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New insights into the genetic etiology of Alzheimer's disease and related dementias

Characterization of the genetic landscape of Alzheimer's disease (AD) and related dementias (ADD) provides a unique opportunity for a better understanding of the associated pathophysiological processes. We performed a two-stage genome-wide association study totaling 111,326 clinically diagnosed/'proxy' AD cases and 677,663 controls. We found 75 risk loci, of which 42 were new at the time of analysis. Pathway enrichment analyses confirmed the involvement of amyloid/tau pathways and highlighted microglia implication. Gene prioritization in the new loci identified 31 genes that were suggestive of new genetically associated processes, including the tumor necrosis factor alpha pathway through the linear ubiquitin chain assembly complex. We also built a new genetic risk score associated with the risk of future AD/dementia or progression from mild cognitive impairment to AD/dementia. The improvement in prediction led to a 1.6- to 1.9-fold increase in AD risk from the lowest to the highest decile, in addition to effects of age and the *APOE* ϵ 4 allele.

AD is the most common form of dementia. The heritability is high, estimated to be between 60% and 80%¹. This strong genetic component provides an opportunity to determine the pathophysiological processes in AD and to identify new biological features, new prognostic/diagnostic markers and new therapeutic targets through translational genomics. Characterizing the genetic risk factors in AD is therefore a major objective; with the advent of high-throughput genomic techniques, a large number of putative AD-associated loci/genes have been reported². However, much of the underlying heritability remains unexplained. Hence, increasing the sample size of genome-wide association studies (GWASs) is an obvious solution that has already been used to characterize new genetic risk factors in other common, complex diseases (e.g., diabetes).

GWAS meta-analysis

The European Alzheimer & Dementia Biobank (EADB) consortium brings together the various European GWAS consortia already working on AD. A new dataset of 20,464 clinically diagnosed AD cases and 22,244 controls has been collated from 15 European countries. The EADB GWAS results were meta-analyzed with a proxy-AD GWASs of the UK Biobank (UKBB) dataset. The UKBB's proxy-AD designation is based on questionnaire data in which individuals are asked whether their parents had dementia. This method has been used successfully in the past³ but is less specific than a clinical or pathological diagnosis of AD; hence, we will refer to these cases as proxy AD and related dementia (proxy-ADD). EADB stage I (GWAS meta-analysis) was based on 39,106 clinically diagnosed AD cases, 46,828 proxy-ADD cases (as defined in the Supplementary Note), 401,577 controls (Supplementary Tables 1 and 2) and 21,101,114 variants that passed our quality control (Fig. 1; see Supplementary Fig. 1 for the quantile–quantile plot and genomic inflation factors). We selected all variants with a *P* value below 1×10^{-5} in stage I. We defined nonoverlapping regions around these variants, excluded the region corresponding to *APOE* and examined the remaining variants in a large follow-up sample that included AD cases and controls from the ADGC, FinnGen and CHARGE consortia (stage II; 25,392 AD cases and 276,086 controls). A signal was considered as significant on the genome-wide level if it (1) was nominally associated ($P \leq 0.05$) in stage II, (2) had the same direction of association in the stage I and II analyses and (3) was associated with the ADD risk with

$P \leq 5 \times 10^{-8}$ in the stage I and stage II meta-analysis. Furthermore, we applied a PLINK clumping procedure⁴ to define potential independent hits within the stage I results (Methods). After validation by conditional analyses (Supplementary Note and Supplementary Tables 3 and 4), this approach enabled us to define 39 signals in 33 loci already known to be associated with the risk of developing ADD^{5–10} and identify 42 loci defined as new at the time of analysis (Tables 1 and 2, Supplementary Table 5 and Supplementary Figs. 2–29). Of the 42 new loci, 17 had $P \leq 5 \times 10^{-8}$ in stage I and 25 were associated with $P \leq 5 \times 10^{-8}$ after follow-up (stage I and stage II meta-analysis, including the ADGC, CHARGE and FinnGen data). We also identified 6 loci with $P \leq 5 \times 10^{-8}$ in the stage I and stage II analysis but with $P > 0.05$ in stage II (Supplementary Table 6). It is noteworthy that the magnitude of the associations in stage I did not change substantially if we restricted the analysis to clinically diagnosed AD cases (Supplementary Table 7 and Supplementary Fig. 30). Similarly, none of the signals observed appeared to be especially driven by the UKBB data (Supplementary Table 7 and Supplementary Figs. 2–29). Nine of these loci (*APP*, *CCDC6*, *GRN*, *LILRB2*, *NCK2*, *TNIP1*, *TMEM106B*, *TSPAN14* and *SHARPIN*) were recently reported in three articles using part of the GWAS data included in our study^{11–13}. We also generated a detailed analysis of the human leukocyte antigen (*HLA*) locus on the basis of the clinically diagnosed AD cases (Supplementary Tables 8 and 9, Supplementary Figs. 31 and 32 and Supplementary Note).

Genetic overlap with other neurodegenerative diseases

We tested the association of the lead variants within our new loci with the risk of developing other neurodegenerative diseases or AD-related disorders (Supplementary Fig. 33 and Supplementary Tables 10–12). We also performed more precise colocalization analyses (using Coloc R package, <https://cran.r-project.org/web/packages/coloc/index.html>) for five loci known to be associated with Parkinson's disease (*IDUA* and *CTSB*), types of frontotemporal dementia (*TMEM106B* and *GRN*) and amyotrophic lateral sclerosis (*TNIP1*) (Supplementary Tables 13 and 14). The *IDUA* signal for Parkinson's disease was independent of the signal in ADD (coloc posterior probability (PP)₃ = 99.9%), but we were not able to determine whether the *CTSB* signals colocalized. The *TMEM106B* and *GRN* signals in frontotemporal lobar degeneration with TAR DNA-binding protein (TDP-43) inclusions (frontotemporal lobar

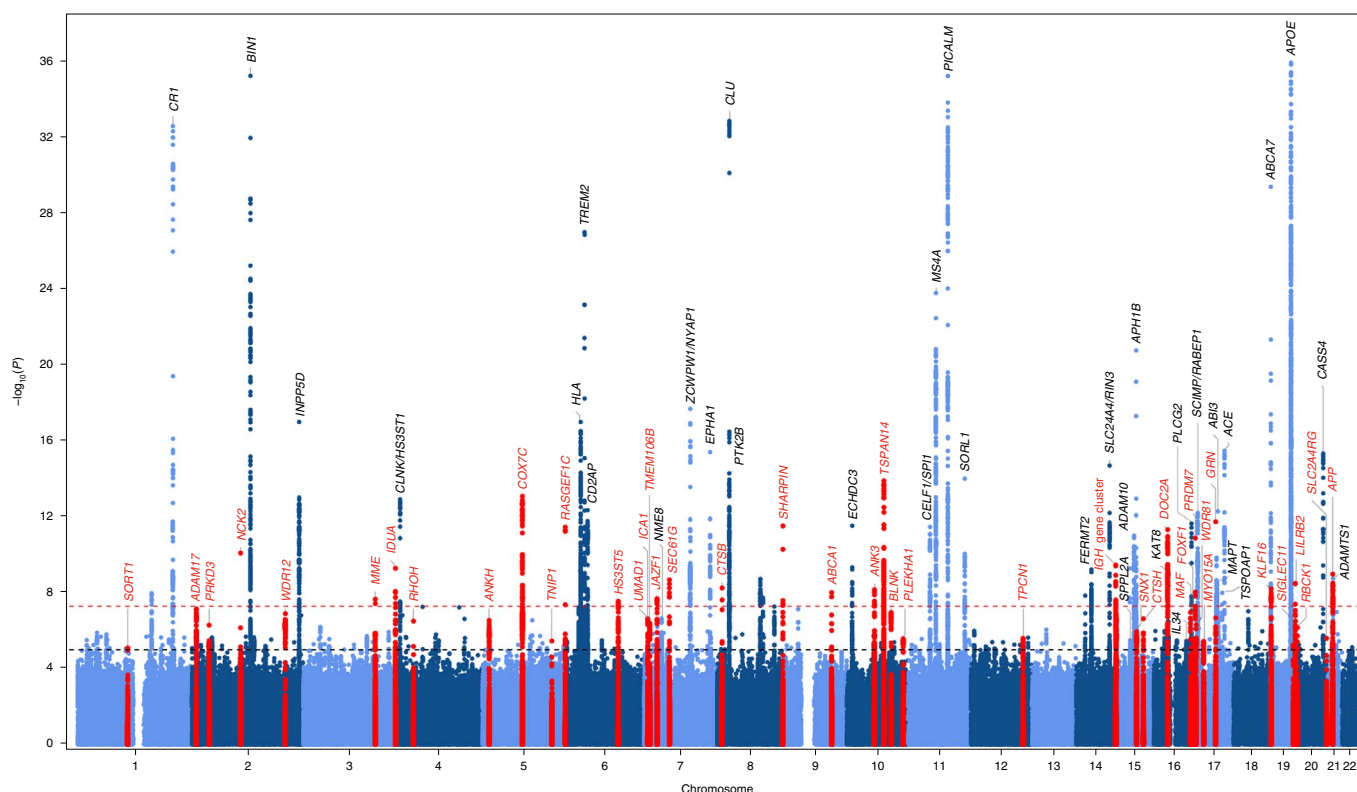


Fig. 1 | Manhattan plot of the stage I results. P values are two-sided raw P values derived from a fixed-effect meta-analysis. Variants with a P value below 1×10^{-36} are not shown. Loci with a genome-wide significant signal are annotated (known loci in black and new loci in red). Variants in new loci are highlighted in red. The red dotted line represents the genome-wide significance level ($P = 5 \times 10^{-8}$), and the black dotted line represents the suggestive significance level ($P = 1 \times 10^{-5}$).

degeneration TDP) probably share causal variants with ADD (coloc $PP4 = 99.8\%$ and coloc $PP4 = 80.1\%$, respectively). Lastly, we were not able to determine whether the *TNIP1* signals colocalized for ADD and amyotrophic lateral sclerosis.

Pathway analyses

Next, we sought to perform a pathway enrichment analysis on the stage I association results to gain better biological understanding of this newly expanded genetic landscape for ADD. Ninety-three gene sets were still statistically significant after correction for multiple testing ($q \leq 0.05$; Methods and Supplementary Table 15). As described previously, the most significant gene sets are related to amyloid and tau⁵; other significant gene sets are related to lipids, endocytosis and immunity (including macrophage and microglial cell activation). When restricting this analysis to the meta-analysis based on the clinically diagnosed AD cases, 54 gene sets were significant ($q \leq 0.05$). Of these 54 gene sets, 33 reached $q \leq 0.05$ in the stage I analysis and all reached $P \leq 0.05$. This indicates that the inclusion of proxy-ADD cases does not cause disease-relevant biological information to be missed and underlines the additional power of this type of analysis.

We next performed a single-cell expression enrichment analysis by using the average gene expression per nucleus (Av. Exp.) data in the human Allen Brain Atlas (49,495 nuclei from 8 human brains). Only the microglial expression reached a high level of significance ($P = 1.7 \times 10^{-8}$; Supplementary Table 16); greater expression corresponded to a more significant association with ADD. After adjusting for microglial Av. Exp., the remaining associations became nonsignificant; this indicates that microglial Av. Exp. drives all the other cell-type associations. These results were observed whatever the brain region studied (Supplementary Table 16). A similar result

was observed using a mouse single-cell dataset¹⁴ (Supplementary Table 17 and Supplementary Note).

Lastly, we looked at whether the relationship between an elevated microglia Av. Exp. and a genetic association with the ADD risk was specific to particular biological processes (Supplementary Table 18) by analyzing the interaction between microglia Av. Exp. and pathway membership in MAGMA¹⁵. Of the five most significant interaction signals ($q \leq 10^{-3}$), two were directly associated with endocytosis processes (GO:0006898 and GO:0031623); this suggested a functional relationship between microglia and endocytosis, which is known to be involved in phagocytosis (Supplementary Table 18). It is noteworthy that we also detected an interaction between GO:1902991 (regulation of amyloid precursor protein (APP) catabolic process) and the gene expression level in microglia ($q = 1.4 \times 10^{-3}$; Supplementary Table 18). Even though these data suggest a functional relationship between microglia and APP/amyloid beta ($A\beta$) peptide pathways, this observation reinforces the likely involvement of microglial endocytosis in AD, a mechanism that is also strongly involved in APP metabolism¹⁶. Of note, there are overall similarities in the interaction effects of human and mouse microglia expression with genes in biological pathways of relevance to the AD genetic risk (Supplementary Table 18 and Supplementary Note).

Gene prioritization

We next attempted to identify the genes most likely to be responsible for the association signal with ADD at each new locus. To this end, we studied the downstream effects of ADD-associated variants on molecular phenotypes (i.e., expression, splicing, protein expression, methylation and histone acetylation) in various *cis*-quantitative trait locus (*cis*-QTL) catalogues from AD-relevant tissues, cell types and brain regions. We investigated the genetic

Table 1 | Summary of association results in the stage I and stage II analysis for known loci with a genome-wide significant signal

Variant ^a	Chromosome	Position ^b	Gene ^c	Known locus	Minor/major allele	MAF ^d	OR ^e	95% CI	P value
rs679515	1	207577223	CR1	CR1	T/C	0.188	1.13	1.11-1.15	7.2 × 10 ⁻⁴⁶
rs6733839	2	127135234	BIN1	BIN1	T/C	0.389	1.17	1.16-1.19	6.1 × 10 ⁻¹¹⁸
rs10933431	2	233117202	INPP5D	INPP5D	G/C	0.234	0.93	0.92-0.95	3.6 × 10 ⁻¹⁸
rs6846529	4	11023507	CLNK	CLNK/HS3ST1	C/T	0.283	1.07	1.05-1.08	2.2 × 10 ⁻¹⁷
rs6605556	6	32615322	HLA-DQA1	HLA	G/A	0.161	0.91	0.90-0.93	7.1 × 10 ⁻²⁰
rs10947943	6	41036354	UNC5CL	TREM2	A/G	0.142	0.94	0.93-0.96	1.1 × 10 ⁻⁹
rs143332484	6	41161469	TREM2	TREM2	T/C	0.013	1.41	1.32-1.50	2.8 × 10 ⁻²⁵
rs75932628	6	41161514	TREM2	TREM2	T/C	0.003	2.39	2.09-2.73	2.5 × 10 ⁻³⁷
rs60755019	6	41181270	TREML2	TREM2	G/A	0.004	1.55	1.33-1.80	2.1 × 10 ⁻⁸
rs7767350	6	47517390	CD2AP	CD2AP	T/C	0.271	1.08	1.06-1.09	7.9 × 10 ⁻²²
rs6966331	7	37844191	EPDR1	NME8	T/C	0.349	0.96	0.94-0.97	4.6 × 10 ⁻¹⁰
rs7384878	7	100334426	SPDYE3	ZCWPW1/NYAP1	C/T	0.31	0.92	0.91-0.94	1.1 × 10 ⁻²⁶
rs11771145	7	143413669	EPHA1	EPHA1	A/G	0.348	0.95	0.93-0.96	3.3 × 10 ⁻¹⁴
rs73223431	8	27362470	PTK2B	PTK2B	T/C	0.369	1.07	1.06-1.08	4.0 × 10 ⁻²²
rs11787077	8	27607795	CLU	CLU	T/C	0.392	0.91	0.90-0.92	1.7 × 10 ⁻⁴⁴
rs7912495	10	11676714	USP6NL	ECHDC3	G/A	0.462	1.06	1.05-1.08	9.7 × 10 ⁻¹⁹
rs10437655	11	47370397	SPI1	CELF1/SPI1	A/G	0.399	1.06	1.04-1.07	5.3 × 10 ⁻¹⁴
rs1582763	11	60254475	MS4A4A	MS4A	A/G	0.371	0.91	0.90-0.92	3.7 × 10 ⁻⁴²
rs3851179	11	86157598	EED	PICALM	T/C	0.358	0.9	0.89-0.92	3.0 × 10 ⁻⁴⁸
rs74685827	11	121482368	SORL1	SORL1	G/T	0.019	1.19	1.13-1.25	2.8 × 10 ⁻¹¹
rs11218343	11	121564878	SORL1	SORL1	C/T	0.039	0.84	0.81-0.87	1.4 × 10 ⁻²¹
rs17125924	14	52924962	FERMT2	FERMT2	G/A	0.089	1.1	1.07-1.12	8.3 × 10 ⁻¹⁶
rs7401792	14	92464917	SLC24A4	SLC24A4/RIN3	G/A	0.371	1.04	1.02-1.05	4.8 × 10 ⁻⁸
rs12590654	14	92472511	SLC24A4	SLC24A4/RIN3	A/G	0.328	0.93	0.92-0.95	4.2 × 10 ⁻²¹
rs8025980	15	50701814	SPPL2A	SPPL2A	G/A	0.345	0.96	0.94-0.97	1.3 × 10 ⁻⁸
rs602602	15	58764824	MINDY2	ADAM10	A/T	0.28	0.94	0.93-0.96	2.1 × 10 ⁻¹⁵
rs117618017	15	63277703	APH1B	APH1B	T/C	0.144	1.11	1.09-1.13	2.2 × 10 ⁻²⁵
rs889555	16	31111250	BCKDK	KAT8	T/C	0.281	0.95	0.94-0.97	2.0 × 10 ⁻¹¹
rs4985556	16	70660097	IL34	IL34	A/C	0.115	1.07	1.05-1.09	6.0 × 10 ⁻¹⁰
rs12446759	16	81739398	PLCG2	PLCG2	G/A	0.403	0.95	0.94-0.96	1.2 × 10 ⁻¹³
rs72824905	16	81908423	PLCG2	PLCG2	G/C	0.008	0.74	0.68-0.81	8.5 × 10 ⁻¹²
rs7225151	17	5233752	SCIMP	SCIMP/RABEP1	A/G	0.124	1.08	1.05-1.10	4.1 × 10 ⁻¹³
rs199515	17	46779275	WNT3	MAPT	G/C	0.219	0.94	0.93-0.96	9.3 × 10 ⁻¹³
rs616338	17	49219935	ABI3	ABI3	T/C	0.012	1.32	1.23-1.42	2.8 × 10 ⁻¹⁴
rs2526377	17	58332680	TSPOAP1	TSPOAP1	G/A	0.445	0.95	0.94-0.97	1.6 × 10 ⁻¹²
rs4277405	17	63471557	ACE	ACE	C/T	0.384	0.94	0.93-0.95	8.8 × 10 ⁻²⁰
rs12151021	19	1050875	ABCA7	ABCA7	A/G	0.336	1.1	1.09-1.12	1.6 × 10 ⁻³⁷
rs6014724	20	56423488	CASS4	CASS4	G/A	0.09	0.89	0.87-0.91	4.1 × 10 ⁻²¹
rs2830489	21	26775872	ADAMTS1	ADAMTS1	T/C	0.281	0.95	0.94-0.97	1.7 × 10 ⁻¹⁰

P values are two-sided raw P values derived from a fixed-effect meta-analysis. CI, confidence interval; OR, odds ratio; MAF, minor allele frequency. ^aReference single-nucleotide polymorphism (SNP) (rs) number, according to dbSNP build 153. ^bGRCh38 assembly. ^cNearest protein-coding gene according to GENCODE release 33. ^dWeighted average MAF across all discovery studies. ^eApproximate OR calculated with respect to the minor allele.

colocalization between association signals for the ADD risk and those for the molecular phenotypes and the association between the ADD risk and these phenotypes by integrating *cis*-QTL information into our ADD GWAS. Moreover, we considered the lead variant annotation (the allele frequency, protein-altering effects and nearest protein-coding gene) and a genome-wide, high-content short interfering RNA screen for APP metabolism¹⁷. Based on this evidence, we developed a systematic gene prioritization strategy

that yielded a total weighted score of between 0 and 100 for each gene (Supplementary Fig. 34 and Supplementary Note). This score was used to compare and prioritize genes in the new loci within 1 Mb upstream and 1 Mb downstream of the lead variants. Genes either were ranked as tier 1 (greater likelihood of being the causal risk gene responsible for the ADD signal) or tier 2 (lower likelihood and the absence of a minimum level of evidence as a causal risk gene) or were not ranked.

