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Consensus meta-analysis of genome-wide association studies for Alzheimer's disease and related dementias

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To better characterize the genetic architecture underlying Alzheimer's disease (AD) and related dementias (ADRD), we performed a meta-analysis of European-ancestry genome-wide association studies in 128,681 cases or proxy cases of ADRD and 849,833 (proxy) controls. We identified 91 genetic loci associated with ADRD risk, of which 16 are new and 56 are specifically detected in clinically diagnosed AD cases. We also provide a list of 18 loci (15 new) requiring further external validation. A polygenic score combining the effects of ADRD loci other than *APOE* was primarily associated with AD rather than non-AD pathology. Individuals in the tenth decile of the score exhibited a twofold increased risk of presenting with Braak neurofibrillary tangles stage of >4 and moderate-to-severe neuritic amyloid plaque pathology at death compared to individuals in the median score group. In conclusion, our study validated a large number of loci associated with the risk of clinically diagnosed AD, while further investigations are required to confirm the impact of the other loci on AD clinical diagnosis and of each locus on AD pathology.

More than 90 genetic loci are associated with Alzheimer's disease and related dementia (ADRD). Most of them were identified through large-scale genome-wide association studies (GWASs) performed in European-ancestry samples by, among others, the International Genomics of Alzheimer's Project (IGAP), the European Alzheimer and Dementia Biobank (EADB) and the Psychiatric Genomics Consortium (PGC)—AD Working Group (PGC-ALZ)[1–7]. Although the latest GWASs on ADRD partly overlapped, they used different imputation panels or analytical approaches and some results were discordant across studies. They all included, to varying extents, large biobank samples using International Classification of Diseases codes to identify AD cases, proxy ADRD cases (that is, individuals reporting at least one parent or sibling with dementia) or both. This strategy increases the power to identify AD loci but also can blur the distinction between AD and non-AD dementia signals, as the AD phenotype definition is less specific in those samples. To better characterize the genetic architecture and pathophysiology underlying AD and ADRD, we joined efforts across the three consortia to perform a consensus meta-analysis of ADRD GWAS across all our samples of European ancestry, the UK Biobank (UKBB) and FinnGen. To further delineate the impact of known genomic loci on AD compared to ADRD, we performed sensitivity analyses by excluding proxy or large biobank samples.

The meta-analysis included 72,721 AD cases, 55,960 proxy ADRD cases, 614,267 controls and 235,566 proxy controls from 52 studies, corresponding to a rough effective sample size of 230,631 (Supplementary Note and Supplementary Table 1). After quality control, we considered associations for 20,045,120 variants (Supplementary Figs. 1 and 2). We identified 91 genome-wide significant (GWS) loci ($P \leq 5 \times 10^{-8}$, defined as 'tier 1'), of which 16 loci (*EIF4G3*, *PTPRC*, *MGAT5*, *PPP2R3A*, *ADGRL3*, *FAM193B*, *TMEM184A*, *DOCK4*, *IPMK*, *UBFD1*, *VMAC*, *VAV1*, *LRRC25*, *CEP89*, *LILRB1/LILRB4* and *SRC*) were new in European-ancestry samples at the time of analysis, although *ADGRL3* was recently identified in a multi-ancestry GWAS[8] (Fig. 1, Supplementary Tables 2 and 3 and Supplementary Figs. 3–55). After the stepwise conditional analysis,

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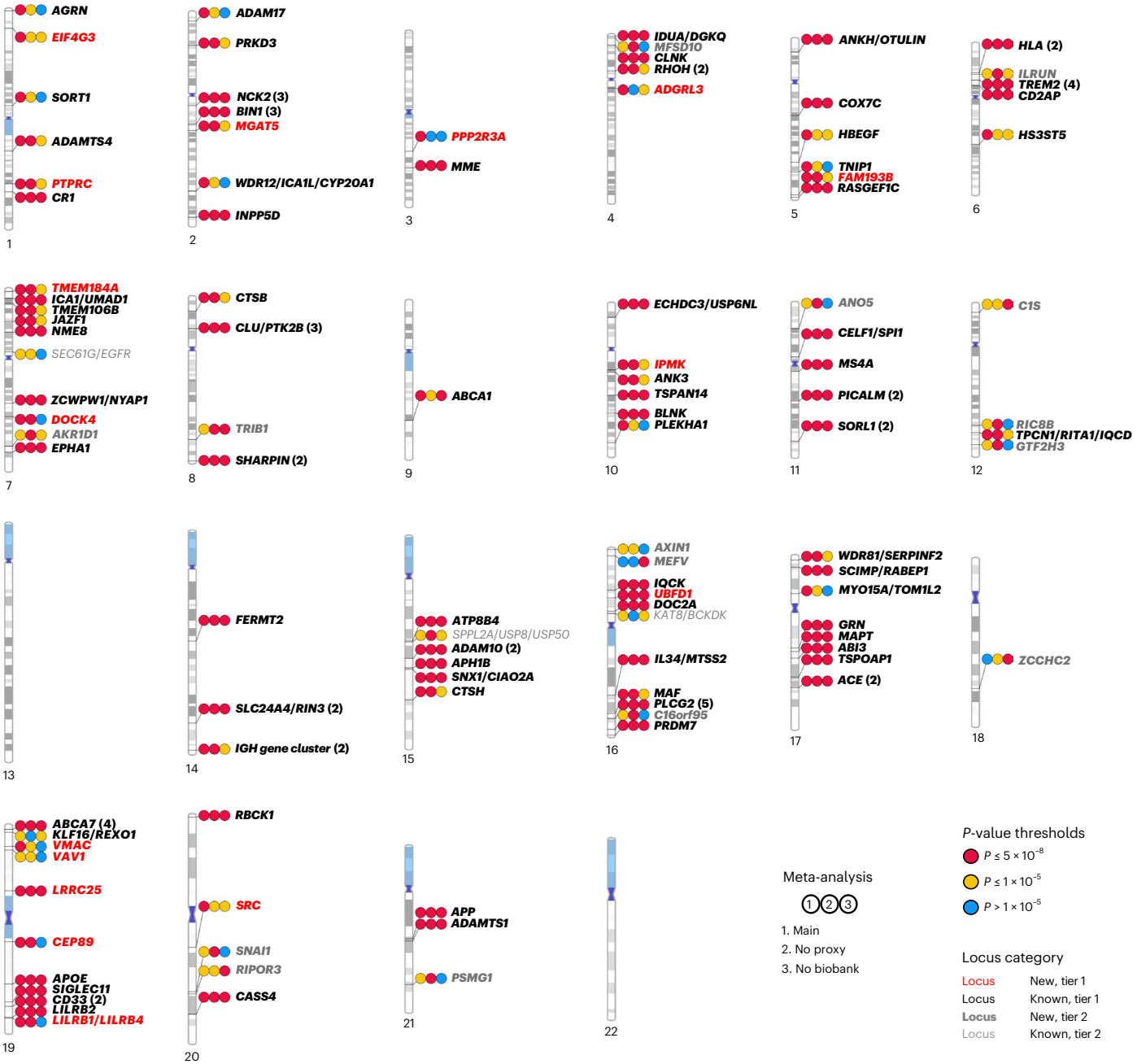

Fig. 1 | Ideogram of the tier 1 and 2 loci. Tier 1 loci are considered genuine GWS signals, with $P \leq 5 \times 10^{-8}$ in the unconditional analysis and $P \leq 1 \times 10^{-7}$ in conditional analyses within or across loci. Tier 2 loci are GWS signals requiring further external validation because (1) the *P* value was $> 1 \times 10^{-7}$ after conditional analyses or (2) they were GWS only in the sensitivity no-proxy and no-biobank meta-analyses. For each locus, the figure shows the *P*-value categories for the association with ADRD or AD risk in the main, no-proxy and no-biobank meta-analyses—$P \leq 5 \times 10^{-8}$, $P \leq 1 \times 10^{-5}$, $P > 1 \times 10^{-5}$ (two-sided raw *P* values derived from a fixed-effect meta-analysis with an inverse-variance-weighted approach). We considered the *P* value of the lead variant when the locus was detected in the meta-analysis and otherwise the minimum *P* value across all index variants of the locus. New tier 1 loci are in bold red, known tier 1 loci in bold black, known tier 2 loci in gray and new tier 2 loci in bold gray. Numbers in parentheses refer to the number of GWS independent signals within the locus according to the main meta-analysis.

