁴APHP, Hôpital Brousse, equipe INSERM 1178, MOODS, Villejuif, France. ¹⁰⁵Université Paris-Saclay, UVSQ, Inserm, CESP, Team MOODS, Le Kremlin-Bicêtre,

Paris, France. ¹⁰⁶APHP, Hôpital Broca, Paris, France. ¹⁰⁷School of Public Health, Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX, USA. ¹⁰⁸Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA. ¹⁰⁹Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy. ¹¹⁰Inserm U1172, CHU, DISTALz, LiCEND, Univ Lille, Lille, France. ¹¹¹CHU CNR-MAJ, Lille, France. ¹¹²Servicio de Inmunología, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain. ¹¹³Division of Clinical Geriatrics, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet, Stockholm, Sweden. ¹¹⁴Department of Psychiatry and Psychotherapy, University of Cologne, Medical Faculty, Cologne, Germany. ¹¹⁵Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany. ¹¹⁶Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust, Tønsberg, Norway. ¹¹⁷Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway. ¹¹⁸Institute of Clinical Medicine, University of Oslo, Oslo, Norway. ¹¹⁹Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus. ¹²⁰Laboratory of Neuropsychiatry, IRCCS Santa Lucia Foundation, Rome, Italy. ¹²¹Beth K. and Stuart C. Yudofsky Division of Neuropsychiatry, Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA. ¹²²Ageing Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden. ¹²³MAC—Memory Clinic, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. ¹²⁴Molecular Markers Laboratory, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. ¹²⁵Sorbonne University, GRC n° 21, Alzheimer Precision Medicine (APM), AP-HP, Pitié-Salpêtrière Hospital, Paris, France. ¹²⁶EA 4468, Sorbonne Paris Cité, Université Paris Descartes, Paris, France. ¹²⁷Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden. ¹²⁸Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden. ¹²⁹Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK. ¹³⁰UK Dementia Research Institute at UCL, London, UK. ¹³¹Institute of Clinical Medicine Neurology, University of Eastern Finland, Kuopio, Finland. ¹³²Neurocenter, neurology, Kuopio University Hospital, Kuopio, Finland. ¹³³Institute for Gerontology and Aging Research Network—Jönköping (ARN-J), School of Health and Welfare, Jönköping University, Jönköping, Sweden. ¹³⁴Neurology Unit, ‘San Gerardo’ hospital, Monza, Italy. ¹³⁵Department of Geriatrics, Clinic of Medicine, St Olavs Hospital, University Hospital of Trondheim, Trondheim, Norway. ¹³⁶Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. ¹³⁷Department of Neuroscience “Rita Levi Montalcini”, University of Torino, Torino, Italy. ¹³⁸Laboratorio de Genética, Hospital Universitario Central de Asturias, Oviedo, Spain. ¹³⁹Memory Clinic, Department of Neurology, 2nd Faculty of Medicine and Motol University Hospital, Charles University, Prague, Czech Republic. ¹⁴⁰International Clinical Research Center, St. Anne’s University Hospital Brno, Brno, Czech Republic. ¹⁴¹Department of Psychiatry and Psychotherapy, School of Medicine Klinikum rechts der Isar, Technical University of Munich, Munich, Germany. ¹⁴²Population Health Unit, Finnish Institute for Health and Welfare, Helsinki, Finland. ¹⁴³Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, Goettingen, Germany. ¹⁴⁴German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany. ¹⁴⁵Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal. ¹⁴⁶Department of Psychiatry and Psychotherapy, Universitätsklinikum Erlangen, Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany. ¹⁴⁷Department of Population & Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA. ¹⁴⁸Cleveland Institute for Computational Biology, Case Western Reserve University, Cleveland, OH, USA. ¹⁴⁹Translational Neuroscience Laboratory, McLean Hospital, Harvard Medical School, Belmont, MA, USA. ¹⁵⁰Department of Geriatric Psychiatry, University Hospital of Psychiatry Zürich, Zürich, Switzerland. ¹⁵¹University of Zürich, Zürich, Switzerland. ¹⁵²Old age Psychiatry, University Hospital of Lausanne, Lausanne, Switzerland. ¹⁵³Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital, Würzburg, Germany. ¹⁵⁴Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilians-Universität LMU, Munich, Germany. ¹⁵⁵German Center for Neurodegenerative Diseases (DZNE), Munich, Germany. ¹⁵⁶Schools