Table 2 | Summary of association results in the stage I and stage II analysis for new loci at the time of analysis with a genome-wide significant signal

Locus number	Variant ^a	Chromosome	Position ^b	Gene ^c	Minor/major allele	MAF ^d	OR ^e	95% CI	P value
1	rs141749679	1	109345810	<i>SORT1</i>	C/T	0.004	1.38	1.24-1.54	7.5 × 10 ⁻⁹
2	rs72777026	2	9558882	<i>ADAM17</i>	G/A	0.144	1.06	1.04-1.08	2.7 × 10 ⁻⁸
3	rs17020490	2	37304796	<i>PRKD3</i>	C/T	0.145	1.06	1.04-1.08	3.3 × 10 ⁻⁹
4	rs143080277	2	105749599	<i>NCK2</i>	C/T	0.005	1.47	1.33-1.63	2.1 × 10 ⁻¹³
5	rs139643391	2	202878716	<i>WDR12</i>	T/TC	0.131	0.94	0.92-0.96	1.1 × 10 ⁻⁸
6	rs16824536	3	155069722	<i>MME</i>	A/G	0.054	0.92	0.89-0.95	3.6 × 10 ⁻⁸
6	rs61762319	3	155084189	<i>MME</i>	G/A	0.026	1.16	1.11-1.21	2.2 × 10 ⁻¹¹
7	rs3822030	4	993555	<i>IDUA</i>	G/T	0.429	0.95	0.94-0.96	8.3 × 10 ⁻¹²
8	rs2245466	4	40197226	<i>RHOH</i>	G/C	0.343	1.05	1.03-1.06	1.2 × 10 ⁻⁹
9	rs112403360	5	14724304	<i>ANKH</i>	A/T	0.073	1.09	1.06-1.12	2.3 × 10 ⁻⁹
10	rs62374257	5	86927378	<i>COX7C</i>	C/T	0.23	1.07	1.05-1.09	1.4 × 10 ⁻¹⁵
11	rs871269	5	151052827	<i>TNIP1</i>	T/C	0.326	0.96	0.95-0.97	8.7 × 10 ⁻⁹
12	rs113706587	5	180201150	<i>RASGEF1C</i>	A/G	0.11	1.09	1.07-1.12	2.2 × 10 ⁻¹⁶
13	rs785129	6	114291731	<i>HS3ST5</i>	T/C	0.35	1.04	1.03-1.06	2.4 × 10 ⁻⁹
14	rs6943429	7	7817263	<i>UMAD1</i>	T/C	0.42	1.05	1.03-1.06	1.0 × 10 ⁻¹⁰
15	rs10952097	7	8204382	<i>ICA1</i>	T/C	0.114	1.07	1.05-1.10	6.8 × 10 ⁻⁹
16	rs13237518	7	12229967	<i>TMEM106B</i>	A/C	0.411	0.96	0.94-0.97	4.9 × 10 ⁻¹¹
17	rs1160871	7	28129126	<i>JAZF1</i>	G/GTCTT	0.222	0.95	0.93-0.97	9.8 × 10 ⁻⁹
18	rs76928645	7	54873635	<i>SEC61G</i>	T/C	0.103	0.93	0.91-0.95	1.6 × 10 ⁻¹⁰
19	rs1065712	8	11844613	<i>CTSB</i>	C/G	0.053	1.09	1.06-1.12	1.9 × 10 ⁻⁹
20	rs34173062	8	144103704	<i>SHARPIN</i>	A/G	0.081	1.13	1.09-1.16	1.7 × 10 ⁻¹⁶
21	rs1800978	9	104903697	<i>ABCA1</i>	G/C	0.13	1.06	1.04-1.08	1.6 × 10 ⁻⁹
22	rs7068231	10	60025170	<i>ANK3</i>	T/G	0.403	0.95	0.94-0.96	3.3 × 10 ⁻¹³
23	rs6586028	10	80494228	<i>TSPAN14</i>	C/T	0.196	0.93	0.91-0.94	2.0 × 10 ⁻¹⁹
24	rs6584063	10	96266650	<i>BLNK</i>	G/A	0.043	0.89	0.86-0.92	6.7 × 10 ⁻¹¹
25	rs7908662	10	122413396	<i>PLEKHA1</i>	G/A	0.467	0.96	0.95-0.97	2.6 × 10 ⁻⁹
26	rs6489896	12	113281983	<i>TPCN1</i>	C/T	0.076	1.08	1.05-1.10	1.8 × 10 ⁻⁹
27	rs7157106	14	105761758	<i>IGH</i> gene cluster	A/G	0.36	1.05	1.03-1.07	2.0 × 10 ⁻⁸
27	rs10131280	14	106665591	<i>IGH</i> gene cluster	A/G	0.133	0.94	0.92-0.96	4.3 × 10 ⁻¹⁰
28	rs3848143	15	64131307	<i>SNX1</i>	G/A	0.22	1.05	1.04-1.07	8.4 × 10 ⁻¹¹
29	rs12592898	15	78936857	<i>CTSH</i>	A/G	0.133	0.94	0.92-0.96	4.2 × 10 ⁻⁹
30	rs1140239	16	30010081	<i>DOC2A</i>	T/C	0.379	0.94	0.93-0.96	2.6 × 10 ⁻¹³
31	rs450674	16	79574511	<i>MAF</i>	C/T	0.373	0.96	0.95-0.98	3.2 × 10 ⁻⁸
32	rs16941239	16	86420604	<i>FOXF1</i>	A/T	0.029	1.13	1.08-1.17	1.3 × 10 ⁻⁸
33	rs56407236	16	90103687	<i>PRDM7</i>	A/G	0.069	1.11	1.08-1.14	6.5 × 10 ⁻¹⁵
34	rs35048651	17	1728046	<i>WDR81</i>	T/TGAG	0.214	1.06	1.04-1.08	7.7 × 10 ⁻¹¹
35	rs2242595	17	18156140	<i>MYO15A</i>	A/G	0.112	0.94	0.92-0.96	1.1 × 10 ⁻⁹
36	rs5848	17	44352876	<i>GRN</i>	T/C	0.289	1.07	1.06-1.09	2.4 × 10 ⁻²⁰
37	rs149080927	19	1854254	<i>KLF16</i>	G/GC	0.48	1.05	1.04-1.07	5.1 × 10 ⁻¹⁰
38	rs9304690	19	49950060	<i>SIGLEC11</i>	T/C	0.24	1.05	1.03-1.07	4.7 × 10 ⁻⁹
39	rs587709	19	54267597	<i>LILRB2</i>	C/T	0.325	1.05	1.04-1.07	3.6 × 10 ⁻¹¹
40	rs1358782	20	413334	<i>RBCK1</i>	A/G	0.246	0.95	0.94-0.97	1.6 × 10 ⁻⁸
41	rs6742	20	63743088	<i>SLC2A4RG</i>	T/C	0.221	0.95	0.93-0.97	2.6 × 10 ⁻⁹
42	rs2154481	21	26101558	<i>APP</i>	C/T	0.476	0.95	0.94-0.97	1.0 × 10 ⁻¹²

P values are two-sided raw P values derived from a fixed-effect meta-analysis. ^ars number, according to dbSNP build 153. ^bGRCh38 assembly. ^cNearest protein-coding gene according to GENCODE release 33. ^dWeighted average MAF across all discovery studies. ^eApproximate OR calculated with respect to the minor allele.

From all newly identified loci, this gene prioritization yielded 31 tier 1 genes and 24 tier 2. The 55 prioritized genes, the details of the analyses and the supporting evidence are summarized in Fig. 2a and the Supplementary Note (Supplementary Tables 19–30 and Supplementary Figs. 35–45). Among the 31 tier 1 genes, we observed that 25 of these genes were the only prioritized gene in their respective locus. For the remaining 6 tier 1 genes, we also found tier 2 genes in their respective locus. We also identified five loci containing several tier 2 prioritized genes. In one of these loci, locus 39 (L39), the tier 2 prioritized gene *LILRB2* had strong additional support from published literature (Supplementary Note). In five loci, our prioritization score did not identify sufficient molecular evidence to prioritize genes with exception of being the nearest gene (L10, L12, L13, L14 and L32). Finally, we excluded the complex IGH cluster (L27) from gene prioritization analyses due to genomic complexity of the telomeric locus as a consequence of known fusion events¹⁸.

We highlight two examples, L18 and L23. In L18, the lead variant, *rs76928645* (MAF = 10%), is intergenic and is located more than 100 kb downstream or upstream of the two nearest protein-coding genes (*SEC61G* and *EGFR*, respectively). Our gene prioritization analyses suggested that *EGFR* was the only risk gene (Fig. 3). We found that both the lead variant (*rs76928645*) and the other nearby variants in linkage disequilibrium (LD) are significant expression QTLs (eQTLs) for regulating *EGFR* expression downstream. The eQTL signals in brain strongly colocalized with the GWAS signal (with eQTL coloc PP4s of 98.3% in the temporal cortex (TCX) and 99.5% in the dorsolateral prefrontal cortex (DLPFC)). Accordingly, the fine-mapped expression transcriptome-wide association study (eTWAS) associations (Fine-mapping Of CaUsal gene Sets (FOCUS) posterior inclusion probability (PIP) = 1; eTWAS $P = 6.9 \times 10^{-9}$, eTWAS $Z = +5.8$ in the TCX; eTWAS $P = 3.1 \times 10^{-11}$, eTWAS $Z = +6.6$ in the DLPFC) indicated that genetic downregulation of *EGFR* expression is associated with a lower ADD risk (Fig. 3; Supplementary Tables 22, 24 and 26; and Supplementary Figs. 36a, 39 and 41).

In L23, we observed numerous eQTL-GWAS and methylation QTL (mQTL)-GWAS hits for *TSPAN14* that support the hypothesis that increased brain expression of *TSPAN14* is associated with increased ADD risk. We also identified several splice junctions in *TSPAN14* whose genetic regulation signals in lymphoblastoid cell lines (LCLs) and brain colocalized with the ADD association signal. These splice junctions were also associated with ADD risk (Fig. 4, Supplementary Tables 22–28 and Supplementary Figs. 36–42 and 44c). As three of these splice junctions were related to new complex cryptic splicing events that were predicted to result in two cryptic exons not previously described in known *TSPAN14* transcripts (based on GENCODE v38), we designed a long-read single-molecule (Nanopore) sequencing experiment (Supplementary Note) to validate these cryptic exons on a total of 93 complementary DNA (cDNA) samples derived from LCLs, frontal cortex and hippocampus and consequently validated those cryptic exons (Fig. 4). All three of the validated cryptic splicing events occur within the ADAM10-interacting domain of *TSPAN14*. Cryptic exon 1 is at least 45 bp long, and cryptic exon 2 is 118 bp long.

Lastly, we used STRING v11 (ref. ¹⁹) to analyze protein–protein interaction for (1) previously known AD genes from GWASs, (2) our prioritized new genes (tier 1 in Fig. 2a and Supplementary Table 20) and (3) a combination of the two (Supplementary Note). The largest networks contained 14, 8 and 30 proteins, respectively (Supplementary Fig. 46). These networks were larger than would be expected by chance (respectively, $P < 2 \times 10^{-5}$, $P = 2.8 \times 10^{-3}$ and $P < 2 \times 10^{-5}$ based on comparison with 50,000 randomly simulated protein lists matched for the number of proteins and the total number of interactions for each protein). Notably, the number of interactions between our prioritized genes and previously known genes is also significantly greater than would be expected ($P < 1 \times 10^{-4}$), indicating that the newly prioritized genes are biologically relevant in AD. No such enrichment ($P = 0.88$) was observed for the remaining genes in the new loci, again highlighting the value of our prioritization approach.

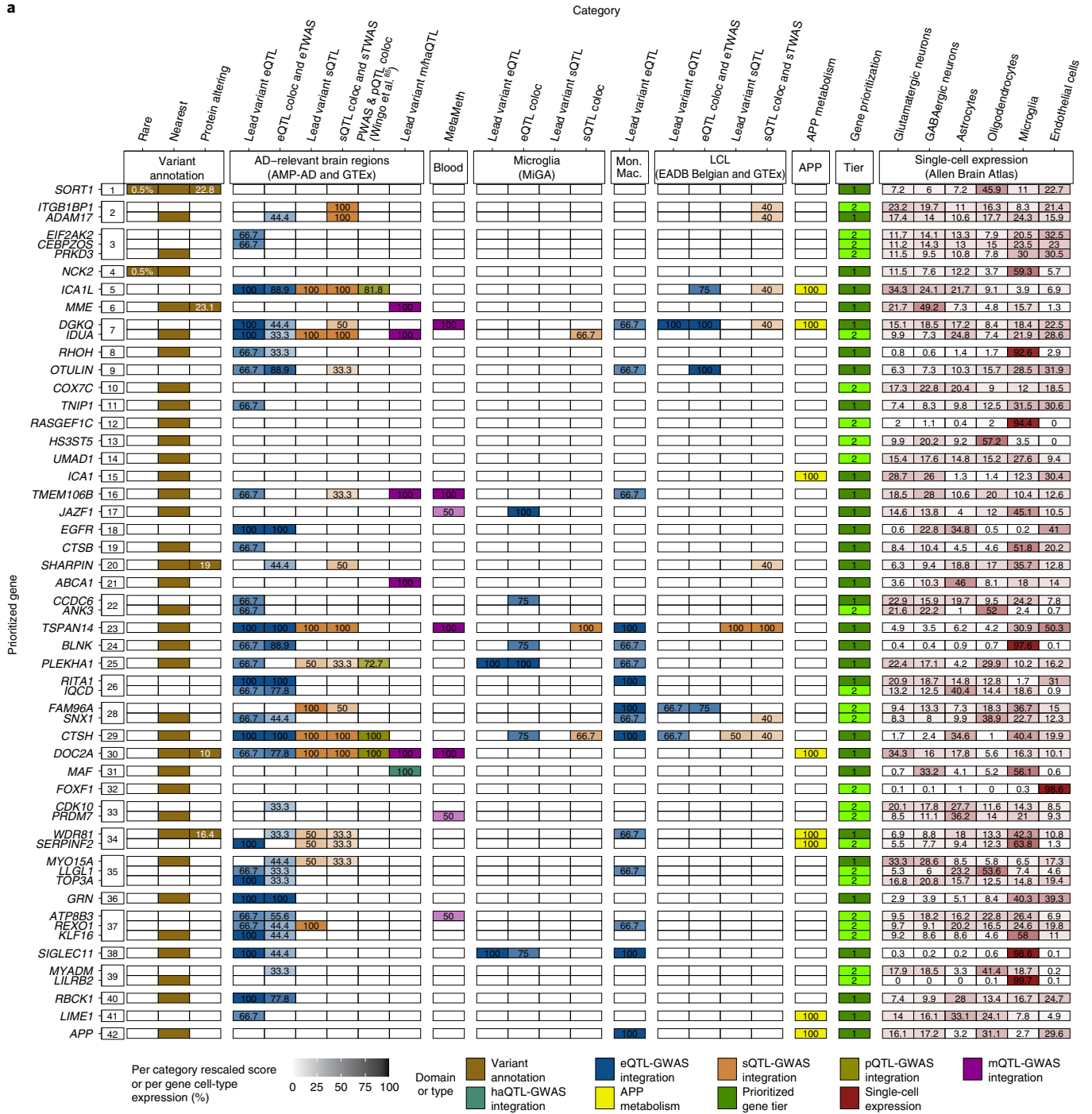
We next performed a pathway enrichment analysis of the tier 1 genes using STRING. We found that several gene sets linked to the immune system remained statistically significant after correction for multiple testing (Fig. 2b and Supplementary Table 31), especially regulation of the tumor necrosis factor (TNF)-mediated signaling pathway (GO:0010803). We report the potential genetic implication of the linear ubiquitin chain assembly complex (LUBAC), which is a major regulator of the aforementioned signaling pathway²⁰. Two of the LUBAC's three complements are encoded by the new tier 1 prioritized genes *SHARPIN* and *RBCK1*, and the complex's function is directly regulated by *OTULIN* (also a new tier 1 prioritized gene).

GRS

We next looked at whether the genetic ADD burden (as measured by a genetic risk score (GRS)) generated from our genome-wide significant variants ($n = 83$, excluding *APOE*; Supplementary Table 32) might influence the rate of conversion to AD in (1) individuals from several prospective, population-based cohorts and (2) patients with mild cognitive impairment (MCI) in prospective memory clinic studies (Supplementary Table 33). We used Cox regression models to assess the association after adjustment for age at baseline, sex, the number of *APOE*- $\epsilon 4$ and *APOE*- $\epsilon 2$ alleles, and genetic principal components (PCs).