we identified 25 independent secondary signals across 16 loci (Fig. 1, Supplementary Table 3 and Supplementary Figs. 3–55). Compared to refs. 4–6,9, the independent association signals detected in the *CD33*, *HLA*, *PICALM* and *RHOH* loci are new and we detected additional independent signals in *ABCA7*, *BIN1*, *PTK2B*/*CLU*, *NCK2* and *PLCG2* (Fig. 1). While some main and secondary signals are likely linked to the same gene—for example, the low-frequency variants in *SORL1* and *ABCA7*—some may be linked to two different genes in the same locus. Of note, in addition to the 91 tier 1 loci, we detected five loci in which significance decreased after conditional analyses ($P > 1 \times 10^{-7}$) performed either within or across loci, suggesting a slight inflation of the unconditional analysis (Fig. 1 and Supplementary Tables 2–4). Those loci require external validation and were thus classified as 'tier 2'. Three were known (*SEC61G/EGFR*, *SPPL2A/USP8/USP50*, *KAT8/BCKDK*) and two were new in European-ancestry samples (*TRIB1* and *AXIN1*), although *TRIB1* was identified in a recent multi-ancestry GWAS[8]. Additionally, four loci identified in the two previous largest ADRD GWAS meta-analyses on European-ancestry samples[5,6] (*HAVCR2*, *SLC2A4RG*/*LIME1*, *FOXF1*

and *NTN5)* were not GWS in the EADB–IGAP–PGC meta-analysis (Supplementary Table 5 and Supplementary Fig. 56).

We assessed the robustness of the signals according to the AD diagnosis quality by excluding proxy ADRD samples or large biobank samples from the meta-analysis. Overall, the genetic correlation among the three AD phenotypes thus defined was above 0.97 (Supplementary Table 6). Among the 91 tier 1 loci, 75 (82.4%) were GWS in the no-proxy meta-analysis, and 56 (61.5%) in the no-biobank meta-analysis focusing on clinically diagnosed AD cases (Fig. 1 and Supplementary Tables 2 and 7). Ten of the 75 loci detected in both the main and no-proxy meta-analyses were new—*PTPRC*, *MGAT5*, *FAM193B*, *TMEM184A*, *DOCK4*, *IPMK*, *UBFD1*, *LRRC25*, *CEP89* and *LILRB1/LILRB4*. The *UBFD1* and *LRRC25* new loci were also GWS in the no-biobank meta-analysis, while 12 known ADRD loci are now GWS after focusing on clinically diagnosed AD cases compared with refs. 3,4,6 (*NCK2*, *MME*, *ANKH/OTULIN*, *ABCA1*, *BLNK*, *IGH*, *ATP8B4*, *SNX1/CIAO2A*, *IL34/MTSS2*, *SIGLEC11*, *RBCK1* and *APP*). We further examined putative signals detected exclusively in the sensitivity meta-analyses—nine loci were identified only in the no-proxy meta-analysis, while four loci were identified only in the no-biobank meta-analysis (Fig. 1, Supplementary Tables 2 and 7 and Supplementary Figs. 57–61). All 13 of these loci were new and classified as 'tier 2'. The Supplementary Note further describes the GWAS results and provides putative secondary signals at a more lenient significance threshold of $P < 1 \times 10^{-5}$ (Supplementary Table 3).

Among the index variants of the main or secondary tier 1 signals, three were missense variants with a REVEL score of >0.25 (in the *MME*, *TREM2* and *ABCA7* loci); only seven index variants were rare, with minor allele frequency (MAF) of <1%, in the *SORT1*, *NCK2*, *ADGRL3*, *TREM2*, *PLCG2* and *ABCA7* loci (Supplementary Tables 2 and 3). We further assessed the impact of rare variants within the new tier 1 loci on AD risk using a previous gene-based analysis of our samples' sequencing data. In the *SRC* gene, loss-of-function variants and missense variants with a REVEL score of >50 were jointly associated with AD risk (odds ratio (OR) = 4.23, 95% confidence interval (CI) = 2.04–8.79, $P = 1.06 \times 10^{-4}$; Supplementary Table 8) in the Alzheimer Disease European Sequencing (ADES) - Alzheimer's Disease Sequencing Project (ADSP) summary statistics[10].

As in previous GWAS findings, genes enriched for ADRD or AD association signals in the main, no-proxy and no-biobank meta-analyses were overexpressed in microglia across four datasets spanning different brain regions (Supplementary Note, Supplementary Tables 9 and 10 and Supplementary Figs. 62–64). Similar to previous GWAS results, association signals were significantly enriched in biological pathways related to tau, amyloid, lipids, immunity or endosome/lysosome, in the main, no-proxy and no-biobank meta-analyses (Supplementary Table 11). By performing a phenome-wide association study, we also linked some of the new loci (both tiers) to pathways related to tau, lipids or immunity (Supplementary Tables 12–14). For example, the *C16orf95* locus has been associated with phosphorylated tau levels in cerebrospinal fluid as well as with ventricular volume (Supplementary Note)[11,12]. This latter observation supports the validity of some of the tier 2 loci. After exclusion of *APOE*, the no-proxy ADRD phenotype was significantly ($P \leq 3.13 \times 10^{-3}$) genetically correlated with Lewy body dementia ($r = 0.64$, 95% CI = 0.37–0.92), amyotrophic lateral sclerosis ($r = 0.29$, 95% CI = 0.18–0.40), Parkinson's disease ($r = 0.16$, 95% CI = 0.06–0.27) and educational attainment ($r = -0.12$, 95% CI = −0.17 to −0.07; Supplementary Table 6). These results, consistent with previous studies[13,14], were similar when considering the main and no-biobank summary statistics except for educational attainment when using the main meta-analysis results ($r = -0.02$, 95% CI = −0.07 to 0.02). This is in accordance with previous reports of biases observed with genome-wide summary statistics of studies including proxy cases[14–16].

Genetic correlation with ADRD could not be reliably assessed for most of the 11 neuropathology endophenotypes (NPEs) examined, due to limited study sample sizes and/or low heritability of these traits (Supplementary Table 6). These NPEs comprised the following: (1) three AD-related NPEs—Braak neurofibrillary tangles stage, amyloid-β plaques and the CERAD score for neuritic amyloid plaques; (2) five cerebrovascular NPEs—arteriolosclerosis, circle of Willis atherosclerosis, cerebral amyloid angiopathy, gross infarcts and microinfarcts, and (3) three non-AD NPEs—limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC), Lewy bodies and hippocampal sclerosis. To better study the genetic link between ADRD and NPEs, we constructed three polygenic scores (PGSs) based on the tier 1 main and secondary signals (excluding *APOE*) detected in the main, no-proxy and no-biobank meta-analyses, respectively (Supplementary Table 15). We then assessed the association of these PGSs with the 11 NPEs in the Adult Changes in Thought (ACT) cohort ($n = 677$, including 12.9% with dementia) and in the Alzheimer's Disease Centers/National Alzheimer's Coordinating Center (ADC/NACC) dataset ($n = 5{,}808$, including 82.7% with dementia; Supplementary Table 16)[17]. The main score was significantly associated ($P \leq 2.27 \times 10^{-3}$) with the three AD-related NPEs and with LATE-NC in the ADC/NACC dataset, and the signals were in the same direction in the smaller ACT study (Fig. 2a, Supplementary Table 17 and Supplementary Supplementary Note). None of the scores was significantly associated with cerebrovascular NPEs, hippocampal sclerosis or Lewy bodies (Fig. 2a and Supplementary Table 17), while the genetic correlation between ADRD and Lewy body dementia was significant after the exclusion of *APOE*. This may indicate common pathological pathways underlying conversion from the pathology to AD or Lewy body dementia. However, we cannot exclude other explanations, such as a lack of statistical power of the PGS analysis or misdiagnoses among AD and Lewy body dementia cases, impacting genetic correlation. Results were similar across the main, no-proxy and no-biobank PGS (Supplementary Table 17). After adjustment for the AD-related NPEs, only the associations with Braak stage and CERAD score remained significant in ADC/NACC (Fig. 2b and Supplementary Table 17). The association with LATE-NC remained significant at the nominal level only ($P = 3.78 \times 10^{-2}$; Supplementary Table 17); a larger sample size is required to assess whether the association with LATE-NC is due to or not to the frequent co-occurrence of LATE-NC and AD NPEs (Supplementary Note). There was no significant interaction ($P \leq 2.27 \times 10^{-3}$) between the PGS and the number of *APOE* ε4 and ε2 alleles for Braak stage and CERAD score (Supplementary Table 17). In the ADC/NACC dataset, compared to the individuals with a main PGS in the median quintile (40–60%), individuals in the tenth decile had a risk increased by 2.05-fold (95% CI = 1.47–2.85) and 1.96-fold (95% CI = 1.39–2.78) for Braak stage of >4 and moderate-to-severe neuritic amyloid plaque pathology at death, respectively, while individuals in the first decile had a risk decreased by 0.47-fold (95% CI = 0.37–0.61) and 0.43-fold (95% CI = 0.33–0.56), respectively (Fig. 3, Supplementary Tables 18 and 19 and Supplementary Note). Compared with a model considering only age at death, sex and the number of *APOE* ε4 and ε2 alleles, the main PGS allowed a significant improvement ($P \leq 2.27 \times 10^{-3}$) in discrimination measured by the area under the receiver operating characteristic curve (AUC) for both Braak stage and CERAD score in the ADC/NACC dataset (Supplementary Table 20). However, the variance explained by the score remained low—Nagelkerke's pseudo-R-squared (R^2) was 3.98% and 4.37% for Braak stage and CERAD score, respectively, while the variance explained on the liability scale varied between 2.43% and 3.6% for Braak stage, and between 3.32% and 4.93% for CERAD score, depending on the population prevalence considered. The discriminative power, as measured by AUC, was similar for the main, no-proxy and no-biobank PGS ($P > 0.05$; Supplementary Table 21).