of Life Sciences and Medicine, University of Nottingham, Nottingham, UK. ¹⁵⁷Department of Public Health and Caring Sciences/Geriatrics, Uppsala, Sweden. ¹⁵⁸Institute of Medical Biometry, Informatics and Epidemiology, University Hospital of Bonn, Bonn, Germany. ¹⁵⁹Departments of Medicine (Biomedical Genetics), Neurology, Ophthalmology, Epidemiology, and Biostatistics, Boston University Schools of Medicine and Public Health, Boston, MA, USA. ¹⁶⁰Centre for Memory Disturbances, Lab of Clinical Neurochemistry, Section of Neurology, University of Perugia, Perugia, Italy. ¹⁶¹Department of Geriatric Psychiatry, Central Institute for Mental Health Mannheim, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany. ¹⁶²Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands. ¹⁶³1st Department of Neurology Aristotle University of Thessaloniki, Thessaloniki, Greece. ¹⁶⁴Azienda Ospedaliero-Universitaria, Parma, Italy. ¹⁶⁵Nuffield Department of Clinical Neurosciences, Oxford, UK. ¹⁶⁶Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany. ¹⁶⁷Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. ¹⁶⁸Department of Primary Medical Care, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany. ¹⁶⁹Laboratory of Cognitive Neuroscience, School of Psychology, Aristotle University of Thessaloniki, Thessaloniki, Greece. ¹⁷⁰Department of Nutrition and Dietetics, Harokopio University, Athens, Greece. ¹⁷¹Institute of Gerontology and Geriatrics, Department of Medicine, University of Perugia, Perugia, Italy. ¹⁷²Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland. ¹⁷³Neuroepidemiology and Ageing Research Unit, School of Public Health, Imperial College London, London, UK. ¹⁷⁴Stockholms Sjukhem, Research & Development Unit, Stockholm, Sweden. ¹⁷⁵Institute of Biomedicine, University of Eastern Finland, Kuopio, Finland. ¹⁷⁶Brown Foundation Institute of Molecular Medicine, University of Texas Health Sciences Center at Houston, Houston, TX, USA. ¹⁷⁷1st Department of Neurology, Aiginition Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece. ¹⁷⁸Taub Institute for Research in Alzheimer’s Disease and the Aging Brain, The Gertrude H. Sergievsky Center, Department of Neurology, Columbia University, New York, NY, USA. ¹⁷⁹LVR-Hospital Essen, Department of Psychiatry and Psychotherapy, Medical Faculty, University of Duisburg-Essen, Essen, Germany. ¹⁸⁰Department of Psychiatry and Psychotherapy and Experimental and Clinical Research Center (ECRC), Charité-Universitätsmedizin Berlin, Berlin, Germany. ¹⁸¹German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany. ¹⁸²Bristol Medical School (THS), University of Bristol, Southmead Hospital, Bristol, UK. ¹⁸³Experimental Neuro-psychobiology Laboratory, Department of Clinical and Behavioral Neurology, IRCCS Santa Lucia Foundation, Rome, Italy. ¹⁸⁴Unit of Neuroscience, DIMEC, University of Parma, Parma, Italy. ¹⁸⁵Athens Association of Alzheimer’s disease and Related Disorders, Athens, Greece. ¹⁸⁶Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland. ¹⁸⁷Department of Psychiatry, Social Medicine Center East- Donauspital, Vienna, Austria. ¹⁸⁸Center of Mental Health, Clinic and Policlinic of Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Würzburg, Würzburg, Germany. ¹⁸⁹Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK. ¹⁹⁰Campus for Ageing and Vitality, Newcastle upon Tyne, UK. ¹⁹¹Taub Institute on Alzheimer’s Disease and the Aging Brain, Department of Neurology, Columbia University, New York, NY, USA. ¹⁹²Gertrude H. Sergievsky Center, Columbia University, New York, NY, USA. ¹⁹³Department of Neurology, Columbia University, New York, NY, USA. ¹⁹⁴Laboratory for Cognitive Neurology, Department of Neurosciences, University of Leuven, Leuven, Belgium. ¹⁹⁵Neurology Department, University Hospitals Leuven, Leuven, Belgium. ¹⁹⁶Center for Neurosciences, Vrije Universiteit Brussel (VUB), Brussels, Belgium. ¹⁹⁷Reference Center for Biological Markers of Dementia (BIODEM), University of Antwerp, Antwerp, Belgium. ¹⁹⁸Institute Born-Bunge, University of Antwerp, Antwerp, Belgium. ¹⁹⁹Department of Neurology, VUB University Hospital Brussels (UZ Brussel), Brussels, Belgium. ²⁰⁰Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland, Kuopio, Finland. ²⁰¹Department of Neurology and Clinical Neurophysiology, University Hospital of