In population-based cohorts with clinically diagnosed AD cases, the GRS was significantly associated with conversion to AD; this was shown in a fixed-effect meta-analysis (hazard ratio (HR) (95%CI) per average risk allele = 1.076 (1.064–1.088), $P = 9.2 \times 10^{-40}$; Fig. 5 and Supplementary Table 34). Likewise, the GRS was significantly associated with AD conversion in patients with MCI (HR = 1.056 (1.040–1.072), $P = 2.8 \times 10^{-12}$; Fig. 5 and Supplementary Table 35). Furthermore, we found that the GRS association increased significantly when the new variants discovered in the present study were added to the previously described variants (Supplementary Table 36) for both population-based studies (HR = 1.052 (1.037–1.068), $P = 1.5 \times 10^{-11}$) and MCI cohorts (HR = 1.034 (1.013–1.055), $P = 1.4 \times 10^{-3}$).

Fig. 2 | Gene prioritization. **a**, Summary of weighted scores for each evidence category for the prioritized genes in the 42 new genome-wide-significant loci. Using our gene prioritization method, we considered the genes within 1 Mb of each new lead variant and prioritized a total of 55 genes in 42 new loci at two different confidence levels (31 tier 1 genes and 24 tier 2 genes). The leftmost squares indicate the new locus index number. The different types of evidence are colored according to the seven different domains to which they belonged. Weighted scores for each evidence category are rescaled to a 0–100 scale, and the proportions of mean human brain cell-type-specific expression for each gene are also rescaled to a 0–100 scale; darker colors represent higher scores or higher expression proportions. Tier 1 genes are shown in dark green, and tier 2 genes are shown in light green. Only tier 1 and tier 2 genes are shown for each locus. Supplementary Fig. 35 shows full results. MAFs and CADD (v1.6) PHRED scores for rare and/or protein-altering rare variants are labeled in white within the respective squares. **b**, Pathway enrichment analysis based on the tier 1 gene list. Only the ten strongest associations (according to STRING software) are presented here. coloc, colocalization; eQTL, expression QTL; eTWAS, expression transcriptome-wide association study; GO, Gene Ontology; haQTL, histone acetylation QTL; Mon. Mac., monocytes and macrophages; sTWAS, splicing transcriptome-wide association study; m/haQTL, methylation/histone acetylation QTL; sQTL, splicing QTL; FDR, false discovery rate.



b

GO term	Term description	Number of tier 1 genes	Number of genes in pathway	FDR	Matching proteins in the network
GO:001775	Cell activation	12	1,024	4.09×10^{-5}	GRN, CTSH, BLNK, NCK2, DGKQ, EGFR, APP, ADAM17, CTSS, RHOH, TSPAN14, MME
GO:0002376	Immune system process	15	2,370	2.60×10^{-4}	GRN, CTSH, BLNK, NCK2, OTULIN, APP, LIME1, ADAM17, TNIP1, CTSS, RBCK1, PLEKHA1, RHOH, TSPAN14, MME
GO:0009966	Regulation of signal transduction	17	3,033	2.60×10^{-4}	GRN, CTSH, BLNK, NCK2, DGKQ, EGFR, OTULIN, APP, ADAM17, TNIP1, RBCK1, PLEKHA1, ABCA1, RHOH, SHARPIN, TSPAN14, RITA1
GO:0010646	Regulation of cell communication	18	3,327	2.60×10^{-4}	GRN, CTSH, BLNK, NCK2, DGKQ, EGFR, OTULIN, APP, ADAM17, TNIP1, RBCK1, PLEKHA1, ABCA1, RHOH, ICA1, SHARPIN, TSPAN14, RITA1
GO:0023051	Regulation of signaling	18	3,360	2.60×10^{-4}	GRN, CTSH, BLNK, NCK2, DGKQ, EGFR, OTULIN, APP, ADAM17, TNIP1, RBCK1, PLEKHA1, ABCA1, RHOH, ICA1, SHARPIN, TSPAN14, RITA1
GO:0045321	Leukocyte activation	10	894	2.60×10^{-4}	GRN, CTSH, BLNK, NCK2, APP, ADAM17, CTSS, RHOH, TSPAN14, MME
GO:0048583	Regulation of response to stimulus	19	3,882	2.60×10^{-4}	GRN, CTSH, BLNK, NCK2, DGKQ, EGFR, OTULIN, APP, LIME1, ADAM17, TNIP1, RBCK1, PLEKHA1, ABCA1, RHOH, SHARPIN, TSPAN14, SIGLEC11, RITA1
GO:0048584	Positive regulation of response to stimulus	14	2,054	2.60×10^{-4}	CTSH, BLNK, NCK2, EGFR, OTULIN, APP, LIME1, ADAM17, TNIP1, RBCK1, PLEKHA1, SHARPIN, TSPAN14
GO:0010803	Regulation of TNF-mediated signaling pathway	4	56	4.30×10^{-4}	OTULIN, ADAM17, RBCK1, SHARPIN
GO:0042058	Regulation of EGFR signaling pathway	4	80	1.50×10^{-3}	NCK2, EGFR, APP, ADAM17

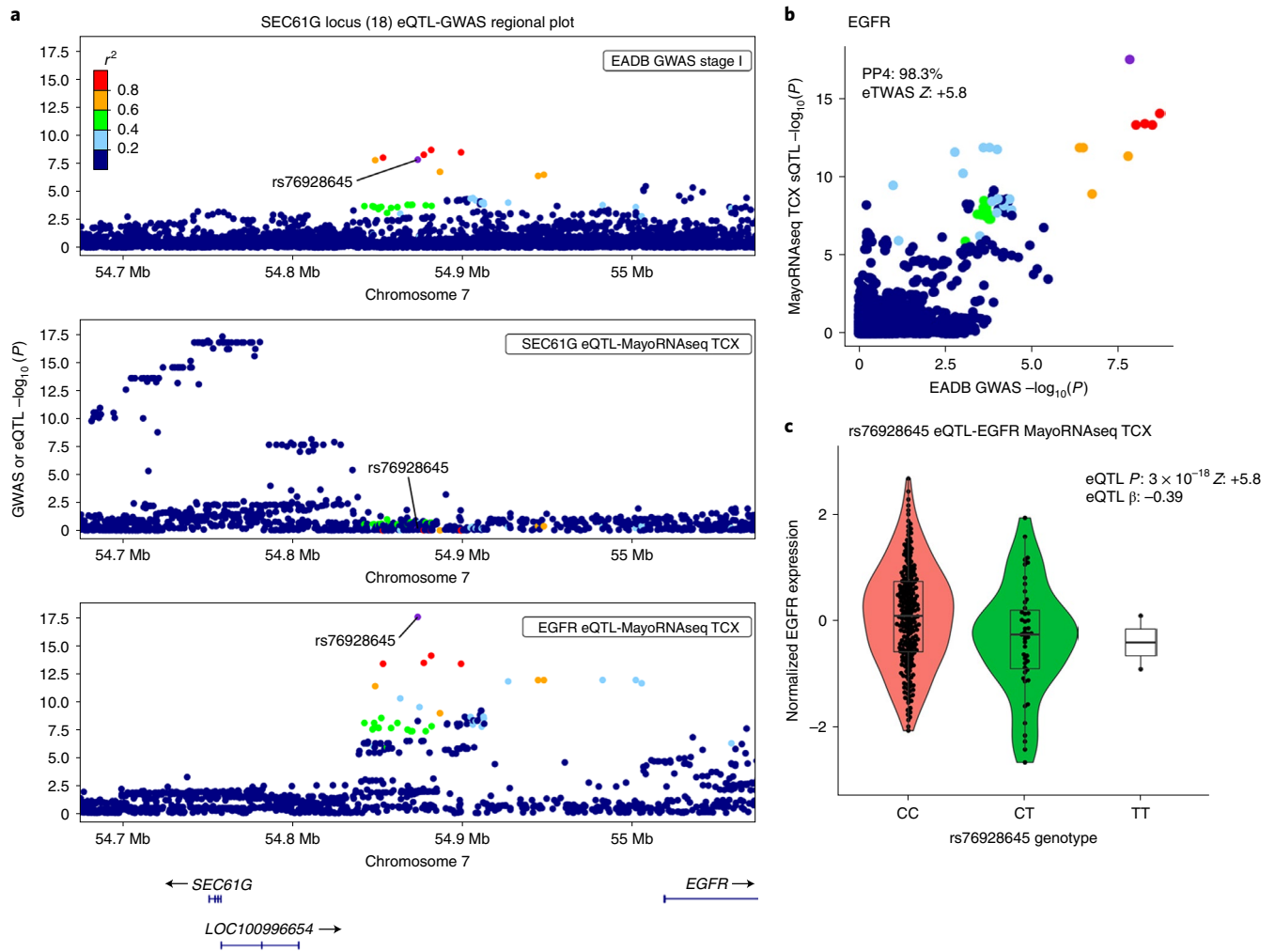


Fig. 3 | Regulation of EGFR expression by the ADD-risk-associated and colocated brain eQTLs within the intergenic SEC61G locus. a, The regional plot of the new SEC61G locus (L18) shows the EADB GWAS stage I ($n = 487,511$) ADD association signal within 200 kb of the intergenic lead variant, *rs76928645* (the two closest protein-coding genes, SEC61G and EGFR, are more than 100 kb from the lead variant), together with the eQTLs in the same region identified for SEC61G and EGFR expression separately in the TCX (MayoRNAseq TCX eQTL catalog based on $n = 259$ individuals). The *rs76928645* lead variant is shown in purple, and LD r^2 values (calculated for the EADB Trans-Omics for Precision Medicine (TOPMed) dataset ($n = 42,140$) with respect to the lead variant) are indicated on a color scale. y axis, $-\log_{10}$ for the GWAS or eQTL P value; x axis, hg38 genomic position on chromosome 7. **b**, Colocalization between the EGFR eQTL signal (MayoRNAseq TCX, $n = 259$ individuals) and the EADB GWAS stage I ($n = 487,511$) signal (eQTL coloc PP4 = 98.3%); with the significant eTWAS association (eTWAS $P = 6.9 \times 10^{-9}$ and eTWAS $Z = 5.8$) and fine-mapped (FOCUS PIP = 1) eTWAS association in the same catalog. y axis, eQTL $-\log_{10}(P)$ value; x axis, GWAS $-\log_{10}(P)$ value. LD r^2 values and color scales are as in **a**. **c**, The eQTL violin plot shows a significant association (eQTL $P = 3 \times 10^{-18}$) between the *rs76928645* lead variant genotype and EGFR expression in the TCX (MayoRNAseq TCX, $n = 259$ individuals), where the protective allele T is associated with lower EGFR expression (eQTL β , -0.39). Each data point represents a sample whose normalized EGFR expression value is indicated on the y axis, and the *rs76928645* genotype information is indicated on the x axis. The lower and upper hinges of the boxes represent the first and third quartiles, the whiskers extend 1.5 times the interquartile range from the hinges and the line represents the median.

Importantly, the results of our meta-analysis suggest that the risk of conversion to AD rises with the number of risk alleles from non-APOE risk variants in the GRS by 1.9-fold in population-based cohorts (HR = 1.93 (1.75–2.13); Fig. 5) and 1.6-fold in MCI cohorts (HR = 1.63 (1.42–1.87); Fig. 6) on top of effects of age and the APOE $\epsilon 4$ allele. These observations result from the comparison of hypothetical individuals with a GRS value at the first decile of the distribution versus those with a GRS value at the ninth decile (Fig. 6). With regard to APOE, carrying an additional APOE- $\epsilon 4$ allele was associated with a slightly higher increase in the AD risk in population-based cohorts (HR = 2.19 (2.03–2.37)) and MCI cohorts (HR = 1.90 (1.73–2.07)). There was no interaction between the GRS and the number of APOE- $\epsilon 4$ alleles (Supplementary Table 37).

In an MCI cohort setting, this effect of the GRS corresponds to a median AD conversion probability within 3 years of 21.9% in patients with a GRS below the first decile (range, 4.1–34.9%) and 37.5% (range, 10.8–56.2%) in patients with a GRS above the ninth decile. There was a consistent increase in probability between these deciles in all cohorts (median (range), 13.8% (6.6–25.0%); Supplementary Table 38).

To better define the GRS discriminative ability regarding AD conversion, we assessed the improvements in three indices of predictive performance after adding the GRS to a Cox model containing age, sex, PCs and the number of APOE- $\epsilon 4$ and APOE- $\epsilon 2$ alleles as covariates (Supplementary Tables 34 and 35). We found a small but consistent increase in the discrimination between AD converters and nonconverters, as indicated by the concordance index (C-index) in

population-based cohorts ($\Delta_{5\text{years}}\text{-C-index}_{\text{fixed-effects}} = 0.002$ (0.0004–0.004)) and MCI cohorts ($\Delta_{3\text{years}}\text{-C-index}_{\text{fixed-effects}} = 0.007$ (0.001–0.012)). This finding was further supported by small-to-moderate increases in the continuous NRI (net reclassification improvement) index in population-based cohorts ($\text{NRI}_{5\text{year-fixed-effects}} = 0.248$ (0.159–0.336)) and MCI cohorts ($\text{NRI}_{3\text{year-fixed-effects}} = 0.232$ (0.140–0.325)); this indicates that the risk assignment is more appropriate to individuals when the GRS is taken into account²¹. Furthermore, an increase in the index of prediction accuracy (IPA) was observed in all of the population-based cohorts (average $\Delta_{5\text{years}}\text{-IPA}_{\text{fixed-effects}} = 0.29\%$ (0.23%–0.35%)) and all but one of the MCI cohorts (average $\Delta_{3\text{years}}\text{-IPA}_{\text{fixed-effects}} = 1.53\%$ (1.31%–1.76%)), indicating an overall improvement in predictive performance. As expected, the amount of improvement in this index varied greatly from one cohort to another, given its dependency on incidence rates. The value of adding the new genetic variants was emphasized by the fact that effect sizes (as measured by the indices of predictive ability) were lower when only previously known AD risk variants were included in the GRS (Supplementary Table 39).

The results were similar when we (1) computed indices for other follow-up time points, (2) applied a random effects meta-analysis, (3) considered conversion to all-cause-dementia as the outcome and (4) excluded the Framingham Heart Study (FHS), as it was part of the stage II of the GWAS from which ORs for PRS computation were extracted (Supplementary Tables 34–44 and Supplementary Fig. 47).

Discussion

Our meta-analysis combined a large, new case–control study with previous GWASs. We identified 75 independent loci for ADD; 33 had been reported previously, and 42 correspond to new signals at the time of this analysis. The prioritized genes and their potential impact on the pathophysiology of AD are described in the Supplementary Note.

Our pathway enrichment analyses removed ambiguities concerning the involvement of tau-binding proteins and APP/A β peptide metabolism in late-onset AD processes at a much higher level than had been described previously⁵. It is noteworthy that new genetic risk factors are often first evaluated in the context of known pathways; many new research approaches were developed to systematically characterize putative links among APP metabolism, tau function and ADD genetic risk factors^{22,23}. This approach can lead to circular reasoning and thus artificial enrichment in specific processes. However, we implicate *ADAM17*, a gene whose protein product is known to carry α -secretase activity as *ADAM10* (ref. ²⁴). This observation suggests that the nonamyloidogenic pathway for APP metabolism might be deregulated in AD. In addition to *APP*, we also identified six highly plausible prioritized (tier 1) genes (*ICAIL*, *DGKQ*, *ICAI*, *DOC2A*, *WDR81* and *LIME1*) that are likely to modulate the metabolism of APP.

These pathway enrichment analyses also confirmed the involvement of innate immunity and microglial activation in ADD (Supplementary Table 15). Our single-cell expression enrichment analysis also highlighted genes expressed in microglia (Supplementary Tables 16 and 17). Indeed, three of our prioritized (tier 1) genes (*RHOH*, *BLNK* and *SIGLEC11*) and two of our tier 2 genes (*LILRB2* and *RASGE1FC*) appeared to be mainly expressed in microglia (>90% relative to the total expression summed across cell types; Fig. 2a and Supplementary Table 45). Importantly, *SIGLEC11* and *LILRB2* have already been linked to A β peptides/amyloid plaques^{25,26}.