In summary, this consensus meta-analysis identified 91 genetic loci associated with ADRD risk, including 16 new loci in European-ancestry samples, and 56 of the loci were associated with the risk of clinically diagnosed AD. We also further characterized the impact of known

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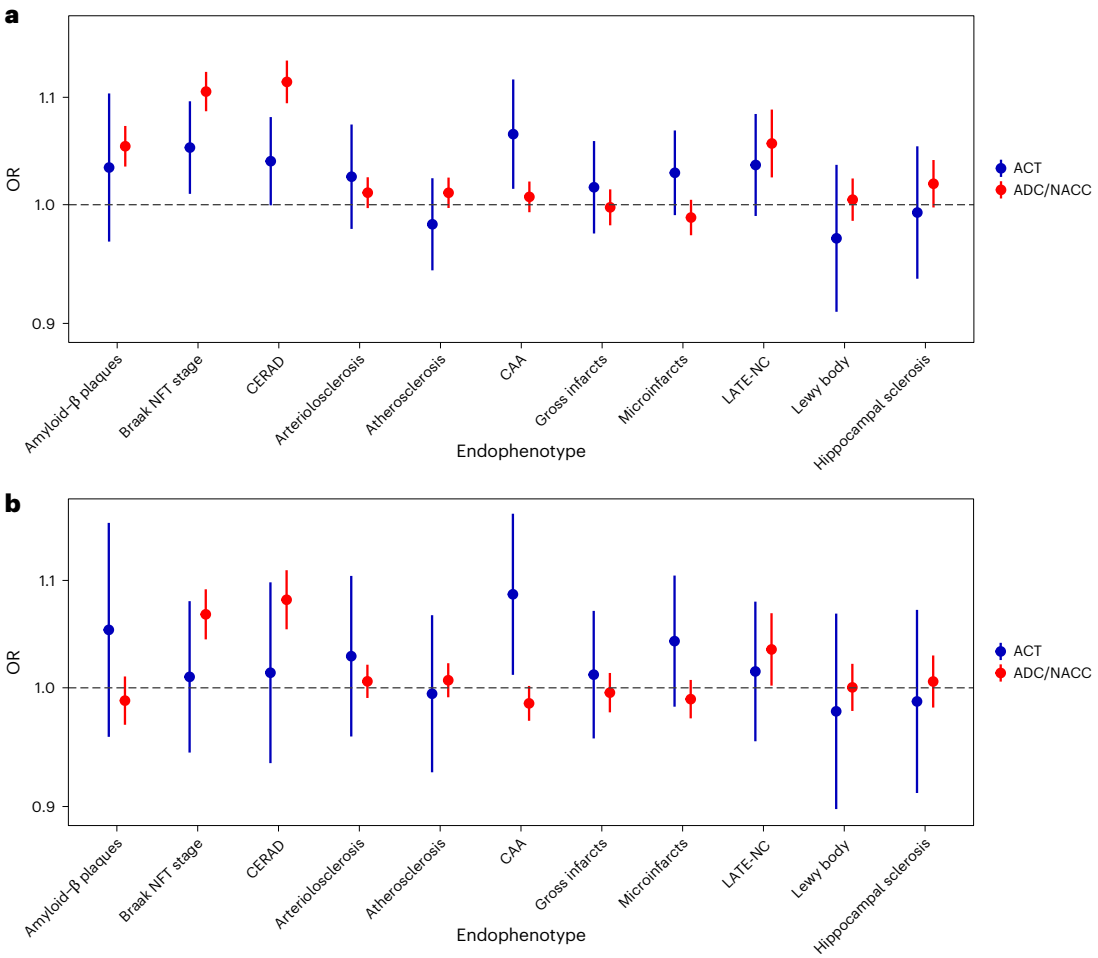

Fig. 2 | Association of the main ADRD PGS with 11 neuropathology endophenotypes in the ACT and ADC/NACC datasets. a,**b**, Analyses were performed with minimal adjustment on age at death, sex, number of *APOE* ε4 and ε2 alleles, PCs and centers (**a**) and additional adjustment on AD neuropathology endophenotypes (**b**). Dots represent OR and bars indicate 95% CI. NFT, neurofibrillary tangles; CAA, cerebral amyloid angiopathy.

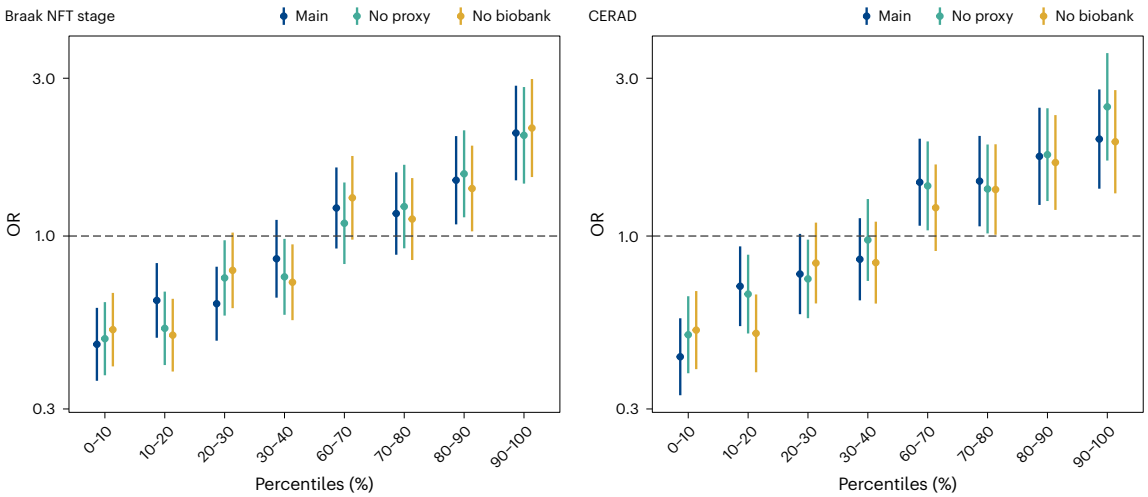

Fig. 3 | Association of the main, no-proxy and no-biobank ADRD PGS deciles with Braak stage and CERAD score in the ADC/NACC dataset. Braak stage was dichotomized into stages 0–3 (n = 1,113) versus stages 4–6 (n = 4,680) groups. CERAD stage was dichotomized into none/mild (n = 1,062) versus moderate/severe (n = 4,738) groups. Analyses were adjusted for age at death, sex, number of *APOE* ε4 and ε2 alleles, PCs and centers. The reference is the median (40–60%) quintile. Dots represent OR and bars indicate 95% CI.