Trondheim, Trondheim, Norway. ²⁰²Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. ²⁰³Department of Laboratory Diagnostics, III Laboratory of Analysis, Brescia Hospital, Brescia, Italy. ²⁰⁴Alzheimer Research Center & Memory Clinic, Andalusian Institute for Neuroscience, Málaga, Spain. ²⁰⁵MRC Prion Unit at UCL, Institute of Prion Diseases, London, UK. ²⁰⁶Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. ²⁰⁷NORMENT, Department of Clinical Science, University of Bergen, Bergen, Norway. ²⁰⁸Institute of Social Medicine, Occupational Health and Public Health, University of Leipzig, Leipzig, Germany. ²⁰⁹Department of Neurology/CIEN Foundation/Queen Sofia Foundation Alzheimer Center, Madrid, Spain. ²¹⁰Azienda Ospedaliero-Universitaria Careggi Largo Brambilla, Florence, Italy. ²¹¹UKDRI Cardiff, Cardiff University, Cardiff, UK. ²¹²Unitat de Genètica Molecular, Institut de Biomedicina de València-CSIC, Valencia, Spain. ²¹³Unidad Mixta de Neurología Genética, Instituto de Investigación Sanitaria La Fe, Valencia, Spain. ²¹⁴Department of Neurosciences, Faculty of Medicine and Nursery, University of the Basque Country, San Sebastián, Spain. ²¹⁵Centro de Biología Molecular Severo Ochoa (UAM-CSIC), Madrid, Spain. ²¹⁶Instituto de Investigación Sanitaria 'Hospital la Paz' (IdIPaz), Madrid, Spain. ²¹⁷Departamento de Especialidades Quirúrgicas, Bioquímica e Inmunología. Facultad de Medicina, Universidad de Málaga, Málaga, Spain. ²¹⁸Fundación Pública Galega de Medicina Xenómica-CIBERER-IDIS, Santiago de Compostela, Spain. ²¹⁹Framingham Heart Study, Framingham, MA, USA. ²²⁰Nuffield Department of Population Health, University of Oxford, Oxford, UK. ²²¹Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia. ²²²Neuroscience Research Australia, Sydney, NSW, Australia. ²²³Department of Sociology, VU University, Amsterdam, The Netherlands. ²²⁴NORMENT Centre, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. ²²⁵Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. ²²⁶Department of Psychiatry, Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, San Antonio, TX, USA. ³⁰⁶These authors contributed equally: Itziar de Rojas, Sonia Moreno-Grau, Niccolò Tesi, Benjamin Grenier-Boley, Victor Andrade, Iris E. Jansen. ³⁰⁷These authors jointly supervised this work: Jordi Clarimón, Mercè Boada, Wiesje M. van der Flier, Alfredo Ramirez, Jean-Charles Lambert, Sven J. van der Lee, Agustín Ruiz. *Lists of authors and their affiliations appears at the end of the paper. ✉email: s.j.vanderlee@amsterdamumc.nl; aruiz@fundacioace.org