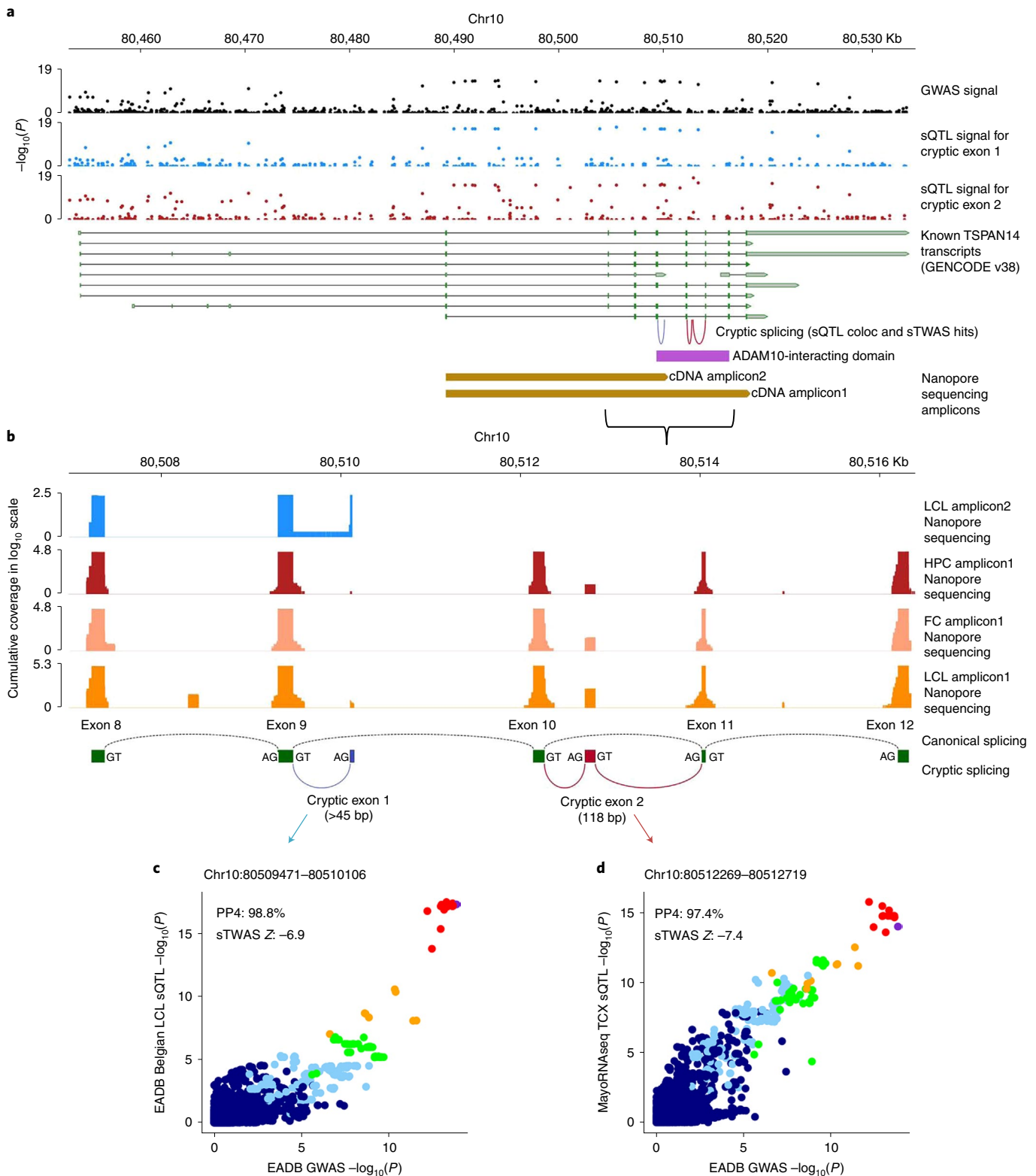
Here, we also provide genetic evidence of the LUBAC's potential implication in ADD. Two of the LUBAC's three complements are encoded by *SHARPIN* and *RBCK1*, and the LUBAC is regulated by *OTULIN*; all three genes were found to be high-confidence, prioritized risk genes in our study. The LUBAC is the only E3 ligase known to form linear ubiquitin chains de novo through ubiquitin's N-terminal methionine. The complex has mostly been studied in the context of inflammation, innate immunity and defense against intracellular pathogens. For instance, the LUBAC is reportedly essential for NLRP3 inflammasome activation²⁷ and thus acts as a key innate immune regulator²⁸. In turn, the NLRP3 inflammasome is essential for the development and progression of A β pathology in mice²⁹ and may drive tau pathology through A β -induced microglial activation³⁰. The LUBAC is also reportedly involved in autophagy, and linear ubiquitin chain modifications of TDP-43-positive neuronal cytoplasmic inclusions have been described as potential inducers of autophagic clearance³¹. Lastly, the LUBAC has been studied as a regulator of TNF- α signaling in particular²⁰.

Interestingly, the TNF- α signaling pathway was also flagged by other genetic findings in our study (Supplementary Fig. 48). For example, *ADAM17* (also known as TNF- α -converting enzyme) is of pivotal importance in the activation of TNF- α signaling³². For *TNIP1*, its gene product (TNF- α -induced protein 3-interacting protein 1) is involved in the inhibition of the TNF- α signaling pathway and nuclear factor κ B activation/translocation³³. Additional signal related to TNF- α is the one found at *SPPL2A* (one of the 33 confirmed loci). The protein encoded by *SPPL2A* is involved in non-canonical shedding of TNF- α ³⁴, and *PGRN* has been described as a TNF receptor ligand and an antagonist of TNF- α signaling³⁵. Several lines of evidence had linked the inhibition of TNF- α signaling with reduction of both A β and tau pathologies in vivo^{36,37}. Although a potential inflammatory connection has been suggested for TNF- α through the activation of NLRP3 inflammasome³⁸, the TNF- α signaling pathway is also involved in many other brain physiological functions (e.g., synaptic plasticity in neurons) and pathophysiological processes (e.g., synapse loss) in the brain³⁹. Furthermore, the involvement of the TNF- α signaling pathway and the LUBAC might be important in cell types other than microglia in AD. It is important

Fig. 4 | Focus on *TSPAN14* locus. **a**, Splicing QTL (sQTL)-GWAS integration results. Known *TSPAN14* transcripts (GENCODE v38; green, coding sequences; gray, noncoding) plotted with $-\log_{10}(P)$ for (1) EADB GWAS stage I ($n = 487,511$) signal (black), (2) sQTL signal for chr10:80509471–80510106 junction (supporting cryptic exon 1) in the EADB Belgian LCL sQTL catalog ($n = 70$ individuals, blue) and (3) sQTL signal for chr10:80512269–80512719 junction in the MayoRNAseq TCX sQTL catalog ($n = 259$ individuals, red); hg38 genomic position is shown above. LCL and brain-based sQTL coloc and sTWS analyses associate ADD risk with these junctions that suggest cryptic splicing within *ADAM10*-interacting domain of *TSPAN14* (magenta), which was predicted to result in two cryptic exons. **b**, Long-read sequencing validation of *TSPAN14* cryptic exons. Nanopore sequencing results (Supplementary Note) in the zoomed-in region of chr10:80506973–80516400 (cumulative coverage in \log_{10} scale). Pooled LCL cDNA sample sequenced for cDNA Amplicon2 shown in blue. cDNA Amplicon1 was sequenced on biologically independent hippocampal (HPC; $n = 16$, red), frontal cortex (FC; $n = 18$, pink) and LCL ($n = 59$, orange) cDNA samples. Green, canonical exons (8–12); dotted black lines, canonical splicing; blue, cryptic exon 1 (>45 bp); red, cryptic exon 2 (118 bp). All annotated junctions use canonical splice donor (GT) and acceptor (AG) sites. **c,d**, sQTL-GWAS colocalization plots for chr10:80509471–80510106 (supporting cryptic exon 1) in the EADB Belgian LCL sQTL catalog ($n = 70$ individuals) (**c**) and chr10:80512269–80512719 (supporting cryptic exon 2) in the MayoRNAseq TCX sQTL catalog ($n = 259$ individuals) (**d**). sQTL signals for the two junctions colocalize with ADD signal (PP4s of 98.8% and 97.4%, respectively), and sTWS associates with increased preference for the cryptic splicing with decreased ADD risk (sTWS $P = 6.28 \times 10^{-12}$ and 1.6×10^{-13} , sTWS $Z = -6.9$ and -7.4 , respectively). y axis, sQTL $-\log_{10}(P)$; x axis, EADB GWAS stage I $-\log_{10}(P)$. LD r^2 values calculated within EADB-TOPMed dataset ($n = 42,140$) based on the lead variant **rs6586028** (purple) are indicated on a color scale.

to note that six of our prioritized (tier 1) genes (*ICA1L*, *EGFR*, *RITA1*, *MYO15A*, *LIME1* and *APP*) are expressed at a low level in microglia (<10%, relative to the total expression summed across cell types; Supplementary Table 45), emphasizing that ADD results from complex crosstalk between different cell types in the brain^{23,40}. It is also noteworthy that the EGFR pathway is known to interact with the TNF- α signaling pathway⁴¹, which suggests interplay between the two signaling pathways during the ADD development.

A better understanding of the etiology of ADD might also result from the observation that the risks of developing ADD and frontotemporal dementia are associated with the same causal variants in *GRN* and *TMEM106B*. This association might be due to the misclassification of clinical diagnosis of AD and the presence of proxy-ADD cases in the UKBB. However, *GRN* and *TMEM106B* have also been linked to brain health and many other neurodegenerative diseases. For instance, *GRN* and *TMEM106B* are reportedly potential genetic



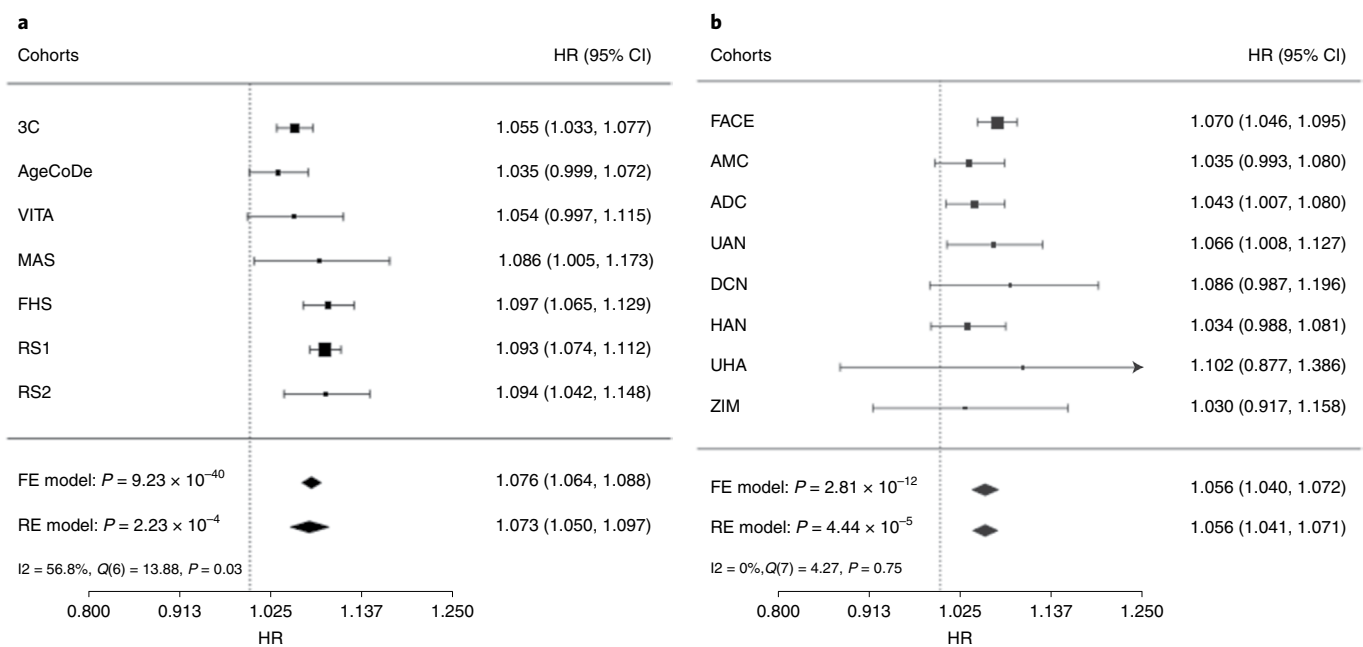


Fig. 5 | Association between the GRS and the risk of progression to AD. a, b, Meta-analysis results of the association between the GRS and the risk of progression to AD in population-based cohorts ($n = 17,545$ independent samples) (**a**) and MCI cohorts ($n = 4,114$ independent samples) (**b**). Data are presented as HR together with 95% CIs derived from Cox regression analyses for each individual cohort. HRs indicate the effect of the GRS as the increment in the AD risk associated with each additional average risk allele in the GRS. Null hypothesis testing is based on a meta-analysis of individual cohort effects using fixed effects (FE) and random effects (RE) models. Resulting HRs and 95% CIs and the respective Z test and associated two-sided P value are shown at the bottom of the figure. Heterogeneity between cohorts is indicated by the I^2 index together with the respective Cochran's Q statistic (distributed as χ^2 statistic), associated degrees of freedom and P value. 3C, Three-City Study; AgeCoDe, German study on aging cognition and dementia; AMC, additional, independent memory clinic cohort from Fundacio ACE; DCN, German Dementia Competence Network study; FACE, Fundacio ACE memory clinic cohort; FHS, Framingham Heart Study; HAN, BALTAZAR multicenter prospective memory clinic study; MAS, Sydney Memory and Ageing Study; RS1, Rotterdam Study first cohort; RS2, Rotterdam Study second cohort; VITA, Vienna Transdanube Aging study; UAN, memory clinic cohort from the Hospital Network Antwerp; UHA, University of Halle memory clinic cohort; ZIM, Heidelberg/Mannheim memory clinic sample.

risk factors for differential aging in the cerebral cortex⁴² and cognitive impairment in amyotrophic lateral sclerosis⁴³ and Parkinson's disease^{44,45}. Lastly, both *GRN* and *TMEM106B* have already been associated with neuropathological features of AD^{46–48}. Taken as a whole, these data may thus emphasize a potential continuum between neurodegenerative diseases in which common pathological mechanisms are driven by *GRN* and *TMEM106B*. Interestingly, both *GRN* and *TMEM106B* are reported to be involved in defective endosome/lysosome trafficking/function^{49,50}, a defect that is also observed in AD.

By applying a GRS derived from all the genome-wide-significant variants discovered in this study, we identified an association with the risk of incident AD in prospective population-based cohorts and with the risk of progression over time from MCI to AD (Fig. 5 and Supplementary Table 33). In patients with MCI, previous associations of AD risk with a GRS built on previously known genetic AD risk variants has been inconsistent⁵¹. It is important to note that the GRS has an impact on the AD risk in addition to that of age and that the GRS's effect is independent of *APOE* status. With a view to translating genetic findings into preventive measures and personalized medicine, we also sought to provide the GRS's added value for risk prediction by calculating the discriminative capacity through three different indices. Overall, the indices suggested that the effect size for the association between the GRS and AD was small but significant. Despite this modest effect, the inclusion of the GRS into the predictive model consistently improved the assignment of the risk of progression, as expressed by the net reclassification improvement (NRI) index²¹. Importantly, the cumulative improvements in risk prediction (due to inclusion of the new variants in the GRS) led

to a 1.6- to 1.9-fold increase in the AD risk from the lowest to the highest decile, in addition to the effects of age and *APOE* status. We also showed that in addition to known risk variants, the new risk variants identified in the present study are significantly associated with progression to AD. The results of future GWASs are expected to further improve AD-risk prediction. Hence, the GRS will help to sharpen the threshold that differentiates between people at risk of progressing to dementia and those who are not.

A recent study estimated that fewer than 100 causal common variants may explain the entire AD risk³²; if that estimate is correct, then our study might have already characterized a large proportion of this genetic component due to common variants. However, several reasons strongly underscore the need for additional efforts to fully characterize the still-missing AD genetic component. First, it is probable that additional, yet-unknown loci bear common variants modulating the risk for AD. Second, identification of rare variants with very low frequencies is a major challenge for genetic studies, because available samples with sequencing data in AD are underpowered. Notably, almost all the genes with rare variants associated with AD risk also present common variants associated with AD risk (i.e., *TREM2*, *SORL1*, *ABCA7*, *ABCA1*, *PLCγ2* and *ADAM10*)⁵³. Third, gene–gene and gene–environment interactions have not yet been studied in detail. Hence, by increasing the GWAS sample size and improving imputation panels, conventional and (above all) more complex analyses will have more statistical power and should enable the characterization of associations with rare/structural variants. Lastly, higher-powered GWASs of multiethnicity populations will be particularly welcome for characterizing potential new genetic risk factors, improving fine-mapping approaches and developing

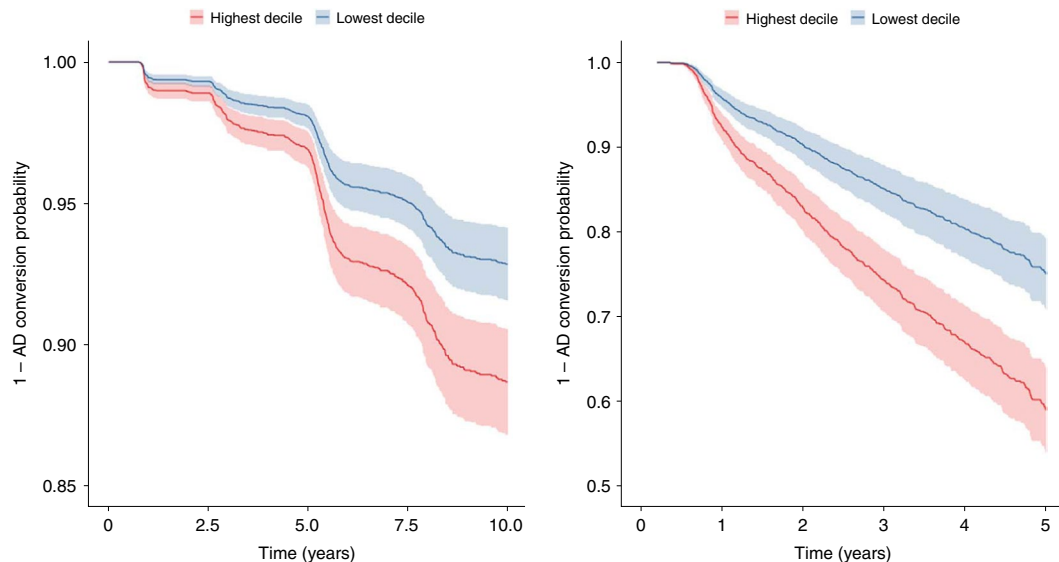


Fig. 6 | Risk of progression to AD according to the GRS. a,b, Representative plots of the progression to AD over 10 years in the population-based 3C study (a) and the progression from MCI to AD over 5 years in the Fundació ACE cohort (b). The figures show the probabilities of conversion (survival probabilities) to AD (y axes) for a hypothetical participant with average covariates (mean values for age and PCs, and the mode for sex and *APOE*) and GRS at the first (lowest) decile (in blue) or a GRS at the ninth (highest) decile (red). The shaded regions correspond to the 95% CI.

specific GRSs (because GRSs developed with European-ancestry populations are known to be less effective with other ancestries).

In conclusion, we have validated 33 previous loci, doubled the total number of genetic loci associated with the ADD risk, expanded our current knowledge of the pathophysiology of ADD, identified new opportunities for the development of GRSs and gene-specific treatments and opened up a pathway to translational genomics and personalized medicine.

Online content

Any methods, additional references, Nature Research 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/s41588-022-01024-z>.