loci by validating—or not—their association with ADRD and AD risk in larger samples and by identifying new secondary signals in some of them. Except for genetic correlation with education, our results were consistent across the main, no-proxy and no-biobank meta-analyses, and the three PGSs, excluding *APOE*, were primarily associated with AD rather than non-AD pathology. However, assessing the sensitivity

of GWAS or GWAS secondary analyses (especially those based on genome-wide statistics[14]) in clinically diagnosed cases will become increasingly important as the proportion of proxy and biobank cases included in the GWAS increases. This will be made easier by the release of the no-proxy and no-biobank summary statistics. Additionally, several ADRD loci were significantly associated with non-AD NPEs, but not with AD NPEs (Supplementary Table 14)[17]. Such results are difficult to interpret, considering the limited statistical power of NPE GWASs to detect variants with small effects on ADRD risk. Further studies using larger numbers of well-characterized AD patients and neuropathological data will thus be required to more precisely delineate the impact of each of the loci on AD pathology versus other neuropathologies. Follow-up analyses of rare damaging and structural variants, using sequencing data and functional studies, will provide further insights into the biological impact of these loci on ADRD and AD.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41588-026-02583-1.

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Methods

Samples

We analyzed genotyping data from European-ancestry samples across 52 studies—46 case–control or cohort studies, 2 family studies (NIA-LOAD and Framingham Heart Study (FHS)) and 4 large biobanks (UKBB, FinnGen, deCODE and HUNT). The samples are described in Supplementary Table 1 and in the Supplementary Note. In the UKBB, proxy ADRD cases included participants who reported at least one biological relative (parent or siblings) affected with dementia, either at baseline or follow-up (Supplementary Note). Eleven NPEs were measured in autopsied individuals from the ACT and ADC/NACC studies (Supplementary Table 16 and Supplementary Note). The NPE definitions and harmonization approach are discussed in ref. 17. Written informed consent was obtained from all study participants or, for those with substantial cognitive impairment, from a caregiver, legal guardian or other proxy. The appropriate review boards from the ADGC, Bonn, CHARGE, EADB, EADI, GERAD, GR@ACE/DEGESCO and PGC-ALZ reviewed and approved the study protocol. Researchers from each participating consortium were actively involved throughout the research process.

Quality control and imputation

Classical quality control protocols were applied to samples and autosomal variants in each study (Supplementary Note). Most of the samples were imputed with the TOPMed reference panel[18,19]; one study was imputed with the Haplotype Reference Consortium panel[20], while the UKBB, FinnGen and deCODE biobanks were imputed using study-specific reference panels (Supplementary Table 22).

GWAS and meta-analyses

Associations between each autosomal variant and ADRD risk were tested within each study under an additive genetic model. Logistic regression was used in most studies. When necessary, relatedness was accounted for using generalized estimating equations or logistic mixed models (Supplementary Note). Analyses were adjusted for principal components (PCs) and center/batches. In a few studies, adjustment was also performed for sex, age or both (Supplementary Table 22). In deCODE, correction for inflation of test statistics due to relatedness and population stratification was performed using the intercept estimate (1.30) from linkage disequilibrium (LD) score regression[21]. In the UKBB-proxy analysis, effect sizes and standard errors were corrected by a factor of two[22,23]. Across all studies, we filtered out duplicated variants and those with (1) missing data for effect size, s.e. or *P* value; (2) an absolute effect size >5 and (3) imputation quality <0.3 (0.8 for the GenADA study). For deCODE and UKBB, data were analyzed in the GRCh37 assembly, and we excluded variants for which conversion of position or alleles from GRCh37 to GRCh38 was not possible or was ambiguous[6]. For the UKBB and the EADB-core HRC study, variants with very large differences in frequency between the TOPMed reference panel and the reference panels used to perform imputation were also excluded[6].

Meta-analyses

Results were combined across studies using a fixed-effects meta-analysis with an inverse-variance weighted approach, as implemented in the METAL (v2020-05-05) software[24]. In the main meta-analysis, all studies were included, and within each study we filtered out variants with an effective allele count (defined as the product of the imputation quality and the expected minimum minor allele count between cases and controls) of <5 (ref. 25). After meta-analysis, we filtered out (1) variants with frequency amplitude of >0.4 (defined as the difference between the maximum and minimum frequencies across all the studies) and (2) variants analyzed in <40% effective number of cases. In each study, the effective number of cases was defined as the raw number of cases, except in the UKBB proxy, where it was computed by dividing the raw number of proxy cases by four[22,26]. Several sensitivity meta-analyses were conducted as follows by

(1) excluding the UKBB-proxy study (no-proxy meta-analysis). The UKBB study was included in the meta-analysis, but only diagnosed cases were considered (Supplementary Note and Supplementary Table 1). Variants with positions of >80 Mb on chromosome 11 were inadvertently missing from the UKBB-diagnosed summary statistics, resulting in a minor loss of power (~6% effective sample size) in a small genomic region (~2%) for the no-proxy sensitivity analyses; this had minimal impact on the results (Supplementary Note). Corrected summary statistics are provided in the GWAS Catalog and on NIAGADS (Data availability);
(2) excluding the UKBB, FinnGen, deCODE and HUNT studies, corresponding to large biobanks using International Classification of Diseases codes to identify AD cases (no-biobank meta-analysis; Supplementary Table 1); and
(3) removing the per-study variant filtering on effective allele count, except in the FHS study (Supplementary Note and Supplementary Table 23).

Additionally, we assessed the sensitivity of results for GWS lead variants from the main meta-analysis after adjustment for age and sex, and after adjustment for age, sex and the number of *APOE* ε4 and ε2 alleles (Supplementary Table 24).

Loci definition

We selected variants with GWS signals and also suggestive variants ($P \leq 1 \times 10^{-5}$) located within ±500 kb of a GWS variant and analyzed in ≥70% effective number of cases. LD across the variants was computed in the EADB-core dataset using genotype dosages with LDstore 2 (ref. 27). For variants not available in EADB-core, LD was computed in 1000 Genomes European samples (v3) using emeraLD[28], which took phase into account. Variants not available in EADB-core or 1000 Genomes were considered as having no LD with other variants. Loci and their boundaries were then defined based on LD and distance between GWS and suggestive variants using a clumping approach similar to that described in ref. 29 (Supplementary Note).

In each locus, the variant with the lowest *P* value (or the highest absolute effect size in case of equal *P* values) was defined as the lead variant. None of the variants with missing LD in both EADB-core and 1000 Genomes was selected as a lead variant.

A locus was considered known if a variant previously associated with AD at the GWS level, according to the GWAS Catalog (version e112_r2024-07-08), was located in this locus[30]. For that, we restricted the GWAS Catalog to 'MAPPED_TRAIT' equal to 'late-onset Alzheimers disease', 'Alzheimer disease', 'Alzheimer disease, family history of Alzheimer's disease', 'family history of Alzheimer's disease' or 'Alzheimer disease, dementia, family history of Alzheimer's disease'.

A gene was assigned to each lead variant—the protein-coding gene in which the lead variant is located, and, otherwise, the nearest protein-coding gene according to Variant Effect Predictor (VEP) (release 109)[31] and considering only transcripts with the GENCODE basic tag. The locus was named according to the gene assigned to its lead variant and to the locus name in the literature for known loci.

The ideogram was generated using PhenoGram (https://ritchielab.org/software/phenogram-downloads).