EADB contributors

A. David Smith^{227,228}, Aldo Saenz²²⁹, Alessandra Bizzarro²³⁰, Alessandra Lauria²³⁰, Alessandro Vacca¹³⁷, Alina Solomon^{113,131}, Anna Anastasiou¹⁶³, Anna Richardson^{231,232}, Anne Boland²³³, Anne Koivisto^{234,235}, Antonio Daniele²³⁶, Antonio Greco²³⁷, Arnaoutoglou Marianthi¹⁶³, Bernadette McGuinness²³⁸, Bertrand Fin²³³, Camilla Ferrari⁶⁶, Carlo Custodero²³⁹, Carlo Ferrarese^{100,134}, Carlos Ingino^{240,241}, Carlos Mangone^{240,242}, Carlos Reyes Toso²⁴⁰, Carmen Martínez^{26,243}, Carolina Cuesta^{244,245}, Carolina Muchnik²⁴⁰, Catharine Joachim²⁴⁶, Cecilia Ortiz²⁴⁷, Céline Besse²³³, Charlotte Johansson^{41,42}, Chiara Paola Zoia¹⁰⁰, Christoph Laske^{248,249}, Costas Anastasiou¹⁷⁰, Dana Lis Palacio^{250,251}, Daniel G. Politis^{244,245,252}, Daniel Janowitz²⁵³, David Craig²³⁸, David M. Mann²⁵⁴, David Neary²³¹, Deckert Jürgen¹⁵³, Delphine Daian²³³, Diyana Belezhanska²⁵⁵, Eduardo Kohler²⁵⁶, Eduardo M. Castaño^{257,258}, Effrosyni Koutsouraki¹⁶³, Elena Chipi¹⁶⁰, Ellen De Roeck¹⁹⁶, Emanuele Costantini²³⁶, Emma R. L. C. Vardy²⁵⁹, Fabrizio Piras¹²⁰, Fausto Roveta¹³⁷, Federica Piras¹²⁰, Federico Ariel Prestia^{245,257}, Francesca Assogna¹²⁰, Francesca Salani¹⁸³, Gessica Sala¹⁰⁰, Giordano Lacidogna²³⁶, Gisela Novack^{257,258}, Gordon Wilcock²⁶⁰, Håkan Thonberg^{41,42}, Heike Kölsch²⁶¹, Heike Weber¹⁵³, Henning Boecker^{54,262}, Ignacio Etchepareborda^{250,251}, Irene Piaceri⁶⁶, Jaakko Tuomilehto^{142,263,264,265}, Jaana Lindström¹⁴², Jan Laczó^{139,140}, Janet Johnston²³⁸, Jean-François Deleuze²³³, Jenny Harris²³¹, Jonathan M. Schott²⁶⁶, Josef Priller^{181,267}, Juan Ignacio Bacha²⁴⁷, Julie Snowden^{231,232}, Julieta Lisso²⁶⁸, Kalina Yonkova Mihova²⁶⁹, Latchezar Traykov²⁵⁵, Laura Morelli^{257,258}, Luis Ignacio Brusco^{240,241}, Malik Rainer²⁵³, Mari Takalo¹⁷⁵, Maria Bjerke^{196,270}, Maria Del Zompo^{47,271}, Maria Serpente⁸⁰, Mariana Sanchez Abalos²⁷², Mario Rios²²⁹, Markku Peltonen¹⁴², Martin J. Herrman¹⁵³, Mary H. Kosmidis¹⁶⁹, Matias Kohler^{250,256}, Matias Rojo²⁴⁰, Matthew Jones^{231,273}, Michela Orsini²³⁶, Nancy Medel²⁶⁸, Natividad Olivar²⁴⁰, Nick C. Fox^{266,274}, Nicola Salvadori¹⁶⁰, Nigel M. Hooper²³², Pablo Galeano^{244,257,258}, Patricia Solis²⁶⁸, Patrizia Bastiani¹⁷¹, Patrizia Mecocci¹⁷¹, Peter Passmore²³⁸, Reinhard Heun²⁶¹, Riitta Antikainen^{275,276,277}, Robert Olosó²³³, Robert Perneczky^{167,278,279,280}, Sandra Germani²⁴⁰, Sara López-García^{2,39}, Seth Love^{182,281}, Shima Mehrabian²⁵⁵, Silvia Bagnoli⁶⁶, Silvia Kochen²⁶⁸, Simona Andreoni¹⁰⁰, Stefan Teipel^{282,283}, Stephen Todd²³⁸, Stuart Pickering-Brown²⁵⁴, Teemu Natunen¹⁷⁵, Thomas Tegos¹⁶³, Tiina Laatikainen^{172,284,285}, Timo Strandberg^{275,286}, Tuomo M. Polvikoski^{189,190}, Vaclav Matoska²⁸⁷, Valentina Ciullo¹²⁰, Valeria Cores^{244,245,252}, Vincenzo Solfrizzi²³⁹, Viviana Lisetti¹⁶⁰ & Zulma Sevillano²⁶⁸