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Céline Bellenguez ^{1,5,6,7} ✉, Fahri Küçükali ^{2,3,4,5,6,7}, Iris E. Jansen ^{5,6,5,6,7}, Luca Kleineidam ^{7,8,9,5,6,7}, Sonia Moreno-Grau ^{10,11,5,6,7}, Najaf Amin ^{12,13,5,6,7}, Adam C. Naj ^{14,15,5,6,7}, Rafael Campos-Martin ^{8,5,6,7}, Benjamin Grenier-Boley¹, Victor Andrade^{7,8}, Peter A. Holmans ¹⁶, Anne Boland¹⁷, Vincent Damotte¹, Sven J. van der Lee ^{5,18}, Marcos R. Costa ^{1,19}, Teemu Kuulasmaa ²⁰, Qiong Yang ^{21,22}, Itziar de Rojas ^{10,11}, Joshua C. Bis ²³, Amber Yaqub ¹², Ivana Prokic ¹², Julien Chapuis ¹, Shahzad Ahmad ^{12,24}, Vilmantas Giedraitis ²⁵, Dag Aarsland^{26,27}, Pablo Garcia-Gonzalez ^{10,11}, Carla Abdelnour^{10,11}, Emilio Alarcón-Martín^{10,28}, Daniel Alcolea ^{11,29}, Montserrat Alegret^{10,11}, Ignacio Alvarez ^{30,31}, Victoria Álvarez^{32,33}, Nicola J. Armstrong³⁴, Anthoula Tsolaki ^{35,36}, Carmen Antúnez³⁷, Ildebrando Appollonio^{38,39}, Marina Arcaro⁴⁰, Silvana Archetti⁴¹, Alfonso Arias Pastor^{42,43}, Beatrice Arosio^{44,45}, Lavinia Athanasiu⁴⁶, Henri Bailly⁴⁷, Nerisa Banaj⁴⁸, Miquel Baquero ⁴⁹, Sandra Barral^{50,51,52}, Alexa Beiser^{20,53}, Ana Belén Pastor ⁵⁴, Jennifer E. Below⁵⁵, Penelope Benchek^{56,57}, Luisa Benussi⁵⁸, Claudine Berr ⁵⁹, Céline Besse¹⁷, Valentina Bessi ^{60,61}, Giuliano Binetti^{58,62}, Alessandra Bizarro⁶³, Rafael Blesa^{11,29}, Mercè Boada ^{10,11}, Eric Boerwinkle^{64,65}, Barbara Borroni⁶⁶, Silvia Boschi⁶⁷, Paola Bossù ⁶⁸, Geir Bråthen ^{69,70}, Jan Bressler ^{64,71}, Catherine Bresner ¹⁶, Henry Brodaty ^{34,72}, Keeley J. Brookes ⁷³, Luis Ignacio Brusco^{74,75,76}, Dolores Buiza-Rueda^{11,77}, Katharina Bürger^{78,79}, Vanessa Burholt ^{80,81}, William S. Bush ⁸², Miguel Calero ^{10,54,83}, Laura B. Cantwell⁸⁴, Geneviève Chene^{85,86}, Jaeyoon Chung ⁸⁷, Michael L. Cuccaro⁸⁸, Ángel Carracedo^{89,90}, Roberta Cecchetti⁹¹, Laura Cervera-Carles ^{11,29}, Camille Charbonnier⁹², Hung-Hsin Chen⁹³, Caterina Chillotti⁹⁴, Simona Ciccone⁴⁵,

Jurgen A. H. R. Claassen⁹⁵, Christopher Clark⁹⁶, Elisa Conti³⁸, Anaïs Corma-Gómez⁹⁷, Emanuele Costantini⁹⁸, Carlo Custodero⁹⁹, Delphine Daian¹⁷, Maria Carolina Dalmasso⁸, Antonio Daniele⁹⁸, Efthimios Dardiotis¹⁰⁰, Jean-François Dartigues¹⁰¹, Peter Paul de Deyn¹⁰², Katia de Paiva Lopes^{103,104,105,106}, Lot D. de Witte¹⁰⁶, Stéphanie Debette¹⁰¹, Jürgen Deckert¹⁰⁷, Teodoro del Ser⁵⁴, Nicola Denning¹⁰⁸, Anita DeStefano^{20,21,109}, Martin Dichgans^{78,110}, Janine Diehl-Schmid¹¹¹, Mónica Diez-Fairen^{30,31}, Paolo Dionigi Rossi⁴⁵, Srdjan Djurovic⁴⁶, Emmanuelle Duron⁴⁷, Emrah Düzel^{112,113}, Carole Dufouil^{85,86}, Gudny Eiriksdottir¹¹⁴, Sebastiaan Engelborghs^{115,116,117,118}, Valentina Escott-Price^{15,108}, Ana Espinosa^{10,11}, Michael Ewers^{78,79}, Kelley M. Faber¹¹⁹, Tagliavini Fabrizio¹²⁰, Sune Fallgaard Nielsen¹²¹, David W. Fardo¹²², Lucia Farotti¹²³, Chiara Fenoglio¹²⁴, Marta Fernández-Fuertes⁹⁷, Raffaele Ferrari^{125,126}, Catarina B. Ferreira¹²⁷, Evelyn Ferri⁴⁵, Bertrand Fin¹⁷, Peter Fischer¹²⁸, Tormod Fladby¹²⁹, Klaus Fließbach^{8,9}, Bernard Fongang¹³⁰, Myriam Fornage^{70,71}, Juan Fortea^{11,29}, Tatiana M. Foroud¹¹⁹, Silvia Fostinelli⁵⁸, Nick C. Fox¹³¹, Emlio Franco-Macías¹³², María J. Bullido^{11,133,134}, Ana Frank-García^{11,133,135}, Lutz Froelich¹³⁶, Brian Fulton-Howard¹³⁷, Daniela Galimberti^{40,124}, Jose Maria García-Alberca^{11,138}, Pablo García-González¹⁰, Sebastian Garcia-Madrona¹³⁹, Guillermo Garcia-Ribas¹³⁹, Roberta Ghidoni⁵⁸, Ina Giegling¹⁴⁰, Giaccone Giorgio¹²⁰, Alison M. Goate¹³⁷, Oliver Goldhardt¹¹¹, Duber Gomez-Fonseca¹⁴¹, Antonio González-Pérez¹⁴², Caroline Graff^{143,144}, Giulia Grande¹⁴⁵, Emma Green¹⁴⁶, Timo Grimmer¹¹¹, Edna Grünblatt^{147,148,149}, Michelle Grunin⁵⁷, Vilmundur Gudnason¹⁵⁰, Tamar Guetta-Baranes¹⁵¹, Annakaisa Haapasalo¹⁵², Georgios Hadjigeorgiou¹⁵³, Jonathan L. Haines⁸², Kara L. Hamilton-Nelson¹⁵⁴, Harald Hampel¹⁵⁵, Olivier Hanon⁴⁷, John Hardy¹²⁶, Annette M. Hartmann¹⁴⁰, Lucrezia Hausner¹³⁶, Janet Harwood¹⁶, Stefanie Heilmann-Heimbach¹⁵⁶, Seppo Helisalmi^{157,158}, Michael T. Heneka^{7,9}, Isabel Hernández^{10,11}, Martin J. Herrmann¹⁰⁷, Per Hoffmann¹⁵⁶, Clive Holmes¹⁵⁹, Henne Holstege^{5,18}, Raquel Huerto Vilas^{42,43}, Marc Hulsman^{5,18}, Jack Humphrey^{103,104,105,160}, Geert Jan Biessels¹⁶¹, Xueqiu Jian¹³⁰, Charlotte Johansson¹⁴³, Gyungah R. Jun⁸⁷, Yuriko Kastumata¹⁶², John Kauwe¹⁶³, Patrick G. Kehoe¹⁶⁴, Lena Kilander²¹, Anne Kinhult Ståhlbom¹⁴³, Miia Kivipelto^{165,166,167,168}, Anne Koivisto^{157,169,170}, Johannes Kornhuber¹⁷¹, Mary H. Kosmidis¹⁷², Walter A. Kukull¹⁷³, Pavel P. Kuksa¹⁵, Brian W. Kunkle¹⁵³, Amanda B. Kuzma⁸⁴, Carmen Lage^{11,174}, Erika J. Laukka^{145,175}, Lenore Launer^{176,177}, Alessandra Lauria⁶³, Chien-Yueh Lee¹⁵, Jenni Lehtisalo^{157,178}, Ondrej Lerch^{179,180}, Alberto Lleó^{11,29}, William Longstreth Jr¹⁸¹, Oscar Lopez²², Adolfo Lopez de Munain^{11,182}, Seth Love¹⁶⁴, Malin Löwemark²¹, Lauren Luckcuck¹⁶, Kathryn L. Lunetta²⁰, Yiyi Ma^{18,183}, Juan Macías⁹⁷, Catherine A. MacLeod¹⁸⁴, Wolfgang Maier^{7,9}, Francesca Mangialasche¹⁶⁵, Marco Spallazzi⁵¹, Marta Marquié^{10,11}, Rachel Marshall¹⁶, Eden R. Martin¹⁵⁴, Angel Martín Montes^{11,133,135}, Carmen Martínez Rodríguez³³, Carlo Masullo¹⁸⁵, Richard Mayeux^{50,186}, Simon Mead¹⁸⁷, Patrizia Mecocci⁹¹, Miguel Medina^{11,54}, Alun Meggy¹⁰⁸, Shima Mehrabian⁵², Silvia Mendoza¹³⁸, Manuel Menéndez-González³³, Pablo Mir^{11,188}, Susanne Moebus¹⁸⁹, Merel Mol¹⁷, Laura Molina-Porcel^{190,191}, Laura Montreal¹⁰, Laura Morelli¹⁹², Fermin Moreno^{11,182}, Kevin Morgan¹⁹³, Thomas Mosley¹⁹⁴, Markus M. Nöthen¹⁵⁶, Carolina Muchnik^{74,195}, Shubhabrata Mukherjee¹⁹⁶, Benedetta Nacmias^{60,197}, Tiia Ngandu¹⁷⁸, Gael Nicolas⁹², Børge G. Nordestgaard^{121,198}, Robert Olaso¹⁷, Adelina Orellana^{10,11}, Michela Orsini⁹⁸, Gemma Ortega^{10,11}, Alessandro Padovani⁶⁵, Caffarra Paolo¹⁹⁹, Goran Papenberg¹⁴⁵, Lucilla Parnetti¹²³, Florence Pasquier²⁰⁰, Pau Pastor^{30,31}, Gina Peloso^{20,53}, Alba Pérez-Cordón¹⁰, Jordi Pérez-Tur^{11,201,202}, Pierre Pericard²⁰³, Oliver Peters^{204,205}, Yolande A. L. Pijnenburg⁵, Juan A. Pineda⁹⁷, Gerard Piñol-Ripoll^{42,43},

Claudia Pisanu ²⁰⁶, Thomas Polak¹⁰⁷, Julius Popp^{207,208,209}, Danielle Posthuma ⁶, Josef Priller^{205,210}, Raquel Puerta ¹⁰, Olivier Quenez ⁹², Inés Quintela⁸⁹, Jesper Qvist Thomassen ²¹¹, Alberto Rábano^{11,54}, Innocenzo Rainero⁶⁶, Farid Rajabli¹⁵⁴, Inez Ramakers²¹², Luis M. Real ^{97,213}, Marcel J. T. Reinders ²¹⁴, Christiane Reitz ^{186,214,215}, Dolly Reyes-Dumeyer^{183,215}, Perry Ridge²¹⁶, Steffi Riedel-Heller ²¹⁷, Peter Riederer²¹⁸, Natalia Roberto¹⁰, Eloy Rodriguez-Rodriguez ^{11,174}, Arvid Rongve ^{219,220}, Irene Rosas Allende^{32,33}, Maitée Rosende-Roca^{10,11}, Jose Luis Royo²²¹, Elisa Rubino²²², Dan Rujescu¹⁴⁰, María Eugenia Sáez ¹⁴², Paraskevi Sakka²²³, Ingvild Saltvedt ^{69,224}, Ángela Sanabria^{10,11}, María Bernal Sánchez-Arjona¹³², Florentino Sanchez-Garcia²²⁵, Pascual Sánchez Juan ^{11,174}, Raquel Sánchez-Valle²²⁶, Sigrid B. Sando^{68,69}, Chloé Sarnowski ⁶⁴, Claudia L. Satizabal ^{21,109,130}, Michela Scamosci⁹¹, Nikolaos Scarmeas^{50,227}, Elio Scarpini^{40,124}, Philip Scheltens⁵, Norbert Scherbaum²²⁸, Martin Scherer²²⁹, Matthias Schmid^{9,230}, Anja Schneider^{7,9}, Jonathan M. Schott ¹³¹, Geir Selbæk ^{129,231}, Davide Seripa²³², Manuel Serrano²³³, Jin Sha¹⁴, Alexey A. Shadrin ⁴⁶, Olivia Skrobot¹⁶⁴, Susan Slifer¹⁵⁴, Gijse J. L. Snijders¹⁰⁶, Hilikka Soinen ¹⁵⁷, Vincenzo Solfrizzi ⁹⁹, Alina Solomon^{157,165}, Yeunjoo Song ⁵⁷, Sandro Sorbi^{60,197}, Oscar Sotolongo-Grau ¹⁰, Gianfranco Spalletta ⁴⁸, Annika Spottke^{9,234}, Alessio Squassina ²³⁵, Eystein Stordal ²³⁶, Juan Pablo Tartan¹⁰, Lluís Tàrraga^{10,11}, Niccolo Tesi^{5,18}, Anbupalam Thalamuthu³⁴, Tegos Thomas^{35,36}, Giuseppe Tosto ^{50,183}, Latchezar Traykov⁵², Lucio Tremolizzo^{38,39}, Anne Tybjærg-Hansen^{198,211}, Andre Uitterlinden ²³⁷, Abbe Ullgren¹⁴³, Ingun Ulstein²³¹, Sergi Valero^{10,11}, Otto Valladares ¹⁵, Christine Van Broeckhoven ^{2,3,238}, Jeffery Vance⁸⁸, Badri N. Vardarajan⁵⁰, Aad van der Lugt²³⁹, Jasper Van Dongen^{2,3,4}, Jeroen van Rooij^{77,239}, John van Swieten⁷⁷, Rik Vandenberghe^{240,241}, Frans Verhey²¹², Jean-Sébastien Vidal ⁴⁷, Jonathan Vogelgsang ^{242,243}, Martin Vyhnalek^{179,180}, Michael Wagner ^{7,9}, David Wallon ²⁴⁴, Li-San Wang¹⁵, Ruiqi Wang^{20,21}, Leonie Weinhold²³⁰, Jens Wiltfang ^{242,245,246}, Gill Windle¹⁸⁴, Bob Woods ¹⁸⁴, Mary Yannakoulia ²⁴⁷, Habil Zare ¹³⁰, Yi Zhao¹⁵, Xiaoling Zhang ²⁴⁸, Congcong Zhu²⁴⁸, Miren Zulaica^{11,249}, EADB, GR@ACE, DEGESCO, EADI, GERAD, Demgene, FinnGen, ADGC, CHARGE, Lindsay A. Farrer ^{20,87,109}, Bruce M. Psaty ^{22,84,250}, Mohsen Ghanbari ¹², Towfique Raj ^{103,104,105,160}, Perminder Sachdev ³⁴, Karen Mather ³⁴, Frank Jessen^{7,9}, M. Arfan Ikram ¹², Alexandre de Mendonça¹²⁷, Jakub Hort^{1177,179}, Magda Tsolaki ^{35,36}, Margaret A. Pericak-Vance ¹⁵², Philippe Amouyel ¹, Julie Williams ^{16,108}, Ruth Frikke-Schmidt ^{198,211}, Jordi Clarimon^{11,29}, Jean-François Deleuze¹⁷, Giacomina Rossi¹²⁰, Sudha Seshadri ^{21,109,130}, Ole A. Andreassen ⁴⁶, Martin Ingelsson²⁵, Mikko Hiltunen^{19,568}, Kristel Slegers ^{2,3,4,568}, Gerard D. Schellenberg^{15,568}, Cornelia M. van Duijn ^{12,13,568}, Rebecca Sims ^{16,568}, Wiesje M. van der Flier ^{5,568}, Agustín Ruiz^{10,11,568}, Alfredo Ramirez ^{7,8,9,130,251,568} and Jean-Charles Lambert ^{1,568} ✉

¹Université de Lille, INSERM, CHU Lille, Institut Pasteur Lille, U1167-RID-AGE, Facteurs de risque et déterminants moléculaires des maladies liées au vieillissement, Lille, France. ²Complex Genetics of Alzheimer's Disease Group, VIB Center for Molecular Neurology, VIB, Antwerp, Belgium. ³Laboratory of Neurogenetics, Institute Born - Bunge, Antwerp, Belgium. ⁴Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium. ⁵Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands. ⁶Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije University, Amsterdam, the Netherlands. ⁷Department of Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, Bonn, Germany. ⁸Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, University of Cologne, Medical Faculty, Cologne, Germany. ⁹German Center for Neurodegenerative Diseases (DZNE Bonn), Bonn, Germany. ¹⁰Research Center and Memory Clinic Fundació ACE, Institut Català de Neurociències Aplicades, Universitat Internacional de Catalunya, Barcelona, Spain. ¹¹CIBERNED, Network Center for Biomedical Research in Neurodegenerative Diseases, National Institute of Health Carlos III, Madrid, Spain. ¹²Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands. ¹³Nuffield Department of Population Health, Oxford University, Oxford, UK. ¹⁴Department of Biostatistics, Epidemiology, and Informatics, Penn Neurodegeneration Genomics Center, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. ¹⁵Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. ¹⁶MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neuroscience, School of Medicine, Cardiff University, Cardiff, UK. ¹⁷CEA, Centre National de Recherche en Génomique Humaine,