Conditional and joint analyses

To identify secondary signals independent of the lead variant signal in the loci, a stepwise conditional analysis was performed in each locus, except *APOE*, with GCTA COJO[32,33] based on the summary statistics of the main meta-analysis, and on the LD computed in the EADB-core samples. For this purpose, EADB-core genetic data were converted to best-guess genotype data using a genotype probability threshold of 0.8. Only variants analyzed in ≥70% effective number of cases were considered, leading to the exclusion of the *ADGRL3* locus from these

analyses. The *P*-value threshold for defining secondary signals was set at 1×10^{-5}. Then, to check the independence of the signals across loci, a joint analysis was performed using GCTA COJO of (1) the 157 index variants of the lead and secondary signals detected by the stepwise conditional analysis (Supplementary Note) and (2) the *ADGRL3* lead variant. These conditional and joint analyses were also performed for the no-proxy and no-biobank sensitivity meta-analyses. To assess the sensitivity of the results of the approximate stepwise conditional analysis to LD and imputation quality, we performed (1) a strict stepwise conditional analysis and (2) an exact conditional analysis. The strict stepwise conditional analysis was performed on variants with imputation quality >0.8 in the EADB-core dataset and analyzed in ≥90% effective number of cases. Exact conditional analyses were performed using SNPTEST[34,35] on raw data from a subset of studies—(1) between the index variants of the lead and secondary signals within the same locus; and (2) between the index variants of the main and secondary signals at the *KAT8*/*BCKDK* and *DOC2A* loci on the one hand and the *APH1B* and *SNX1*/*CIAO2A* loci on the other hand (Supplementary Note). The following studies were considered: EADB-core, Bonn, DemGene, EADI, GERAD, Gothenburg, STSA, TwinGene and all the case–control ADGC studies. Exact conditional results were combined across studies using an inverse-variance-weighted approach, as implemented in METAL.

To compare signals across the main, no-proxy and no-biobank meta-analyses, we performed two joint analyses using GCTA COJO. We jointly analyzed all index variants of the lead and secondary signals from the following: (1) the main and no-biobank meta-analyses and (2) the main and no-proxy meta-analyses. Analyses were restricted to loci with a secondary signal in at least one of the two meta-analyses being compared, while all variants were jointly tested across those loci. Both joint analyses were performed on the summary statistics of the main meta-analysis. From each joint analysis, we excluded one index variant from each pair in LD ($r^2 > 0.75$ in the EADB-core dataset, as computed by PLINK 2.0) to avoid collinearity. In each such pair, the index variant from the main meta-analysis was retained.

Rare-variant analysis

We extracted 65 protein-coding genes with the GENCODE basic tag (v43) located within the 16 new tier 1 loci, based on the start and end positions of each locus. Of these, 51 genes were available in the ADES-ADSP summary statistics for the comparison of gene-based rare-variant burdens between 12,652 AD cases and 8,693 controls[10] (Supplementary Table 8). These samples largely overlap with the ones included in the meta-analysis. We considered a significance threshold of $P < 9.8 \times 10^{-4}$, corresponding to a Bonferroni correction for 51 tests.

Single-cell enrichment analysis

We assessed the association between gene overexpression in specific cell types relative to average gene expression and gene associations with ADRD risk using the three-step process implemented in FUMA (v1.6.1)[36]. As input, we used the MAGMA gene-level results provided for the pathway analysis. We tested six models—one primary model and five sensitivity models—corresponding to the primary, common-only, no-APOE, larger-window, no-proxy and no-biobank gene-level summary statistics. We used gene expression data from six datasets of adult human brain tissue—GSE168408_Human_Prefrontal_Cortex_level2_Adult[37], GSE168408_Human_Prefrontal_Cortex_level1_Adult[37], PsychENCODE_Adult[38], DroNc_Human_Hippocampus[39], Allen_Human_MTG_level1 (middle temporal gyrus) and Allen_Human_MTG_level2 (ref. 40). The FUMA three-step process is further described in the Supplementary Note.

Pathway analyses

Pathway analyses were performed using MAGMA (v1.08)[41,42], with correction for the number of variants in each gene, LD between variants and LD between genes. LD was computed from the EADB-core dataset using high-quality imputed genotypes (imputation quality of >0.8) and setting as missing genotypes with genotype probability of <0.9. The measure of pathway enrichment was the MAGMA 'competitive' test (in which the association statistic for genes in the pathway is compared with those for all other protein-coding genes), as recommended in ref. 43. We applied the 'mean' test statistic, which sums the −log(*variant P*) across all genes. The total sample size (*n*) was used. A total of 8,034 gene sets were considered for analysis (Supplementary Note). Eight pathway analyses were performed using results from the following: (1) the main meta-analysis ('primary' model); (2) the main meta-analysis restricted to common variants (MAF > 0.01; 'common-only' model); (3) the main meta-analysis after excluding the *APOE* region (44–46 Mb on chromosome 19 in GRCh38; 'no-APOE' model); (4) the main meta-analysis, but mapping variants to genes using a 35-kb upstream and 10-kb downstream window ('larger-window' model); (5) the no-proxy meta-analysis ('no-proxy' model); (6) the no-proxy meta-analysis restricted to common variants ('common-only no-proxy' model); (7) the no-biobank meta-analysis ('no-biobank' model) and (8) the no-biobank meta-analysis restricted to common variants ('common-only no-biobank' model).

Phenome-wide association study

Using FUMA (v1.5.2)[44], we extracted all variants in LD ($r^2 > 0.75$) with the index variants of the new tier 1 and tier 2 loci in the EUR population from 1000 Genomes Phase 3. The index variant rs7481951 was not available in FUMA and was replaced by rs10833712, its best tag variant ($r^2 = 0.827$) according to TopLD[45]. We then extracted from the GWAS Catalog (e112_r2024-07-08) all traits associated with these variants at the GWS level.

We also extracted the results for the frequent (MAF > 1%) index variants of the tier 1 and tier 2 loci from the GWAS of 11 NPEs[17]. The samples included in the NPE GWAS largely overlap with the ones included in the ADRD meta-analysis.

Genetic correlation analyses

Using the no-proxy ADRD GWAS summary statistics, we computed with LDSC (v1.0.1)[21,46] the genetic correlation between ADRD and Parkinson's disease[47], frontotemporal dementia[48], frontotemporal lobar degeneration with neuronal inclusions of TAR DNA-binding protein 43 (ref. 49), Lewy body dementia[50], amyotrophic lateral sclerosis[51], educational attainment[52], stroke and its subtypes[53] and 11 NPEs[17]. For amyotrophic lateral sclerosis, frontotemporal lobar degeneration with neuronal inclusions of TAR DNA-binding protein 43, Lewy body dementia, Parkinson's disease and the stroke phenotypes, we used the harmonized version of the summary statistics available in the GWAS Catalog[54]. We used the precomputed 'eur_w_ld_chr' LD scores derived from 1000 Genomes European data. The analysis was restricted to HapMap 3 variants and excluded variants in the *APOE* locus, A/T or C/G alleles, variants with MAF of <1%, with duplicated rsID and indels. Correlation was considered significant at $P < 3.13 \times 10^{-3}$, corresponding to a Bonferroni correction for the 16 phenotypes for which genetic correlation could be computed. The no-proxy summary statistics were selected for this analysis to maximize power while avoiding biases that can arise when using genome-wide summary statistics from studies including proxy cases[14–16]. However, we assessed the sensitivity of the results using the main and no-biobank ADRD summary statistics.