²²⁷University of Oxford (OPTIMA), Oxford, UK. ²²⁸OPTIMA, Department of Pharmacology, University of Oxford, Oxford, UK. ²²⁹Dirección de Atención de Adultos Mayores del Min., Salud Desarrollo Social y Deportes de la Pcia. de Mendoza, Mendoza, Argentina. ²³⁰Geriatrics Unit Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy. ²³¹Cerebral Function Unit, Greater Manchester Neurosciences Centre, Salford Royal Hospital, Salford, UK. ²³²Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK. ²³³Centre National de Recherche en Génomique Humaine (CNRGH), Institut de Biologie François Jacob, CEA, Université Paris-Saclay, F-91057 Evry, France. ²³⁴Department of Neurology, Kuopio University Hospital, Kuopio, Finland. ²³⁵Institute of Clinical Medicine-Neurology, University of Eastern Finland, Kuopio, Finland. ²³⁶Institute of Neurology, Catholic University of Sacred Heart, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. ²³⁷Research Laboratory, Complex Structure of Geriatrics, San Giovanni Rotondo, Fondazione IRCCS Casa Sollievo della Sofferenza, Foggia, Italy. ²³⁸Centre for Public Health, School of Medicine, Queen's University Belfast, Belfast, UK. ²³⁹Clinica Medica "Frugoni" and Geriatric Medicine-Memory Unit, University of Bari Aldo Moro, Bari, Italy. ²⁴⁰CENECON-FMED-UBA, Buenos Aires, Argentina. ²⁴¹ENERI, Vienna, Austria. ²⁴²Htal Santojani, Buenos Aires, Argentina. ²⁴³Servicio de Neurología, Hospital de Cabueñes, Gijón, Spain. ²⁴⁴UBA, Buenos Aires, Argentina. ²⁴⁵HIGA Eva Perón, Billinghamurst, Argentina. ²⁴⁶University of Oxford, Oxford, UK. ²⁴⁷Neurología Clínica, Madrid, Spain. ²⁴⁸German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany. ²⁴⁹Section for Dementia Research, Hertie Institute for Clinical Brain Research and Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany. ²⁵⁰Hospital Dr. Lucio Molas, Santa Rosa, Argentina. ²⁵¹Fundacion Ayuda Enfermo Renal y Alta Complejidad (FERNAC), Santa Rosa, Argentina. ²⁵²CONICET, Buenos Aires, Argentina. ²⁵³Institute for Stroke and Dementia Research (ISD), University Hospital, Ludwig-Maximilian University Munich, Munich, Germany. ²⁵⁴Faculty of Medical and Human Sciences, Institute of Brain, Behaviour and Mental Health, Manchester, UK. ²⁵⁵Clinic of Neurology UH 'Alexandrovská', Medical University—Sofia, Sofia, Bulgaria. ²⁵⁶Fundacion Sinapsis, Santa Rosa, Argentina. ²⁵⁷Laboratory of Brain Aging and Neurodegeneration- FIL, Buenos Aires, Argentina. ²⁵⁸IIBBA (CONICET), Buenos Aires, Argentina. ²⁵⁹Salford Royal NHS Foundation Trust, Salford, England. ²⁶⁰Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK. ²⁶¹Department of Psychiatry, University of Bonn, Bonn, Germany. ²⁶²Department of Radiology, University Hospital Bonn, Bonn, Germany. ²⁶³Department of Public Health, University of Helsinki, Helsinki, Finland. ²⁶⁴National School of Public Health, Madrid, Spain. ²⁶⁵South Ostrobothnia Central Hospital, Seinäjoki, Finland. ²⁶⁶Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, UK. ²⁶⁷Department of Neuropsychiatry, Charité, Berlin, Germany. ²⁶⁸ENYS (Estudio en Neurociencias y Sistemas Complejos) CONICET-Hospital El Cruce 'Nestor Kirchner'-UNAJ, Buenos Aires, Argentina. ²⁶⁹Molecular Medicine Center, Department of Medical chemistry and biochemistry, Medical University of Sofia, Sofia, Bulgaria. ²⁷⁰Laboratory of Neurochemistry, UZ Brussel, Brussel, Belgium. ²⁷¹Unit of Clinical Pharmacology, Teaching Hospital of Cagliari, AOUCA, Cagliari, Italy. ²⁷²Programa del Adulto Mayor-Min, Salud de la Pcia. de Jujuy, San Salvador de Jujuy, Argentina. ²⁷³Division of Neuroscience and Experimental Psychology, University of Manchester, Manchester, UK. ²⁷⁴UK Dementia Research Institute at UCL, UCL Queen Square Institute of Neurology, University College London, London, UK. ²⁷⁵Center for Life Course Health Research, University of Oulu, Oulu, Finland. ²⁷⁶Medical Research Center Oulu, Oulu University Hospital, Oulu, Finland. ²⁷⁷Oulu City Hospital, Oulu, Finland. ²⁷⁸German Center for Neurodegenerative Diseases (DZNE, Munich), Munich, Germany. ²⁷⁹Department of Psychiatry and Psychotherapy, University Hospital LMU Munich, Munich, Germany. ²⁸⁰Ageing Epidemiology Research Unit (AGE), School of Public Health, Imperial College London, London, UK. ²⁸¹University of Bristol Institute of Clinical Neurosciences, School of Clinical Sciences, Frenchay Hospital, Bristol, UK. ²⁸²German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany. ²⁸³Department of Psychosomatic Medicine, Rostock University Medical Center, Rostock, Germany. ²⁸⁴Finnish Institute for Health and Welfare, Helsinki, Finland. ²⁸⁵Joint Municipal Authority for North Karelia Social and Health Services (Siun Sote), Joensuu, Finland. ²⁸⁶Helsinki University Hospital, University of Helsinki, Helsinki, Finland. ²⁸⁷Department of Clinical Biochemistry, Hematology and Immunology, Na Homolce Hospital, Prague, Czech Republic.