Université Paris-Saclay, Evry, France. ¹⁸Section Genomics of Neurodegenerative Diseases and Aging, Department of Human Genetics Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands. ¹⁹Brain Institute, Federal University of Rio Grande do Norte, Natal, Brazil. ²⁰Institute of Biomedicine, University of Eastern Finland, Kuopio, Finland. ²¹Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA. ²²Framingham Heart Study, Framingham, MA, USA. ²³Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA. ²⁴LACDR, Leiden, the Netherlands. ²⁵Department of Public Health and Carins Sciences/Geriatrics, Uppsala University, Uppsala, Sweden. ²⁶Centre of Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway. ²⁷Institute of Psychiatry, Psychology & Neuroscience, London, UK. ²⁸Department of Surgery, Biochemistry and Molecular Biology, School of Medicine, University of Málaga, Málaga, Spain. ²⁹Department of Neurology, II B Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain. ³⁰Fundació Docència i Recerca MútuaTerrassa and Movement Disorders Unit, Department of Neurology, University Hospital MútuaTerrassa, Terrassa, Spain. ³¹Memory Disorders Unit, Department of Neurology, Hospital Universitari Mutua de Terrassa, Terrassa, Spain. ³²Laboratorio de Genética, Hospital Universitario Central de Asturias, Oviedo, Spain. ³³Servicio de Neurología, Hospital Universitario Central de Asturias- Oviedo and Instituto de Investigación Biosanitaria del Principado de Asturias, Oviedo, Spain. ³⁴Centre for Healthy Brain Ageing, School of Psychiatry, Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia. ³⁵First Department of Neurology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece. ³⁶Alzheimer Hellas, Thessaloniki, Greece. ³⁷Unidad de Demencias, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain. ³⁸School of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy. ³⁹Neurology Unit, San Gerardo Hospital, Monza, Italy. ⁴⁰Fondazione IRCCS Ca'Granda, Ospedale Policlinico, Milan, Italy. ⁴¹Department of Laboratory Diagnostics, III Laboratory of Analysis, Brescia Hospital, Brescia, Italy. ⁴²Unitat Trastorns Cognitius, Hospital Universitari Santa Maria de Lleida, Lleida, Spain. ⁴³Institut de Recerca Biomedica de Lleida (IRBLleida), Lleida, Spain. ⁴⁴Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy. ⁴⁵Geriatric Unit, Fondazione Cà Granda, IRCCS Ospedale Maggiore Policlinico, Milan, Italy. ⁴⁶NORMENT Centre, University of Oslo, Oslo, Norway. ⁴⁷EA 4468, Université de Paris, APHP, Hôpital Broca, Paris, France. ⁴⁸Laboratory of Neuropsychiatry, Department of Clinical and Behavioral Neurology, IRCCS Santa Lucia Foundation, Rome, Italy. ⁴⁹Servei de Neurologia, Hospital Universitari i Politècnic La Fe, Valencia, Spain. ⁵⁰Taub Institute on Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University, New York, NY, USA. ⁵¹Unit of Neurology, University of Parma and AOU, Parma, Italy. ⁵²Clinic of Neurology, UH 'Alexandrovska', Medical University - Sofia, Sofia, Bulgaria. ⁵³Boston University and the NHLBI's Framingham Heart Study, Boston, MA, USA. ⁵⁴CIEN Foundation/Queen Sofia Foundation Alzheimer Center, Madrid, Spain. ⁵⁵Vanderbilt Brain Institute, Vanderbilt University, Nashville, TN, USA. ⁵⁶Cleveland Institute for Computational Biology, Case Western Reserve University, Cleveland, OH, USA. ⁵⁷Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA. ⁵⁸Molecular Markers Laboratory, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. ⁵⁹Neuropsychiatry: Epidemiological and Clinical Research, PSNREC, Université de Montpellier, INSERM U1061, Montpellier, France. ⁶⁰Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy. ⁶¹Azienda Ospedaliero-Universitaria Careggi, Florence, Italy. ⁶²MAC - Memory Clinic, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. ⁶³Geriatrics Unit, Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy. ⁶⁴Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA. ⁶⁵Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA. ⁶⁶Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. ⁶⁷Department of Neuroscience "Rita Levi Montalcini", University of Torino, Torino, Italy. ⁶⁸Experimental Neuro-psychobiology Laboratory, Department of Clinical and Behavioral Neurology, IRCCS Santa Lucia Foundation, Rome, Italy. ⁶⁹Department of Neurology and Clinical Neurophysiology, University Hospital of Trondheim, Trondheim, Norway. ⁷⁰Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway. ⁷¹School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA. ⁷²Dementia Centre for Research Collaboration, School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia. ⁷³Biosciences, School of Science and Technology, Nottingham Trent University, Nottingham, UK. ⁷⁴Centro de Neuropsiquiatria y Neurología de la Conducta (CENECON), Facultad de Medicina, Universidad de Buenos Aires (UBA), C.A.B.A., Buenos Aires, Argentina. ⁷⁵Departamento Ciencias Fisiológicas UAll, Facultad de Medicina, UBA, C.A.B.A., Buenos Aires, Argentina. ⁷⁶Hospital Interzonal General de Agudos Eva Perón, San Martín, Buenos Aires, Argentina. ⁷⁷Department of Neurology, Erasmus MC, Rotterdam, the Netherlands. ⁷⁸Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig Maximilians Universität (LMU), Munich, Germany. ⁷⁹German Center for Neurodegenerative Diseases (DZNE, Munich), Munich, Germany. ⁸⁰Faculty of Medical & Health Sciences, University of Auckland, Auckland, New Zealand. ⁸¹Wales Centre for Ageing & Dementia Research, Swansea University, Wales, New Zealand. ⁸²Department of Population & Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA. ⁸³UFIEC, Instituto de Salud Carlos III, Madrid, Spain. ⁸⁴Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁸⁵INSERM, Bordeaux Population Health Research Center, UMR 1219, ISPED, CIC 1401-EC, Université de Bordeaux, Bordeaux, France. ⁸⁶Pole Santé Publique, CHU de Bordeaux, Bordeaux, France. ⁸⁷Medicine Biomedical Genetics Boston University School of Medicine, Boston, MA, USA. ⁸⁸Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami, Miami, FL, USA. ⁸⁹Grupo de Medicina Xenómica, Centro Nacional de Genotipado (CEGEN-PRB3-ISCI), Universidad de Santiago de Compostela, Santiago de Compostela, Spain. ⁹⁰Fundación Pública Galega de Medicina Xenómica- CIBERER-IDIS, University of Santiago de Compostela, Santiago de Compostela, Spain. ⁹¹Institute of Gerontology and Geriatrics, Department of Medicine and Surgery, University of Perugia, Perugia, Italy. ⁹²Department of Genetics and CNR-MAJ, Normandie University, UNIROUEN, INSERM U1245, CHU Rouen, Rouen, France. ⁹³Division of Genetic Medicine, Vanderbilt University, Nashville, TN, USA. ⁹⁴Unit of Clinical Pharmacology, University Hospital of Cagliari, Cagliari, Italy. ⁹⁵Radboudumc Alzheimer Center, Department of Geriatrics, Radboud University Medical Center, Nijmegen, the Netherlands. ⁹⁶Institute for Regenerative Medicine, University of Zürich, Schlieren, Switzerland. ⁹⁷Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario de Valme, Sevilla, Spain. ⁹⁸Department of Neuroscience, Catholic University of Sacred Heart, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. ⁹⁹University of Bari, "A. Moro", Bari, Italy. ¹⁰⁰School of Medicine, University of Thessaly, Larissa, Greece. ¹⁰¹Bordeaux Population Health Research Center, University Bordeaux, INSERM, Bordeaux, France. ¹⁰²Department of Neurology, University Medical Center Groningen, Groningen, the Netherlands. ¹⁰³Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹⁰⁴Department of Genetics and Genomic Sciences & Icahn Institute for Data Science and Genomic Technology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹⁰⁵Estelle and Daniel Maggin Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹⁰⁶Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹⁰⁷Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital, Wuerzburg, Germany. ¹⁰⁸UKDRI@ Cardiff, School of Medicine, Cardiff University, Cardiff, UK. ¹⁰⁹Department of Neurology, Boston University School of Medicine, Boston, MA, USA. ¹¹⁰Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. ¹¹¹Klinikum rechts der Isar, Department of Psychiatry and Psychotherapy, Technical University of Munich, School of Medicine, Munich, Germany. ¹¹²Institute of Cognitive Neurology and Dementia Research (IKND), Otto-Von-Guericke University, Magdeburg, Germany. ¹¹³German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany. ¹¹⁴Icelandic Heart Association, Kopovagur, Iceland. ¹¹⁵Center for Neurosciences, Vrije Universiteit Brussel (VUB), Brussels, Belgium. ¹¹⁶Reference Center for Biological Markers of Dementia (BIODEM), Institute Born-Bunge, University of Antwerp, Antwerp, Belgium. ¹¹⁷Institute Born-Bunge, University of Antwerp, Antwerp, Belgium. ¹¹⁸Department of Neurology, UZ Brussel, Brussels, Belgium. ¹¹⁹Department of Medical and Molecular Genetics, Indiana University, Indianapolis, IN, USA. ¹²⁰Fondazione IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy. ¹²¹Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Herlev, Denmark. ¹²²Sanders-Brown Center on Aging, Department of Biostatistics, University of Kentucky, Lexington, KY, USA. ¹²³Centre for Memory Disturbances, Lab of

Clinical Neurochemistry, Section of Neurology, University of Perugia, Perugia, Italy. ¹²⁴University of Milan, Milan, Italy. ¹²⁵Laboratory of Neurogenetics, Department of Internal Medicine, Texas Tech University Health Science Center, Lubbock, TX, USA. ¹²⁶Reta Lila Weston Research Laboratories, Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK. ¹²⁷Faculty of Medicine, University of Lisbon, Lisbon, Portugal. ¹²⁸Department of Psychiatry, Social Medicine Center East- Donaospital, Vienna, Austria. ¹²⁹Institute of Clinical Medicine, University of Oslo, Oslo, Norway. ¹³⁰Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio, TX, USA. ¹³¹Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK. ¹³²Unidad de Demencias, Servicio de Neurología y Neurofisiología. Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain. ¹³³Instituto de Investigación Sanitaria 'Hospital la Paz' (IdiPaz), Madrid, Spain. ¹³⁴Centro de Biología Molecular Severo Ochoa (UAM-CSIC), Madrid, Spain. ¹³⁵Hospital Universitario la Paz, Madrid, Spain. ¹³⁶Department of Geriatric Psychiatry, Central Institute for Mental Health, Mannheim, University of Heidelberg, Heidelberg, Germany. ¹³⁷Department of Genetics and Genomic Sciences, Ronald M. Loeb Center for Alzheimer's Disease Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹³⁸Alzheimer Research Center & Memory Clinic, Andalusian Institute for Neuroscience, Málaga, Spain. ¹³⁹Hospital Universitario Ramon y Cajal, IRYCIS, Madrid, Spain. ¹⁴⁰Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria. ¹⁴¹Department of Biostatistics, Epidemiology, and Informatics Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ¹⁴²CAEBI, Centro Andaluz de Estudios Bioinformáticos, Sevilla, Spain. ¹⁴³Center for Alzheimer Research, Department NVS, Division of Neurogeriatrics, Karolinska Institutet, Stockholm, Sweden. ¹⁴⁴Unit for Hereditary Dementias, Karolinska University Hospital-Solna, Stockholm, Sweden. ¹⁴⁵Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden. ¹⁴⁶Institute of Public Health, University of Cambridge, Cambridge, UK. ¹⁴⁷Department of Child and Adolescent Psychiatry and Psychotherapy, University Hospital of Psychiatry Zurich, University of Zurich, Zurich, Switzerland. ¹⁴⁸Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland. ¹⁴⁹Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland. ¹⁵⁰Icelandic Heart Association, Faculty of Medicine, University of Iceland, Reykjavik, Iceland. ¹⁵¹Human Genetics, School of Life Sciences, Life Sciences Building, University Park, University of Nottingham, Nottingham, UK. ¹⁵²AI Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland. ¹⁵³Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus. ¹⁵⁴The John P. Hussman Institute for Human Genomics, University of Miami, Miami, FL, USA. ¹⁵⁵GRC 21, Alzheimer Precision Medicine Initiative (APMI), Sorbonne University, AP-HP, Pitié-Salpêtrière Hospital, Paris, France. ¹⁵⁶Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany. ¹⁵⁷Institute of Clinical Medicine, Neurology, University of Eastern, Kuopio, Finland. ¹⁵⁸Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland, Kuopio, Finland. ¹⁵⁹Clinical and Experimental Science, Faculty of Medicine, University of Southampton, Southampton, UK. ¹⁶⁰Nash Family Department of Neuroscience & Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹⁶¹Department of Neurology, UMC Utrecht Brain Center, Utrecht, the Netherlands. ¹⁶²Biostatistics, University of Kentucky College of Public Health, Lexington, KY, USA. ¹⁶³Department of Biology, Brigham Young University, Provo, UT, USA. ¹⁶⁴Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK. ¹⁶⁵Division of Clinical Geriatrics, Center for Alzheimer Research, Care Sciences and Society (NVS), Karolinska Institutet, Stockholm, Sweden. ¹⁶⁶Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland. ¹⁶⁷Neuroepidemiology and Ageing Research Unit, School of Public Health, Imperial College London, London, UK. ¹⁶⁸Research & Development, UnitStockholms Sjukhem, Stockholm, Sweden. ¹⁶⁹Department of Neurology, Kuopio University Hospital, Kuopio, Finland. ¹⁷⁰Department of Neurosciences, University of Helsinki and Department of Geriatrics, Helsinki University Hospital, Helsinki, Finland. ¹⁷¹Department of Psychiatry and Psychotherapy, Universitätsklinikum Erlangen, and Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany. ¹⁷²Laboratory of Cognitive Neuroscience, School of Psychology, Aristotle University of Thessaloniki, Thessaloniki, Greece. ¹⁷³Department of Epidemiology, University of Washington, Seattle, WA, USA. ¹⁷⁴Neurology Service, Marqués de Valdecilla University Hospital (University of Cantabria and IDIVAL), Santander, Spain. ¹⁷⁵Stockholm Gerontology Research Center, Stockholm, Sweden. ¹⁷⁶Laboratory of Epidemiology, Demography, and Biometry, National Institute of Aging, The National Institutes of Health, Bethesda, MD, USA. ¹⁷⁷Intramural Research Program/National Institute on Aging/National Institutes of Health, Bethesda, MD, USA. ¹⁷⁸Public Health Promotion Unit, Finnish Institute for Health and Welfare, Helsinki, Finland. ¹⁷⁹Memory Clinic, Department of Neurology, Charles University, 2nd Faculty of Medicine and Motol University Hospital, Praha, Czechia. ¹⁸⁰International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czechia. ¹⁸¹Departments of Neurology and Epidemiology, University of Washington, Seattle, WA, USA. ¹⁸²Department of Neurology, Hospital Universitario Donostia, OSAKIDETZA-Servicio Vasco de Salud, San Sebastian, Spain. ¹⁸³Department of Neurology, Columbia University, New York, NY, USA. ¹⁸⁴School of Health Sciences, Bangor University, Bangor, UK. ¹⁸⁵Institute of Neurology, Catholic University of the Sacred Heart, Rome, Italy. ¹⁸⁶Gertrude H. Sergievsky Center, Columbia University, New York, NY, USA. ¹⁸⁷MRC Prion Unit at UCL, UCL Institute of Prion Diseases, London, UK. ¹⁸⁸Unidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología. Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain. ¹⁸⁹Institute for Urban Public Health, University Hospital of University Duisburg-Essen, Essen, Germany. ¹⁹⁰Neurological Tissue Bank of the Biobanc-Hospital Clinic-IDIBAPS, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain. ¹⁹¹Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Department, Hospital Clinic, Barcelona, Spain. ¹⁹²Laboratory of Brain Aging and Neurodegeneration, FIL-CONICET, Buenos Aires, Argentina. ¹⁹³Human Genetics, School of Life Sciences, University of Nottingham, Nottingham, UK. ¹⁹⁴Memory Impairment and Neurodegenerative Dementia (MIND) Center, University of Mississippi Medical Center, Jackson, MS, USA. ¹⁹⁵Laboratorio de Bioquímica Molecular, Facultad de Medicina, Instituto de Investigaciones Médicas A. Lanari, UBA, C.A.B.A, Buenos Aires, Argentina. ¹⁹⁶Department of Medicine, University of Washington, Seattle, WA, USA. ¹⁹⁷IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy. ¹⁹⁸Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. ¹⁹⁹DIMEC, University of Parma, Parma, Italy. ²⁰⁰Resources and Research Memory Center (MRRC) of Distal, LicendUniversity of Lille, INSERM, CHU Lille, UMR1172, Lille, France. ²⁰¹Institut de Biomedicina de València-CSIC CIBERNED, València, Spain. ²⁰²Unitat Mixta de de Neurologia y Genética, Institut d'Investigació Sanitària La Fe, València, Spain. ²⁰³US 41-UMS 2014-PLBS, bilille, Université de Lille, CNRS, INSERM, CHU Lille, Institut Pasteur de Lille, Lille, France. ²⁰⁴Institute of Psychiatry and Psychotherapy, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität Zu Berlin, and Berlin Institute of Health, Berlin, Germany. ²⁰⁵German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany. ²⁰⁶Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy. ²⁰⁷CHUV, Old Age Psychiatry, Department of Psychiatry, Lausanne, Switzerland. ²⁰⁸Old Age Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland. ²⁰⁹Department of Geriatric Psychiatry, University Hospital of Psychiatry Zürich, Zürich, Switzerland. ²¹⁰Department of Neuropsychiatry and Laboratory of Molecular Psychiatry, Charité, Charitéplatz 1, Berlin, Germany. ²¹¹Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark. ²¹²Department of Psychiatry & Neuropsychologie, Maastricht University, Alzheimer Center Limburg, Maastricht, the Netherlands. ²¹³Departamento de Especialidades Quirúrgicas Bioquímica e Inmunología, Facultad de Medicina, Instituto de Investigaciones Médicas A. Lanari, UBA, C.A.B.A, Buenos Aires, Argentina. ²¹⁴Delft Bioinformatics Lab, Delft University of Technology, Delft, the Netherlands. ²¹⁵Taub Institute, Columbia University, New York, NY, USA. ²¹⁶Bioinformatics, College of Life Sciences, Brigham Young University, Provo, UT, USA. ²¹⁷Institute of Social Medicine, Occupational Health and Public Health, University of Leipzig, Leipzig, Germany. ²¹⁸Center of Mental Health, Clinic and Policlinic of Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Würzburg, Wuerzburg, Germany. ²¹⁹Department of Research and Innovation, Helse Fonna, Haugesund Hospital, Haugesund, Norway. ²²⁰Institute of Clinical Medicine (K1), The University of Bergen, Bergen, Norway. ²²¹Departamento de Especialidades Quirúrgicas, Bioquímicas e Inmunología, School of Medicine, University of Málaga, Málaga, Spain. ²²²Department of Neuroscience and Mental Health, AOU Città della Salute e della Scienza di Torino, Torino, Italy. ²²³Athens Association of Alzheimer's Disease and Related Disorders, Athens, Greece. ²²⁴Department of Geriatrics, St. Olav's Hospital, Trondheim