PGS analyses

We constructed three PGSs using the tier 1 main and secondary signals (except *APOE*) detected in the main, no-proxy and no-biobank meta-analyses, respectively (Supplementary Table 15), and tested their association with the 11 NPEs in the ADC/NACC and ACT studies. Ordinal NPEs (amyloid-β plaques, CERAD score, arteriolosclerosis, atherosclerosis, cerebral amyloid angiopathy, LATE-NC and Lewy body) were dichotomized in two groups (none/mild versus moderate/severe),

as well as Braak neurofibrillary tangle stage (stages 0–3 versus stages 4–6). We first considered the GWS lead and secondary tier 1 signals detected in the main analysis as candidate signals. For each PGS (main, no-proxy and no-biobank), we then (1) selected only the candidate signals that were GWS in the respective meta-analysis and (2) selected the index variant of each of those signals in the respective meta-analysis. A total of 115, 91 and 65 variants were finally considered to compute the main, no-proxy and no-biobank PGS, respectively (Supplementary Note). These scores were computed for each individual with PLINK 2.0 using the function 'score' as the weighted average of the number of risk-increasing alleles for each variant, using dosages, and were scaled to obtain the PGS[55]:

$$\mathrm{PGS} = \frac{n}{\sum_{i=1}^{n} \log(\mathrm{OR}_i)} \times \sum_{i=1}^{n} \log(\mathrm{OR}_i) \times d_i$$

where n is the number of variants included in the score, and OR_i and d_i are the OR and dosage, respectively, of the risk allele of variant i. Each OR represents the impact of the variant on ADRD risk and was estimated by repeating the meta-analysis after excluding the biobanks (UKBB, FinnGen, deCODE and HUNT) and the studies overlapping with the NPE datasets (ACT, ADC/NACC, ROSMAP1 and CSDC). ORs were then estimated with GCTA COJO by performing for each score separately a joint analysis of all variants included, following the same pipeline as in the conditional and joint analyses described above (Supplementary Table 15). The effect size estimated for chr4:993555:G:T was considered for the tag variant chr4:973547:G:T. Associations between each binary NPE and each PGS were measured using logistic regression in the ADC/NACC and ACT studies separately. Models were adjusted for age at death, sex, number of *APOE* ε4 and ε2 alleles, ten PCs and centers. Effect sizes were then meta-analyzed across studies in METAL using a fixed-effects inverse-variance weighted approach. An association was considered significant if the P value was $<2.27 \times 10^{-3}$, corresponding to a Bonferroni correction for 22 tests (11 NPEs analyzed in two studies). Sensitivity analyses were conducted by additionally adjusting for the following: (1) AD diagnosis, coded in three categories (not impaired, AD/mild cognitive impairment and unknown/other dementia); (2) the three AD NPEs; (3) both AD diagnosis and the three AD NPEs or (4) AD NPEs and LATE-NC. For the Braak stage and CERAD score, we additionally tested the interaction between PGS and the number of *APOE* ε4 and ε2 alleles.

The OR for the association with the PGS measures the effect of carrying one additional average-risk allele. These ORs cannot be compared across the three scores because the average risk differs for each. To allow comparisons across scores, we divided each genetic score into quintiles and deciles based on the pooled distribution of PGS across all individuals from the ADC/NACC and ACT studies. We then computed in ADC/NACC the association of Braak stage and CERAD score with PGS deciles using the same model as the raw genetic scores, with the median quintile as the reference group. To allow comparison with the smaller ACT study, association results were also computed per quintiles in both ACT and ADC/NACC.

The discriminative performance of the PGS was assessed through three statistics as follows: (1) the AUC; (2) Nagelkerke's pseudo-R^2 (ref. 56) and (3) R^2 on the liability scale. AUC was computed for each study separately with the 'auc' function from the pROC (v1.18.5) R package[57], for both the null logistic model, including only age, sex, *APOE* ε4 and ε2, PCs and centers, and the full model, which additionally included the PGS. The AUCs between the two models were then compared with the DeLong's test[58] as implemented in the 'roc.test' function. The same pipeline was applied to compare AUCs across models, including the main, no-proxy and no-biobank PGSs. Nagelkerke pseudo-R^2 was computed with the 'nagelkerke' function from the R package rcompanion (v2.5.0)[59]. We also computed the variance explained by each PGS on the observed scale as the difference in the fraction of variance explained by a linear model under the full and null models. It was then transformed to the liability scale using the approach as described in ref. 60, with population prevalence values ranging from 0.1 to 0.9.

Reporting summary

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

Data availability

Summary statistics of the main, no-proxy and no-biobank meta-analyses are available through the European Bioinformatics Institute GWAS Catalog (https://www.ebi.ac.uk/gwas/) with accessions GCST90704646, GCST90704647 and GCST90704648 and through NIAGADS (https://dss.niagads.org/). Genetic scores are available in Supplementary Table 15 and through the PGS Catalog (https://www.pgscatalog.org/) with accessions PGS005389, PGS005390 and PGS005391.

Code availability

The software we used is referenced in the Methods and Supplementary Note, and the corresponding URLs are provided in the Supplementary Note. Additional scripts are available on Zenodo (https://doi.org/10.5281/zenodo.18324799)[61].

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Author contributions

EADB, EADI and Bonn consortia contributed to this study—C.B coordinated the project. V.G., K.A.M., M.V.F., P.G.K., M.T., C.v.D., R.F.-S., R.G., P.S-J., K.S., M.I., M. Hiltunen, R.S., W.v.d.F., O.A.A., A. Ruiz, A. Ramirez and J.-C.L. coordinated the consortia. C.B., A.C., N.A., S.J.v.d.L., M.M., K.P., F.K., B.G.-B., S.H., I.d.R., A.N., M.C.D., L. Kleineidam, J.L.B. and S.P. comprised the analysis team. S.J.v.d.L., O.P., A. Schneider, M.D., D.R., N. Scherbaum, J.D., S.R.-H., L.H., L.M.P., E.D., T.G., J. Wiltfang, S.H.-H., S. Moebus, M. Schmid, T.T., N. Scarmeas, O.D.-I., F.M., J.P.-T., M.J.B., P.P., R.S.-V., V.Á., M.B., P.G.-G., R.P., P. Mir, L.M.R., G.P.-R., J.M.G.-A., E.R.-R., H. Soininen, A.d.M., S. Mehrabian, J.H., M.V., N. Sandau, J.L., J.Q.T., Y.A.L.P., H.H., H. Seelaar, I. Ramakers, J. Papma, M. Hulsman, G.-J.B., C.G., H.T., A.U., G.P., V.G., M.L., L. Kilander, J. Williams, P.H., P.A., A.B., J.-F.D., G.N., C.D., F.P., O.H., S.D., E.G., J. Popp, D.G., B.A., P. Mecocci, V.S., L.P., A. Squassina, L.T., B.B., M.W., B.N., M. Spallazzi, D.S., I. Rainero, A.D., P.B., C.M., G.R., F.J., K.A.M., M.V.F., P.G.K., M.T., C.v.D., R.F.-S., R.G., P.S.-J., K.S., M.I., M. Hiltunen, R.S., W.v.d.F., O.A.A., A. Ruiz, A. Ramirez and J.-C.L. contributed to sample collection. J.-C.L and C.B. comprised the writing group. The CHARGE consortium contributed to this study—B.F., J.C.B, M.G.-G., V.G., L.L., E.B., T.H.M., C.D., S.D., M.F. and S. Seshadri coordinated the consortium. B.F., A.Y., M.S., X.J., A.M., J.C.B, J.J.H., H.Z., J.B., S. Sigurdsson, M.G., A.S.B., C. Sarnowski, C.v.D., C. Satizabal and Y.Q. performed data analyses. V.G., L.L., H.J.G., M.A.I., B.M.P., W.T.L., F.J.W., E.B., T.H.M., O.L.L., M.K.I., C.D., S.D., M.F. and S. Seshadri contributed to sample collection. B.F., M.S., X.J., J.C.B, C.D., S.D., M.F. and S. Seshadri comprised the CHARGE writing group. The ADGC consortium contributed to this study—A.C.N., F.R., N.K., C.Z., W.-P.L., N.R.W., Y.Z., J.J.F., Y.Y.L., R.M.S., T.I., O.V., K.L.L., B.W.K., L.-S.W., L.A.F., J.L.H., R.M., M.A.P.-V. and G.D.S. designed and conceived ADGC study. G.T., J.B.M., Y.E.S., X.Z., E.A., A.A., M.S.A., R.L.A., M.A., L.G.A., S.E.A., S. Asthana, C.S.A., C.T.B., R.C.B., L.L.B., T.G.B., J.T.B., G.W.B., D. Beekly, D.A. Bennett, J.B., T.D.B., D. Blacker, B.F.B., J.D. Bowen, A. Boxer, J.B.B., J.R.B., J.M.B., J.D. Buxbaum, N.J.C., L.B.C., C. Cao, C.S.C., C.M.C., R.M.C., M.M.C., M.-F.C., N.A.C., H.C.C., J.C., S. Craft, P.K.C., D.H.C., E.A.C., C. Cruchaga, M.L.C., M.C., E.D., B.D., P.L.D.J., C.D., J.D., M. Dick, D.W.D.,