The GR@ACE study group

C. Abdelnour^{1,2}, N. Aguilera¹, E. Alarcon^{1,31}, M. Alegret^{1,2}, A. Benaque¹, M. Boada^{1,2}, M. Buendia¹, P. Cañabate^{1,2}, A. Carracedo^{18,218}, A. Corbatón-Anchuelo⁶, I. de Rojas¹, S. Diego¹, A. Espinosa^{1,2}, A. Gailhagenet¹, P. García-González¹, S. Gil¹, M. Guitart¹, A. González-Pérez¹⁹, I. Hernández^{1,2}, M. Ibarria¹, A. Lafuente¹, J. Macias²³, O. Maroñas¹⁸, E. Martín¹, M. T. Martínez⁶², M. Marquié¹, A. Mauleón¹, L. Montreal¹, S. Moreno-Grau^{1,2}, M. Moreno¹, A. Orellana¹, G. Ortega^{1,2}, A. Pancho¹, E. Pelejá¹, A. Pérez-Cordon¹, J. A. Pineda²³, S. Preckler¹, I. Quintela³¹, L. M. Real^{8,31}, M. Rosende-Roca¹, A. Ruiz^{1,2}, M. E. Sáez¹⁹, A. Sanabria^{1,2}, M. Serrano-Rios⁶¹, O. Sotolongo-Grau¹, L. Tárraga^{1,2}, S. Valero^{1,2} & L. Vargas¹

DEGESCO consortium

A. D. Adarmes-Gómez^{2,22}, E. Alarcón-Martín^{1,31}, M. D. Alonso²⁸⁸, I. Álvarez^{37,38}, V. Álvarez^{26,138}, G. Amer-Ferrer²⁸⁹, M. Antequera¹³, C. Antúnez¹³, M. Baquero³⁶, M. Bernal²², R. Blesa^{2,24}, M. Boada^{1,2}, D. Buiza-Rueda^{2,22}, M. J. Bullido^{2,215,216}, J. A. Burguera³⁶, M. Calero^{2,21,40}, F. Carrillo^{2,22}, M. Carrión-Claro^{2,22}, M. J. Casajeros²⁹⁰, J. Clarimón^{2,24}, J. M. Cruz-Gamero³¹, M. M. de Pancorbo²⁹¹, I. de Rojas^{1,2}, T. del Ser²¹⁶, M. Diez-Fairen^{37,38}, R. Escuela^{2,22}, L. Garrote-Espina^{2,22}, J. Fortea^{2,24}, E. Franco-Macías²², A. Frank-García^{2,29,216}, J. M. García-Alberca²⁰⁴, S. Garcia Madrona⁴⁰, G. Garcia-Ribas⁴⁰, P. Gómez-Garre^{2,22}, I. Hernández^{1,2}, S. Hevilla²⁰⁴, S. Jesús^{2,22}, M. A. Labrador Espinosa^{2,22}, C. Lage^{2,39}, A. Legaz¹³, A. Lleó^{2,24}, A. Lopez de Munain^{32,33}, S. López-García^{2,39}, D. Macias-García^{2,22}, S. Manzanares^{289,292}, M. Marín²², J. Marín-Muñoz¹³, T. Marín²⁰⁴, M. Marquié^{1,2}, A. Martín Montes^{2,29,215}, B. Martínez¹³, C. Martínez^{26,243},