University Hospital, Trondheim, Norway. ²²⁵Department of Immunology, Hospital Universitario Doctor Negrín, Las Palmas de Gran Canaria, Las Palmas, Spain. ²²⁶Neurology Department-Hospital Clínic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain. ²²⁷First Department of Neurology, Aiginition Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece. ²²⁸LVR-Hospital Essen, Department of Psychiatry and Psychotherapy, Medical Faculty, University of Duisburg-Essen, Essen, Germany. ²²⁹Department of Primary Medical Care, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany. ²³⁰Institute of Medical Biometry, Informatics and Epidemiology, University Hospital of Bonn, Bonn, Germany. ²³¹Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway. ²³²Laboratory for Advanced Hematological Diagnostics, Department of Hematology and Stem Cell Transplant, Vito Fazzi Hospital, Lecce, Italy. ²³³Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, CIBERDEM, Hospital Clínico San Carlos, Madrid, Spain. ²³⁴Department of Neurology, University of Bonn, Bonn, Germany. ²³⁵Department of Biomedical Sciences, Section of Neuroscience and Clinical Pharmacology, University of Cagliari, Cagliari, Italy. ²³⁶Department of Psychiatry, Namsos Hospital, Namsos, Norway. ²³⁷Department of Internal Medicine and Biostatistics, Erasmus MC, Rotterdam, the Netherlands. ²³⁸Neurodegenerative Brain Diseases Group, VIB Center for Molecular Neurology, VIB, Antwerp, Belgium. ²³⁹Department of Neurology, ErasmusMC, Rotterdam, the Netherlands. ²⁴⁰Laboratory for Cognitive Neurology, Department of Neurosciences, University of Leuven, Leuven, Belgium. ²⁴¹Neurology Department, University Hospitals Leuven, Leuven, Belgium. ²⁴²Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, Goettingen, Germany. ²⁴³Department of Psychiatry, Harvard Medical School, McLean Hospital, Belmont, MA, USA. ²⁴⁴Department of Neurology and CNR-MAJ, F 76000, Normandy Center for Genomic and Personalized Medicine, Normandie University, UNIROUEN, INSERM U1245, CHU Rouen, Rouen, France. ²⁴⁵German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany. ²⁴⁶Medical Science Department, iBiMED, Aveiro, Portugal. ²⁴⁷Department of Nutrition and Diabetics, Harokopio University, Athens, Greece. ²⁴⁸Department of Medicine (Biomedical Genetics), Boston University School of Medicine, Boston, MA, USA. ²⁴⁹Neurosciences Area, Instituto Biodonostia, San Sebastian, Spain. ²⁵⁰Department of Health Service, University of Washington, Seattle, WA, USA. ²⁵¹Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany. ²⁵²These authors contributed equally: Céline Bellenguez, Fhari Kuçukali, Iris Jansen, Luca Kleineidam, Sonia Moreno-Grau, Najaf Amin, Adam Naj and Rafael Campos-Martin. ²⁵³These authors jointly supervised this work: Mikko Hiltunen, Kristel Sleegers, Gerard Schellenberg, Cornelia van Duijn, Rebecca Sims, Wiesje van der Flier, Agustin Ruiz, Alfredo Ramirez and Jean-Charles Lambert. ²⁵⁴e-mail: celine.bellenguez@pasteur-lille.fr; Jean-Charles.Lambert@pasteur-lille.fr

EADB

Jan Laczó^{179,180}, Vaclav Matoska²⁵², Maria Serpente¹²⁴, Francesca Assogna⁴⁸, Fabrizio Piras⁴⁸, Federica Piras⁴⁸, Valentina Ciullo⁴⁸, Jacob Shofany⁴⁸, Carlo Ferrarese^{38,39}, Simona Andreoni³⁸, Gessica Sala³⁸, Chiara Paola Zoia³⁸, Maria Del Zompo²³⁵, Alberto Benussi⁶⁶, Patrizia Bastiani²⁵³, Mari Takalo²⁵⁴, Teemu Natunen²⁵⁴, Tiina Laatikainen^{166,178}, Jaakko Tuomilehto^{166,178}, Riitta Antikainen^{255,256}, Timo Strandberg^{255,257}, Jaana Lindström¹⁷⁸, Markku Peltonen¹⁷⁸, Richard Abraham²⁵⁸, Ammar Al-Chalabi²⁵⁹, Nicholas J. Bass²⁶⁰, Carol Brayne²⁶¹, Kristelle S. Brown²⁶², John Collinge¹⁸⁷, David Craig²⁶³, Pangiotis Deloukas²⁶⁴, Nick Fox²⁶⁵, Amy Gerrish²⁶⁵, Michael Gill²⁶⁶, Rhian Gwilliam²⁶⁴, Denise Harold²⁶⁷, Paul Hollingworth²⁵⁸, Jarret A. Johnston²⁶⁸, Lesley Jones²⁵⁸, Brian Lawlor²⁶⁶, Gill Livingston²⁶⁰, Simon Lovestone²⁶⁹, Michelle Lupton^{270,271}, Aoibhinn Lynch²⁶⁶, David Mann²⁷², Bernadette McGuinness²⁶⁸, Andrew McQuillin²⁶⁰, Michael C. O'Donovan²⁵⁸, Michael J. Owen²⁵⁸, Peter Passmore²⁶⁸, John F. Powell^{270,271}, Petra Proitsis^{270,271}, Martin Rossor²⁶⁵, Christopher E. Shaw²⁵⁹, A. David Smith²⁷³, Hugh Gurling²⁷⁴, Stephen Todd²⁷⁵, Catherine Mummery²⁷⁶, Nathalie Ryan²⁷⁶, Giordano Lacidogna⁹⁸, Ad Adarmes-Gómez^{11,77}, Ana Mauleón¹⁰, Ana Pancho¹⁰, Anna Gailhagenet¹⁰, Asunción Lafuente¹⁰, D. Macias-García^{11,77}, Elvira Martín¹⁰, Esther Pelejà¹⁰, F. Carrillo^{11,77}, Isabel Sastre Merlín^{11,134}, L. Garrote-Espina^{11,77}, Liliana Vargas¹⁰, M. Carrion-Claro^{11,77}, M. Marín⁹⁶, Ma Labrador^{11,77}, Mar Buendia¹⁰, María Dolores Alonso²⁷⁷, Marina Guitart¹⁰, Mariona Moreno¹⁰, Marta Ibarria¹⁰, Mt Perrián^{11,77}, Nuria Aguilera¹⁰, P. Gómez-Garre^{11,77}, Pilar Cañabate¹⁰, R. Escuela^{11,77}, R. Pineda-Sánchez^{1,77}, R. Vigo-Ortega^{11,77}, S. Jesús^{11,77}, Silvia Preckler¹⁰, Silvia Rodrigo-Herrero¹³², Susana Diego¹⁰, Alessandro Vacca⁶⁷, Fausto Roveta⁶⁷, Nicola Salvadori¹¹², Elena Chipi¹¹², Henning Boecker^{9,278}, Christoph Laske^{279,280}, Robert Perneczky^{81,281}, Costas Anastasiou²⁴⁷, Daniel Janowitz⁷⁸, Rainer Malik⁷⁸, Anna Anastasiou³⁵, Kayenat Parveen⁷, Carmen Lage²⁸², Sara López-García²⁸², Anna Antonell²²⁶, Kalina Yonkova Mihova²⁸³, Diyana Belezhanska⁵², Heike Weber²⁸⁴, Silvia Kochen²⁸⁵, Patricia Solis²⁸⁵, Nancy Medel²⁸⁵, Julieta Lisso²⁸⁵, Zulma Sevillano²⁸⁵, Daniel G. Politis^{285,286}, Valeria Cores^{285,286}, Carolina Cuesta^{285,286}, Cecilia Ortiz²⁸⁷, Juan Ignacio Bacha²⁸⁷, Mario Rios²⁸⁸, Aldo Saenz²⁸⁸, Mariana Sanchez Abalos²⁸⁹, Eduardo Kohler²⁹⁰, Dana Lis Palacio²⁹¹, Ignacio Etchepareborda²⁹¹, Matias Kohler²⁹¹, Gisela Novack²⁹², Federico Ariel Prestia²⁹², Pablo Galeano²⁹², Eduardo M. Castaño²⁹², Sandra Germani²⁹³,

Carlos Reyes Toso²⁹³, Matias Rojo²⁹³, Carlos Ingino²⁹³, Carlos Mangone²⁹³, David C. Rubinsztein²⁹⁴, Stefan Teipel²⁹⁵, Nathalie Fievet¹, Vincent Deramerourt²⁰⁰, Charlotte Forsell^{143,144}, Håkan Thonberg^{143,144}, Maria Bjerke⁸⁹, Ellen De Roeck⁸⁹, María Teresa Martínez-Larrad²⁹⁶ and Natividad Olivar²⁹³

²⁵²Department of Clinical Biochemistry, Hematology and Immunology, Na Homolce Hospital, Prague, Czechia. ²⁵³Institute of Gerontology and Geriatrics, Department of Medicine, University of Perugia, Perugia, Italy. ²⁵⁴Institute of Biomedicine, University of Eastern Finland, Kuopio, Finland. ²⁵⁵Center for Life Course Health Research, University of Oulu, Oulu, Finland. ²⁵⁶Medical Research Center Oulu, Oulu University Hospital, Oulu, Finland. ²⁵⁷University of Helsinki and Helsinki University Hospital, Helsinki, Finland. ²⁵⁸Division of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK. ²⁵⁹Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK. ²⁶⁰Division of Psychiatry, University College London, London, UK. ²⁶¹Institute of Public Health, University of Cambridge, Cambridge, UK. ²⁶²Institute of Genetics, Queens Medical Centre, University of Nottingham, Nottingham, UK. ²⁶³Ageing Group, Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK. ²⁶⁴The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK. ²⁶⁵Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK. ²⁶⁶Mercer's Institute for Research on Ageing, St James' Hospital, Dublin, Ireland. ²⁶⁷School of Biotechnology, Dublin City University, Dublin, Ireland. ²⁶⁸Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queens University Belfast, Belfast, UK. ²⁶⁹Department of Psychiatry, University of Oxford, Oxford, UK. ²⁷⁰Genetic Epidemiology, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia. ²⁷¹Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK. ²⁷²Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. ²⁷³Oxford Project to Investigate Memory and Ageing (OPTIMA), University of Oxford, Level 4, John Radcliffe Hospital, Oxford, UK. ²⁷⁴Department of Mental Health Sciences, University College London, London, UK. ²⁷⁵Ageing Group, Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK. ²⁷⁶Dementia Research Centre, UCL, London, UK. ²⁷⁷Servei de Neurologia Hospital Clínic, Universitari de València, Valencia, Spain. ²⁷⁸Department of Radiology, University Hospital Bonn, Bonn, Germany. ²⁷⁹German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany. ²⁸⁰Section for Dementia Research, Department of Psychiatry, Hertie Institute for Clinical Brain Research, Tübingen, Germany. ²⁸¹Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany. ²⁸²Service of Neurology, University Hospital Marqués de Valdecilla, IDIVAL, University of Cantabria, Santander, Spain. ²⁸³Molecular Medicine Center, Department of Medical chemistry and biochemistry, Medical University of Sofia, Sofia, Bulgaria. ²⁸⁴Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital of Würzburg, Würzburg, Germany. ²⁸⁵ENYS (Estudio en Neurociencias y Sistemas Complejos) CONICET- Hospital El Cruce "Nestor Kirchner" - UNAJ, Buenos Aires, Argentina. ²⁸⁶HIGA Eva Perón, Buenos Aires, Argentina. ²⁸⁷Neurología Clínica, Buenos Aires, Argentina. ²⁸⁸Dirección de Atención de Adultos Mayores del Min. Salud Desarrollo Social y Deportes de la Pcia. de Mendoza, Mendoza, Argentina. ²⁸⁹Laboratorio de Genética Forense del Ministerio Público de la Pcia de La Pampa, La Pampa, Argentina. ²⁹⁰Fundacion Sinapsis, Santa Rosa, Argentina. ²⁹¹Hospital Dr. Lucio Molas, Santa Rosa; Fundacion Ayuda Enfermo Renal y Alta Complejidad (FERNAC), Santa Rosa, Argentina. ²⁹²Laboratory of Brain Aging and Neurodegeneration (FIL), Buenos Aires, Argentina. ²⁹³Centro de Neuropsiquiatría y Neurología de la Conducta (CENECON), Facultad de Medicina, Universidad de Buenos Aires (UBA), C.A.B.A., Buenos Aires, Argentina. ²⁹⁴Cambridge Institute for Medical Research and UK Dementia Research Institute, University of Cambridge, Cambridge, UK. ²⁹⁵German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany. ²⁹⁶Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, CIBERDEM, Hospital Clínico San Carlos, Madrid, Spain.

GR@ACE

Nuria Aguilera^{10,11}, Mar Buendia¹⁰, Amanda Cano¹⁰, Pilar Cañabate^{10,11}, Susana Diego¹⁰, Anna Gailhagenet¹⁰, Marina Guitart¹⁰, Marta Ibarria¹⁰, Asunción Lafuente¹⁰, Juan Macias⁹⁷, Olalla Maroñas²⁹⁷, Elvira Martín¹⁰, Mariona Moreno¹⁰, Raúl Nuñez-Llaves¹⁰, Clàudia Olivé¹⁰, Ana Pancho¹⁰, Ester Pelejá¹⁰, Silvia Preckler¹⁰ and Liliana Vargas¹⁰

²⁹⁷Grupo de Medicina Xenómica, Centro Nacional de Genotipado (CEGEN-PRB3-ISCIII), Universidad de Santiago de Compostela, Santiago de Compostela, Spain.

DEGESCO

Astrid D. Adarmes-Gómez^{11,188}, María Dolores Alonso²⁹⁸, Guillermo Amer-Ferrer²⁹⁹, Martirio Antequera³⁷, Juan Andrés Burguera⁴⁹, Fátima Carrillo^{11,188}, Mario Carrión-Claro^{11,188}, María José Casajeros¹³⁹, Marian Martinez de Pancorbo³⁰⁰, Rocío Escuela^{11,188}, Lorena Garrote-Espina^{11,188}, Pilar Gómez-Garre^{11,188}, Saray Hevilla¹³⁸, Silvia Jesús^{11,188}, Miguel Angel Labrador Espinosa^{11,188}, Agustina Legaz³⁷, Sara López-García^{11,174}, Daniel Macias-García^{11,188}, Salvadora Manzanares^{299,301}, Marta Marín¹³², Juan Marín-Muñoz³⁷, Tamara Marín¹³⁸, Begoña Martínez³⁷, Victoriana Martínez³⁷, Pablo Martínez-Lage Álvarez³⁰², Maite Mendioroz Iriarte³⁰³, María Teresa Perrián-Tocino^{11,188}, Rocío Pineda-Sánchez^{11,188},

**Diego Real de Asúa³⁰⁴, Silvia Rodrigo¹³², Isabel Sastre^{11,134}, Maria Pilar Vicente³⁷,
Rosario Vigo-Ortega^{11,188} and Liliana Vivancos³⁷**

²⁹⁸Servei de Neurologia, Hospital Clínic Universitari de València, Valencia, Spain. ²⁹⁹Department of Neurology, Hospital Universitario Son Espases, Palma, Spain. ³⁰⁰BIOMICs, País Vasco; Centro de Investigación Lascaray, Universidad del País Vasco UPV/EHU, Vitoria-Gasteiz, Spain. ³⁰¹Fundación para la Formación e Investigación Sanitarias de la Región de Murcia, Palma, Spain. ³⁰²Centro de Investigación y Terapias Avanzadas, Fundación CITA-Alzheimer, San Sebastian, Spain. ³⁰³Navarrabiomed, Pamplona, Spain. ³⁰⁴Hospital Universitario La Princesa, Madrid, Spain.

EADI

**Jacques Epelbaum³⁰⁵, Didier Hannequin²⁴⁴, Dominique Campion⁹², Vincent Deramecourt²⁰⁰,
Nathalie Fievet¹, Christophe Tzourio¹⁰¹, Alexis Brice³⁰⁶ and Bruno Dubois³⁰⁷**

³⁰⁵UMR 7179 CNRS/MNHN, Brunoy, France. ³⁰⁶Sorbonne Université, Paris Brain Institute, APHP, INSERM, CNRS, Paris, France. ³⁰⁷Department of Neurology, Institute of Memory and Alzheimer's Disease (IM2A), Pitié-Salpêtrière Hospital, AP-HP, Boulevard de l'Hôpital, Paris, France.

GERAD

**Denise Harold²⁶⁷, Paul Hollingworth²⁵⁸, Amy Gerrish²⁶⁵, Amy Williams¹⁶, Charlene Thomas¹⁶,
Chloe Davies¹⁶, William Nash¹⁶, Kimberley Dowzell¹⁶, Atahualpa Castillo Morales^{16,108},
Mateus Bernardo-Harrington^{16,108}, James Turton³⁰⁸, Jenny Lord³⁰⁸, Kristelle Brown²⁶², Emma Vardy³⁰⁹,
Elizabeth Fisher³¹⁰, Jason D. Warren³¹⁰, Martin Rossor²⁹, Natalie S. Ryan²⁷⁶, Rita Guerreiro³¹⁰,
James Uphill¹⁸⁷, John Collinge¹⁸⁷, Michelle Lupton^{270,271}, Ammar Al-Chalabi²⁵⁹, Christopher E. Shaw²⁵⁹,
Nick Bass²⁶⁰, Richard Abraham²⁵⁸, Reinhard Heun³¹¹, Heike Kölsch³¹², Britta Schürmann³¹²,
André Lacour⁹, Christine Herold⁹, Simon Lovestone²⁶⁹, Bernadette McGuinness²⁶⁸,
David Craig²⁶³, Janet A. Johnston²⁶⁸, Michael Gill²⁶⁶, Peter Passmore²⁶³, Stephen Todd²⁷⁵,
John Powell^{270,271}, Petra Proitsi^{270,271}, Yogen Patel³¹³, Angela Hodges³¹¹, Tim Becker^{9,314},
A. David Smith²⁷³, Donald Warden²⁷³, Gordon Wilcock²⁷³, Robert Clarke³¹⁰, Aoibhinn Lynch²⁶⁶,
Brian Lawlor²⁶⁶, Andrew McQuillin²⁶⁰, Gill Livingston²⁶⁰, David C. Rubinsztein²⁹⁴, Carol Brayne²⁶¹,
Rhian Gwilliam²⁶⁴, Panagiotis Deloukas²⁶⁴, Yoav Ben-Shlomo³¹⁵, David Mann²⁷², Nigel M. Hooper²⁷²,
Stuart Pickering-Brown²⁷², Rebecca Sussams³¹⁶, Nick Warner³¹⁷, Anthony Bayer³¹⁸, Isabella Heuser³¹⁹,
Dmitriy Drichel³²⁰, Norman Klopp³²¹, Manuel Mayhaus³²², Matthias Riemenschneider³²²,
Sabrina Pinchler³²², Thomas Feulner³²², Wei Gu³²², Hendrik van den Bussche²²⁹, Michael Hüll³²³,
Lutz Frölich³²⁴, H-Erich Wichmann³²¹, Karl-Heinz Jöckel³²⁵, Michael O'Donovan²⁵⁸, Lesley Jones²⁵⁸ and
Michael Owen²⁵⁸**

³⁰⁸Institute of Genetics, Queen's Medical Centre, University of Nottingham, Nottingham, UK. ³⁰⁹Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, UK. ³¹⁰Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK.