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Competing interests

In the EADB, EADI and Bonn cohorts, A. Squassina received speaker fees from Johnson & Johnson. L.M.-P. reported personal fees from Biogen for consulting activities outside this work. In the PGC-ALZ consortium, H.Z. has served on scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, LabCorp, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics and Wave; has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk and Roche; and is a cofounder of Brain Biomarker Solutions in Gothenburg AB (BBS), part of the GU Ventures Incubator Program (outside the submitted study). G.S. has received honoraria for giving lectures at symposia sponsored by Eisai and Eli Lilly, and has served on advisory boards of Eisai, Eli Lilly and Roche. K.B. has served as a consultant and on advisory boards for AbbVie, AC Immune, ALZPath, AriBio, Beckman Coulter, BioArctic, Biogen, Eisai, Lilly, Moleac, Neurimmune, Novartis, Ono Pharma, Prothena, Quanterix, Roche Diagnostics, Sanofi and Siemens Healthineers; has served at data monitoring committees for Julius Clinical and Novartis; has given lectures, produced educational materials and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai and Roche Diagnostics; and is a cofounder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is part of the GU Ventures Incubator Program, outside the submitted study. S.K. has served on scientific advisory boards and as a speaker and/or consultant for Roche, Eli Lilly, Geras Solutions, Optoceutics, Biogen, Eisai, Merry Life, Triolab and BioArctic, unrelated to the present study. In the CHARGE consortium, B.M.P. serves on the Steering Committee of the Yale Open Data Access Project, supported by Johnson & Johnson. In the ADGC consortium, J.A.P. has received compensation for serving as a section editor for Springer Nature and as a grant reviewer with the Department of Defense and the Research Grants Council of Hong Kong. M.S.A. is an advisor to Eli Lilly. L.G.A. receives compensation as a consultant for Biogen, Two Labs, IQVIA, National Institutes of Health (NIH), Florida Department of Health, NIH Biobank, Eli Lilly, GE Healthcare and Eisai; has received compensation for lectures and related activities from AAN, MillerMed, AiSM, and Health and Hospitality, and has received travel and meeting support from the Alzheimer's Association. She also participates on data safety monitoring or advisory boards for IQVIA, NIA R01 AG061111, the UAB Nathan Shock Center and the New Mexico Exploratory ADRC; has received compensation for leadership roles in the Medical Science Council Alzheimer Association Greater IN Chapter, the Alzheimer Association Science Program Committee and the FDA PCNS Advisory Committee; holds stock or stock options Cassava Neurosciences and Golden Seeds; and has received materials support from AVID Pharmaceuticals, Life Molecular Imaging and Roche Diagnostics. S.E.A. has received honoraria and/or travel expenses for lectures from AbbVie, Eisai and Biogen and has served on scientific advisory boards of Cortexyme; has received consulting fees from Athira, Cassava, Cognito Therapeutics, EIP Pharma and Orthogonal Neuroscience; and has received research grant support from NIH, the Alzheimer's Association, the Alzheimer's Drug Discovery Foundation, AbbVie, Amylyx, EIP Pharma, Merck, Janssen/Johnson & Johnson, Novartis and vTv. S. Asthana reported receiving grants from the National Institute on Aging/NIH, Genentech, Merck, Toyama Chemical and Lundbeck outside the submitted study. L.L.B. has served as deputy editor for 'Alzheimer's and Dementia' for the Alzheimer's Association. D. Blacker is a consultant for Biogen. B.F.B. has received institutional support from LBDA; is a member of the scientific advisory boards of the Tau Consortium (supported by the Rainwater Charitable Foundation), AFTD, LBDA and GE Healthcare; is a member of the Data Safety Monitoring Board of a trial involving mesenchymal stem cells in multiple system atrophy. J.D.B. has received honoraria for serving on the scientific advisory board and speaker's bureau of Biogen, Celgene, EMD Serono, Genentech and Novartis; has received research support from AbbVie, Alexion, Alkermes, Biogen, Celgene, Sanofi Genzyme, Genentech, Novartis and TG Therapeutics. A.L.B. has received financial support from NIH, the Association for Frontotemporal Degeneration, the Bluefield Project, the Rainwater Charitable Foundation, Regeneron, Eisai and Biogen; and has served as a paid consultant for AGTC, Alector, Amylyx, AviadoBio, Arkuda, Arrowhead, Arvinas, Eli Lilly, Genentech, LifeEdit, Merck, Modalis, Oligomerix, Oscotec, Transposon and Wave. J.M.B. is compensated as a consultant for Stage 2 Innovations and has received honoraria and travel support for speaking from AstraZeneca. J.D. Buxbaum is a consultant to BridgeBio and Rumi; holds a patent for IGF-1 in Phelan-McDermid syndrome; holds an honorary professorship from Aarhus University; receives research support from Takeda and Oryzon; and is a journal editor at Springer Nature. C. Cao has a patent pending for melatonin-insulin-THC treatment and serves as a scientific consultant for MegaNano Biotech. C.M.C. has received grants from the NIH, Eisai, Eli Lilly, Veterans Affairs; has received

nonfinancial support from Amarin; has received data safety monitoring board/travel/advisory board honoraria from Alzheimer's Association, NIH and American Federation for Aging Research Beeson Program. J.C. is currently employed as a senior scientist at Takeda Pharmaceuticals; the company did not influence the study design, analyses or interpretation of the results presented in this study. C. Cruchaga has received research support from GSK and Eisai, is a member of the advisory boards of Vivid Genomics and Circular Genomics, and owns stock. D.W.D. is an editorial board member for 'Acta Neuropathologica', 'Brain', 'Brain Pathology', 'Neuropathology and Applied Neurobiology', 'Annals of Neurology' and 'Neuropathology'; is an editor for the 'International Journal of Clinical and Experimental Pathology' and the 'American Journal of Neurodegenerative Disease'; and receives support from the Mangurian Foundation and the Rainwater Charitable Foundation. N.E.-T. receives research support from the NIH; is a member of multiple scientific advisory boards, including the FHS Executive Committee, Cytox and the NIH TREAT-AD Consortium External Advisory Board Member; has patents pending for 'Human monoclonal antibodies against amyloid β protein and their use as therapeutic agents' and RNAi against targets in Progressive Supranuclear Palsy; is an editorial board member for the 'American Journal of Neurodegenerative Diseases' and 'Alzheimer's and Dementia'; and receives research support from the Florida Health Ed and Ethel Moore Alzheimer's Disease Research Program and an Alzheimer's Association Zenith Award. T.M.F. has received honoraria and travel support from the External Advisory Boards of Alzheimer's Disease Research Centers that might also be a site for the LEADS study. D.R.G. serves on Data Safety Monitoring Boards for Cognition Therapeutics and Proclara Biosciences and is an editor of 'Alzheimer's Research and Therapy'. B.G. has consulted for Piramal Imaging. A.M.G. is a member of the scientific advisory boards/scientific research boards of Genentech and Muna Therapeutics. She has also served as a consultant for Merck. N.R.G.-R. has received royalties for an article in UpToDate and research support for multicenter studies at Eli Lilly, Biogen and AbbVie. J. Hardy is supported by the UK Dementia Research Institute, which receives its funding from DRI, supported by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK; and is also supported by the MRC, Wellcome Trust, the Dolby Family Fund and the National Institute for Health Research University College London Hospitals Biomedical Research Centre. T.J.H. is a member of the scientific advisory board for Vivid Genomics and serves on the Editorial Boards for 'Alzheimer's & Dementia' and 'Alzheimer's & Dementia: Translational Research & Clinical Interventions'. L.S.H. is the web editor for 'JAMA Neurology'. B.T.H. has a family member who works at Novartis and owns stock in Novartis; serves on the scientific advisory board of Dewpoint and owns stock; and serves on a scientific advisory board or is a consultant for AbbVie, Aprinoia Therapeutics, Arvinas, Avrobio, Axial, Biogen, BMS, Cure Alz Fund, Cell Signaling, Eisai, Genentech, Ionis, Latus, Novartis, Sangamo, Sanofi, Seer, Takeda, the US Department of Justice, Vigil, Voyager; and receives research support for his laboratory from research grants from the NIH, Cure Alzheimer's Fund, Tau Consortium and the JPB Foundation, and through sponsored research agreements from Abbvie, BMS and Biogen. G.P.J. was the 2022 Past President of the American Society of Human Genetics. J.H.K. has been a consultant for Biogen. E.B.L. receives royalties from contributions to UpToDate. J.B.L. is a member of the scientific advisory board of Vaxxinity and has received grant support from Biogen and GE Healthcare. A.I.L. is a founder of EmTheraPro. R.B.L. has received research support from the NIH, the FDA and the National Headache Foundation; serves as consultant, advisory board member or has received honoraria or research support from AbbVie/Allergan, Amgen, Biohaven, Dr. Reddy's Laboratories (Promius), electroCore, Eli Lilly, GlaxoSmithKline, Lundbeck, Merck, Novartis, Teva, Vector and Vedanta Research; receives royalties from Wolff's Headache, eighth edition, and Informa; and holds stock in Biohaven and Manistee. D.C.M. receives NIH funding; is the inventor of the FCI-SF and the UAB Research Foundation; owns the FCI-SF through copyright and trademark; has previously received royalty and consulting income from the UAB Research Foundation licensed use and sale of the FCI-SF; and is currently a consultant on an unaffiliated NIH grant using the FCI-SF. A.V.M. is a council member of the Alzheimer's Association International Research Grants Program, on the steering committee of the Alzheimer's Disease Cooperative Study, and on the editorial boards of 'Alzheimer's and Dementia: Translational Research and Clinical Interventions' and the 'Journal of Neuro-ophthalmology'. B.L.M. has received grant support from NIH, the Bluefield Project and the Rainwater Charitable Foundation; has received royalties from books published by Cambridge University Press, Elsevier, Guilford Publications, Johns Hopkins Press, Oxford University Press and Taylor & Francis Group; has received honorarium for serving as a member of the scientific advisory board of the Alzheimer's Disease Research Center at Massachusetts General Hospital, Stanford University and the University of Washington; and has received consulting fees from Genworth. 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Additional information