V. Martínez¹³, P. Martínez-Lage Álvarez²⁹³, M. Medina^{2,216}, M. Mendioroz Iriarte²⁹⁴,
M. Menéndez-González^{25,26}, P. Mir^{2,22}, J. L. Molinuevo²⁹⁵, L. Montreal¹, A. Orellana¹, P. Pastor^{37,38},
J. Pérez Tur^{2,212,213}, T. Periñán-Tocino^{2,22}, R. Pineda-Sanchez^{2,22}, G. Piñol-Ripoll^{2,34,35}, A. Rábano^{2,21,46},
D. Real de Asúa²⁹⁶, S. Rodrigo²², E. Rodríguez-Rodríguez^{2,39}, J. L. Royo³¹, A. Ruiz^{1,2}, R. Sanchez del Valle Díaz¹⁴,
P. Sánchez-Juan^{2,39}, I. Sastre^{2,215}, O. Sotolongo-Grau¹, S. Valero^{1,2}, M. P. Vicente¹³, R. Vigo-Ortega^{2,22} &
L. Vivancos¹³








²⁸⁸Servei de Neurologia, Hospital Clínic Universitari de València, València, Spain. ²⁸⁹Department of Neurology, Hospital Universitario Son Espases, Palma, Spain. ²⁹⁰Hospital Universitario Ramón y Cajal, Madrid, Spain. ²⁹¹BIOMICS, País Vasco, Centro de Investigación Lascaray, Universidad del País Vasco UPV/EHU, Leioa, Spain. ²⁹²Fundación para la Formación e Investigación Sanitarias de la Región de Murcia, El Palmar, Spain. ²⁹³Fundación CITA-alzheimer, Centro de Investigación y Terapias Avanzadas, San Sebastián, Spain. ²⁹⁴Navarrabiomed, Pamplona, Spain. ²⁹⁵Barcelona beta Brain Research Center-Fundació Pasqual Maragall, Barcelona, Spain. ²⁹⁶Hospital Universitario La Princesa, Madrid, Spain.

IGAP (ADGC, CHARGE, EADI, GERAD)

C. Macleod²⁹⁷, C. McCracken²⁹⁸, Carol Brayne²⁹⁹, Catherine Bresner¹⁷, Detelina Grozeva¹⁷, Eftychia Bellou¹⁷,
Ewen W. Sommerville¹⁷, F. Matthews³⁰⁰, Ganna Leonenko¹⁷, Georgina Menzies⁵⁰, Gill Windle²⁹⁷,
Janet Harwood¹⁷, Judith Phillips³⁰¹, K. Bennett³⁰², Lauren Luckuck¹⁷, Linda Clare³⁰³, Robert Woods³⁰⁴,
Salha Saad¹⁷ & Vanessa Burholt³⁰⁵

²⁹⁷School of Health Sciences, Bangor University, Bangor, UK. ²⁹⁸Institute of Psychology, Health and Society, University of Liverpool, Liverpool, England. ²⁹⁹School of Clinical Medicine, Cambridge Institute of Public Health, University of Cambridge, Cambridge, England. ³⁰⁰Faculty of Medicine, Institute of Health and Society, University of Newcastle, Callaghan, NSW, Australia. ³⁰¹Dementia Studies, University of Stirling, Stirling, Scotland. ³⁰²School of Psychology, University of Liverpool, Liverpool, England. ³⁰³School of Psychology, Centre for Research in Ageing and Cognitive Health (REACH), University of Exeter, Exeter, England. ³⁰⁴Dementia Services Development Centre, Bangor University, Wales, UK. ³⁰⁵Swansea University, School of Human Sciences, Centre for Innovative Ageing, Swansea, UK.

PGC-ALZ consortia

Iris E. Jansen^{3,9}, Nancy L. Pedersen¹⁰, Arvid Rongve⁶², Chandra A. Reynolds ⁷⁹, Dag Aarsland ^{89,90},
Geir Selbæk ^{116,117,118}, Ida K. Karlsson^{10,133}, Ingvild Saltvedt ^{135,136}, Sara Hägg ¹⁰, Sigrid Botne Sando^{201,202},
Srdjan Djurovic ^{206,207}, Ole A. Andreassen ^{224,225}, Danielle Posthuma⁹