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☒	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection
Data analysis	The software we used is referenced in the Online Methods and Supplementary Information, and the corresponding URLs are provided in the Supplementary Information Bedtools: https://bedtools.readthedocs.io BCFtools: http://samtools.github.io/bcftools/bcftools.html Gene Ontology (downloaded from the NCBI on June 19th, 2023): http://geneontology.org/docs/download-ontology/ Reactome (July 17th, 2023): https://reactome.org/download-data KEGG and Pathway Interaction Database (PID) pathways (MSigDB v2023.1.Hs updated March 2023): https://www.gsea-msigdb.org/gsea/msigdb/index.jsp LocusZoom: https://github.com/statgen/locuszoom-standalone Sanger imputation server: https://imputation.sanger.ac.uk/ Michigan imputation server: https://imputationserver.sph.umich.edu/ SNPTEST 2.5.4-beta1, 2.5.4-beta3, and 2.5.6: https://www.chg.ox.ac.uk/~gav/snptest/ FlashPCA2: https://github.com/gabraham/flashpca EIGENSOFT: https://www.hsph.harvard.edu/alkes-price/software/ PLINK 1.9: https://www.cog-genomics.org/plink/ PLINK 2.0: https://www.cog-genomics.org/plink/2.0/ GMMAT 1.4.2: https://cran.r-project.org/web/packages/GMMAT/index.html SAIGE v.0.35.8.3 and 1.0.9: https://saigegit.github.io/SAIGE-doc/ regenie v2.2.4: https://rgcgithub.github.io/regenie/

GCTA-COJO: https://yanglab.westlake.edu.cn/software/gcta/#COJO
FUMA v1.5.2 and v1.6.1: https://fuma.ctglab.nl/
UCSC LiftOver: https://genome.ucsc.edu/cgi-bin/hgLiftOver
McCarthy group tools: https://www.well.ox.ac.uk/~wrayner/tools/
Human Genome Diversity Project (HGDP) reference panel: http://csg.sph.umich.edu/chaolong/LASER/
Minimac4: https://genome.sph.umich.edu/wiki/Minimac4
LD Score Regression: https://github.com/bulik/ldsc
METAL v2020-05-05: https://github.com/statgen/METAL/tree/master
LDstore 2: http://www.christianbenner.com/
emeraLD: http://github.com/statgen/emeraLD
GWAS catalog version e112_r2024-07-08: https://www.ebi.ac.uk/gwas/
VEP: https://www.ensembl.org/info/docs/tools/vep/index.html
PhenoGram: https://ritchielab.org/software/phenogram-downloads
ADES-ADSP summary statistics: https://doi.org/10.5281/zenodo.6818051
MAGMA v1.08: https://cncr.nl/research/magma/
ontologyIndex R package: https://cran.r-project.org/web/packages/ontologyIndex/index.html
qqman R package: https://cran.r-project.org/web/packages/qqman/index.html
GenABEL R package (estlambda function): https://github.com/GenABEL-Project/GenABEL
rmeta R package (forestplot function): https://cran.r-project.org/web/packages/rmeta/index.html
ggplot2 R package: https://cran.r-project.org/web/packages/ggplot2/index.html
1000 Genomes data, Phase 3: https://www.internationalgenome.org/data
pROC R package: https://cran.r-project.org/web/packages/pROC/index.html
rcompanion R package: https://cran.r-project.org/web/packages/rcompanion/index.html

Additional scripts are available through Zenodo (https://doi.org/10.5281/zenodo.18324799).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Summary statistics of the main, no-proxy and no-biobank meta-analyses are available through the European Bioinformatics Institute GWAS Catalog (https://www.ebi.ac.uk/gwas/) under accessions GCST90704646, GCST90704647 and GCST90704648 and through NIAGADS (https://dss.niagads.org/). Genetic scores are available in Supplementary Table 15 and through the PGS catalog (https://www.pgscatalog.org/) under accessions PGS005389, PGS005390 and PGS005391.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Concordance check between clinical and genetic sex was performed. Statistics on sex are reported in Supplementary Tables 1 and 16 Main GWAS analyses were not adjusted on sex but Supplementary Table 24 provides results after adjustment on sex for the index variants detected in the main meta-analysis
Reporting on race, ethnicity, or other socially relevant groupings	The samples were of European ancestry, and the analyses were adjusted on principal components measuring ancestry. The methods used to define ancestry differ for each study (principal component analyses on genetic data, self-reported ancestry...). Deatils are provided for each study in the Supplementary Materials or in the provided references.
Population characteristics	Summary statistics on age, sex and APOE status are provided for each study in Supplementary Tables 1 and 16.
Recruitment	Individuals were recruited from a lot of different centers, with the different recruitement strategies detailed in the Supplementary Material. This includes recruitment from clinics, nursing homes, disease registries and hospital, but also adult volunteers. Cases were recruited according to clinical diagnosis and defined as probable AD cases with a potential risk of mis-diagnosis (estimated between 10 and 20% in the litterature). A large part of the controls did not have any follow-up, and not all of them were screened for dementia (for example in biobanks) so some may have AD or may develop AD later. In biobanks such as the UK biobank, participants are healthier than in the general population. Additionally, the use of proxy-cases can lead to some biases in genetic analyses performed on genome-wide summary statistics. Sensitivity analyses were thus conducted after exclusion of proxy and biobank samples.
Ethics oversight	The appropriate review boards from the ADGC, Bonn, CHARGE, EADB, EADI, GERAD, GR@ACE/DEGESCO and PGC-ALZ reviewed and approved the study protocol.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No sample-size calculation was performed, we maximized the number of European-ancestry samples with genotyping data and AD status
Data exclusions	A standard quality control of the genetic data was performed in each study, leading to the exclusion of some variants ans some samples. The quality control is detailed in the Supplementary Material or references are provided.
Replication	We did not attempt to replicate the new hits in an independent sample, as we included all the studies in the discovery step. Sensitivity analyses were performed by excluding proxy-samples or biobank samples. Forest plots are provided to assess heterogeneity of the hit results across studies.
Randomization	There was no allocation in experimental groups as we used ADRD (proxy-) cases and controls from retrospective studies.
Blinding	Investigators were blinded during the genotyping process but not during the quality controls, as some of the quality controls are based on the case/control status

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*