³¹¹Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. ³¹²Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany. ³¹³Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. ³¹⁴Institute for Medical Biometry, Informatics and Epidemiology, University of Bonn, Bonn, Germany. ³¹⁵Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK. ³¹⁶Division of Clinical Neurosciences, School of Medicine, University of Southampton, Southampton, UK. ³¹⁷Somerset Partnership NHS Trust, Somerset, UK. ³¹⁸Institute of Primary Care and Public Health, Cardiff University, University Hospital of Wales, Cardiff, UK. ³¹⁹Department of Psychiatry and Psychotherapy, Charité University Medicine, Berlin, Germany. ³²⁰Cologne Center for Genomics, University of Cologne, Cologne, Germany. ³²¹Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Munich, Germany. ³²²Department of Psychiatry and Psychotherapy, University Hospital, Saarland, Germany. ³²³Department of Psychiatry, University of Freiburg, Freiburg, Germany. ³²⁴Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany. ³²⁵Institute for Medical Informatics, Biometry and Epidemiology, University Hospital of Essen, University Duisburg-Essen, Essen, Germany.

Demgene

Shahram Bahrami^{46,326}, Ingunn Bosnes^{327,328}, Per Selnes³²⁹ and Sverre Bergh³³⁰

³²⁶Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. ³²⁷Department of Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. ³²⁸Department of Psychiatry, Hospital Namsos, Nord-Trøndelag Health Trust, Namsos, Norway. ³²⁹Department of Neurology, Akershus University Hospital, Lørenskog, Norway. ³³⁰Centre for Old Age Psychiatry Research, Innlandet Hospital Trust, Ottestad, Norway.

FinnGen

Aarno Palotie³³¹, Mark Daly³³¹, Howard Jacob³³², Athena Matakidou³³³, Heiko Runz³³⁴, Sally John³³⁴, Robert Plenge³³⁵, Mark McCarthy³³⁶, Julie Hunkapiller³³⁶, Meg Ehm³³⁷, Dawn Waterworth³³⁷, Caroline Fox³³⁸, Anders Malarstig³³⁹, Kathy Klinger³⁴⁰, Kathy Call³⁴⁰, Tim Behrens³⁴¹, Patrick Loerch³⁴², Tomi Mäkelä³⁴³, Jaakko Kaprio³³¹, Petri Virolainen³⁴⁴, Kari Pulkki³⁴⁴, Terhi Kilpi³⁴⁵, Markus Perola³⁴⁵, Jukka Partanen³⁴⁶, Anne Pitkäranta³⁴⁷, Riitta Kaarteenaho³⁴⁸, Seppo Vainio³⁴⁸, Miia Turpeinen³⁴⁸, Raisa Serpi³⁴⁸, Tarja Laitinen³⁴⁹, Johanna Mäkelä³⁵⁰, Veli-Matti Kosma³⁵¹, Urho Kujala³⁵², Outi Tuovila³⁵³, Minna Hendolin³⁵³, Raimo Pakkanen³⁵³, Jeff Waring³³², Bridget Riley-Gillis³³², Jimmy Liu³³⁴, Shameek Biswas³³⁵, Dorothee Diogo³³⁸, Catherine Marshall³³⁹, Xinli Hu³³⁹, Matthias Gossel³⁴⁰, Robert Graham³⁴¹, Beryl Cummings³⁴², Samuli Ripatti³³¹, Johanna Schleutker³⁴⁴, Mikko Arvas³⁴⁶, Olli Carpén³⁴⁷, Reetta Hinttala³⁴⁸, Johannes Kettunen³⁴⁸, Arto Mannermaa³⁵¹, Jari Laukkanen³⁵², Valtteri Julkunen³⁵⁴, Anne Remes³⁵⁴, Reetta Kälviäinen³⁵⁴, Jukka Peltola³⁵⁵, Pentti Tienari³⁵⁶, Juha Rinne³⁵⁷, Adam Ziemann³³², Jeffrey Waring³³², Sahar Esmaeeli³³², Nizar Smaoui³³², Anne Lehtonen³³², Susan Eaton³³⁴, Sanni Lahdenperä³³⁴, Janet van Adelsberg³³⁵, John Michon³³⁶, Geoff Kerchner³³⁶, Natalie Bowers³³⁶, Edmond Teng³³⁶, John Eicher³³⁶, Vinay Mehta³³⁸, Padhraig Gormley³³⁸, Kari Linden³³⁹, Christopher Whelan³³⁹, Fanli Xu³³⁷, David Pulford³³⁷, Martti Färkkilä³⁵⁶, Sampsa Pikkarainen³⁵⁶, Airi Jussila³⁵⁸, Timo Blomster³⁵⁹, Mikko Kiviniemi³⁶⁰, Markku Voutilainen³⁵⁷, Bob Georgantas³³², Graham Heap³³², Fedik Rahimov³³², Keith Usiskin³³⁵, Tim Lu⁶, Danny Oh³³⁶, Kirsi Kalpala³³⁹, Melissa Miller³³⁹, Linda McCarthy³³⁷, Kari Eklund³⁵⁶, Antti Palomäki³⁵⁷, Pia Isomäki³⁵⁸, Laura Pirilä³⁵⁷, Oili Kaipainen-Seppänen³⁶⁰, Johanna Huhtakangas³⁵⁹, Apinya Lertratanakul³³², Marla Hochfeld³³⁵, Nan Bing³³⁹, Jorge Esparza Gordillo³³⁷, Nina Mars³³¹, Margit Pelkonen³⁶⁰, Paula Kauppi³⁵⁶, Hannu Kankaanranta³⁵⁵, Terttu Harju³⁵⁹, David Close³³³, Steven Greenberg³³⁵, Hubert Chen³³⁶, Jo Betts³³⁷, Soumitra Ghosh³³⁷, Veikko Salomaa³⁶¹, Teemu Niiranen³⁶¹, Markus Juonala³⁵⁷, Kaj Metsärinne³⁵⁷, Mika Kähönen³⁵⁸, Juhani Junttila³⁵⁹, Markku Laakso³⁵⁴, Jussi Pihlajamäki³⁵⁴, Juha Sinisalo³⁵⁶, Marja-Riitta Taskinen³⁵⁶, Tiinamaija Tuomi³⁵⁶, Ben Challis³³³, Andrew Peterson³³⁶, Audrey Chu³³⁸, Jaakko Parkkinen³³⁹, Anthony Muslin³⁴⁰, Heikki Joensuu³⁵⁶, Tuomo Meretoja³⁵⁶, Lauri Aaltonen³⁵⁶, Johanna Mattson³⁵⁶, Annika Auranen³⁵⁵, Peeter Karihtala³⁵⁹, Saira Kauppila³⁵⁹, Päivi Auvinen³⁵⁹, Klaus Elenius³⁵⁷, Relja Popovic³³², Jennifer Schutzman³³⁶, Andrey Loboda³³⁸, Aparna Chhibber³³⁸, Heli Lehtonen³³⁹, Stefan McDonough³³⁹, Marika Crohns³⁴⁰, Diptee Kulkarni³³⁷, Kai Kaarniranta³⁵⁴, Joni A. Turunen³⁵⁶, Terhi Ollila³⁵⁶, Sanna Seitsonen³⁵⁶, Hannu Uusitalo³⁵⁵, Vesa Aaltonen³⁵⁷, Hannele Uusitalo-Järvinen³⁵⁵, Marja Luodonpää³⁵⁹, Nina Hautala³⁵⁹, Stephanie Loomis³³⁴, Erich Strauss³³⁶, Hao Chen³³⁶, Anna Podgornaia³³⁸, Joshua Hoffman³³⁷, Kaisa Tasanen³⁵⁹, Laura Huilaja³⁵⁹, Katariina Hannula-Jouppi³⁵⁶, Tea Salmi³⁵⁸, Sirkku Peltonen³⁵⁶, Leena Koulou³⁵⁶, Ilkka Harvima³⁵⁴, Ying Wu⁹, David Choy³³⁶, Pirkko Pussinen³⁵⁶, Aino Salminen³⁵⁶, Tuula Salo³⁵⁶, David Rice³⁵⁶, Pekka Nieminen³⁵⁶, Ulla Palotie³⁵⁶, Maria Siponen³⁵⁴, Liisa Suominen³⁵⁴, Päivi Mäntylä³⁵⁴, Ulvi Gursoy³⁵⁷, Vuokko Anttonen³⁵⁹, Kirsi Sipilä³⁵⁹, Justin Wade Davis³³², Danjuma Quarless³³², Slavé Petrovski³³³, Eleonor Wigmore³³³, Chia-Yen Chen³³⁴, Paola Bronson³³⁴, Ellen Tsai³³⁴, Yunfeng Huang³³⁴, Joseph Maranville³³⁵, Elmutaz Shaikho³³⁵, Elhaj Mohammed³³⁵,

Samir Wadhawan³⁶², Erika Kvikstad³⁶², Minal Caliskan³⁶², Diana Chang³³⁶, Tushar Bhangale³³⁶, Sarah Pendergrass³³⁶, Emily Holzinger³³⁸, Xing Chen³³⁹, Åsa Hedman³³⁹, Karen S. King³³⁷, Clarence Wang³⁴⁰, Ethan Xu³⁴⁰, Franck Auge³⁴⁰, Clement Chatelain³⁴⁰, Deepak Rajpal³⁴⁰, Dongyu Liu³⁴⁰, Katherine Call³⁴⁰, Tai-he Xia³⁴⁰, Matt Brauer³⁴¹, Mitja Kurki³³¹, Juha Karjalainen³³¹, Aki Havulinna³³¹, Anu Jalanko³³¹, Priit Palta³³¹, Pietro della Briotta Parolo³³¹, Wei Zhou³⁶³, Susanna Lemmelä³³¹, Manuel Rivas³⁶⁴, Jarmo Harju³³¹, Arto Lehisto³³¹, Andrea Ganna³³¹, Vincent Llorens³³¹, Hannele Laivuori³³¹, Sina Rüeger³³¹, Mari E. Niemi³³¹, Taru Tukiainen³³¹, Mary Pat Reeve³³¹, Henrike Heyne³³¹, Nina Mars³³¹, Kimmo Palin³⁶⁵, Javier Garcia-Tabuenca³⁶⁶, Harri Siirtola³⁶⁶, Tuomo Kiiskinen³³¹, Jiwoo Lee³³¹, Kristin Tsuo³³¹, Amanda Elliott³³¹, Kati Kristiansson³⁴⁵, Kati Hyvärinen³⁶⁷, Jarmo Ritari³⁶⁷, Miika Koskinen³⁴⁷, Katri Pylkäs³⁴⁸, Marita Kalaoja³⁴⁸, Minna Karjalainen³⁴⁸, Tuomo Mantere³⁴⁸, Eeva Kangasniemi³⁵⁰, Sami Heikkinen³⁵¹, Eija Laakkonen³⁵², Csilla Sipeky³⁶⁸, Samuel Heron³⁶⁸, Antti Karlsson³⁴⁴, Dhanaprakash Jambulingam³⁶⁸, Venkat Subramaniam Rathinakannan³⁶⁸, Risto Kajanne³³¹, Mervi Aavikko³³¹, Manuel González Jiménez³³¹, Pietro della Briotta Parola³³¹, Arto Lehistö³³¹, Masahiro Kanai³⁶³, Mari Kaunisto³³¹, Elina Kilpeläinen³³¹, Timo P. Sipilä³³¹, Georg Brein³³¹, Ghazal Awaisa³³¹, Anastasia Shcherban³³¹, Kati Donner³³¹, Anu Loukola³⁴⁷, Päivi Laiho³⁴⁵, Tuuli Sistonen³⁴⁵, Essi Kaiharju³⁴⁵, Markku Laukkanen³⁴⁵, Elina Järvensivu³⁴⁵, Sini Lähteenmäki³⁴⁵, Lotta Männikkö³⁴⁵, Regis Wong³⁴⁵, Hannele Mattsson³⁴⁵, Tero Hiekkalinna³⁴⁵, Teemu Paajanen³⁴⁵, Kalle Pärn³³¹ and Javier Gracia-Tabuenca³⁶⁶

³³¹Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland. ³³²AbbVie, Chicago, IL, USA. ³³³Astra Zeneca, Cambridge, UK. ³³⁴Biogen, Cambridge, MA, USA. ³³⁵Celgene, Summit, NJ, USA. ³³⁶Genentech, San Francisco, CA, USA. ³³⁷GlaxoSmithKline, Brentford, UK. ³³⁸Merck, Kenilworth, NJ, USA. ³³⁹Pfizer, New York, NY, USA. ³⁴⁰Sanofi, Paris, France. ³⁴¹Maze Therapeutics, San Francisco, CA, USA. ³⁴²Janssen Biotech, Beerse, Belgium. ³⁴³HiLIFE, University of Helsinki, Helsinki, Finland. ³⁴⁴Auria Biobank, University of Turku, Hospital District of Southwest Finland, Turku, Finland. ³⁴⁵THL Biobank, The National Institute of Health and Welfare Helsinki, Helsinki, Finland. ³⁴⁶Finnish Red Cross Blood Service, Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland. ³⁴⁷Helsinki Biobank, Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki, Finland. ³⁴⁸Northern Finland Biobank Borealis, University of Oulu, Northern Ostrobothnia Hospital District, Oulu, Finland. ³⁴⁹Oxford Healthy Aging Project, Clinical Trial Service Unit, University of Oxford, Oxford, UK. ³⁵⁰Finnish Clinical Biobank Tampere, University of Tampere, Pirkanmaa Hospital District, Tampere, Finland. ³⁵¹Biobank of Eastern Finland, University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland. ³⁵²Central Finland Biobank, University of Jyväskylä, Central Finland Health Care District, Jyväskylä, Finland. ³⁵³Business Finland, Helsinki, Finland. ³⁵⁴Northern Savo Hospital District, Kuopio, Finland. ³⁵⁵Pirkanmaa Hospital District, Tampere, Finland. ³⁵⁶Hospital District of Helsinki and Uusimaa, Helsinki, Finland. ³⁵⁷Hospital District of Southwest Finland, Turku, Finland. ³⁵⁸Pirkanmaa Hospital District, Tampere, Finland. ³⁵⁹Northern Ostrobothnia Hospital District, Oulu, Finland. ³⁶⁰Northern Savo Hospital District, Kuopio, Finland. ³⁶¹The National Institute of Health and Welfare Helsinki, Helsinki, Finland. ³⁶²Bristol Myers Squibb, New York, NY, USA. ³⁶³Broad Institute, Cambridge, MA, USA. ³⁶⁴University of Stanford, Stanford, CA, USA. ³⁶⁵University of Helsinki, Helsinki, Finland. ³⁶⁶University of Tampere, Tampere, Finland. ³⁶⁷Finnish Red Cross Blood Service, Helsinki, Finland. ³⁶⁸University of Turku, Turku, Finland.

ADGC

Erin Abner³⁶⁹, Perrie M. Adams³⁷⁰, Alyssa Aguirre³⁷¹, Marilyn S. Albert³⁷², Roger L. Albin^{373,374,375}, Mariet Allen³⁷⁶, Lisa Alvarez³⁷⁷, Liana G. Apostolova^{378,379}, Steven E. Arnold³⁸⁰, Sanjay Asthana^{381,382,383}, Craig S. Atwood^{381,382,383}, Gayle Ayres³⁷¹, Clinton T. Baldwin²⁴⁸, Robert C. Barber³⁷⁷, Lisa L. Barnes^{384,385,386}, Sandra Barral^{150,183,186}, Thomas G. Beach³⁸⁷, James T. Becker³⁸⁸, Gary W. Beecham¹⁵⁴, Duane Beekly³⁸⁹, Jennifer E. Below^{93,390}, Penelope Benckek⁵⁷, Bruno A. Benitez³⁹¹, David Bennett^{384,386}, John Bertelson³⁹², Flanagan E. Margaret^{393,394}, Thomas D. Bird^{181,395}, Deborah Blacker^{396,397}, Bradley F. Boeve³⁹⁸, James D. Bowen³⁹⁹, Adam Boxer⁴⁰⁰, James Brewer⁴⁰¹, James R. Burke⁴⁰², Jeffrey M. Burns⁴⁰³, Will S. Bush⁵⁷, Joseph D. Buxbaum^{103,104,106,160}, Nigel J. Cairns⁴⁰⁴, Chuanhai Cao⁴⁰⁵, Christopher S. Carlson⁴⁰⁶, Cynthia M. Carlsson^{382,383}, Regina M. Carney⁴⁰⁷, Minerva M. Carrasquillo³⁷⁶, Scott Chasse⁴⁰⁸, Marie-Francoise Chesselet⁴⁰⁹, Hung-Hsin Chen⁹³, Alessandra Chesi¹⁴, Nathaniel A. Chin^{381,382}, Helena C. Chui⁴¹⁰, Jaeyoon Chung²⁴⁸, Suzanne Craft⁴¹¹,

Paul K. Crane¹⁹⁶, David H. Cribbs⁴¹², Elizabeth A. Crocco⁴¹³, Carlos Cruchaga^{414,415}, Michael L. Cuccaro^{88,154}, Munro Cullum³⁷⁰, Eveleen Darby⁴¹⁶, Barbara Davis⁴¹⁷, Philip L. De Jager⁴¹⁸, Charles DeCarli⁴¹⁹, John DeToledo⁴²⁰, Malcolm Dick⁴²¹, Dennis W. Dickson³⁷⁶, Beth A. Dombroski¹⁴, Rachelle S. Doody⁴¹⁶, Ranjan Duara⁴²², Nilüfer Ertekin-Taner^{376,423}, Denis A. Evans⁴²⁴, Kelley M. Faber¹¹⁹, Thomas J. Fairchild⁴²⁵, Kenneth B. Fallon⁴²⁶, David W. Fardo¹²², Martin R. Farlow⁴²⁷, John J. Farrell²⁴⁸, Victoria Fernandez-Hernandez³⁹¹, Steven Ferris⁴²⁸, Tatiana M. Foroud¹¹⁹, Matthew P. Frosch⁴²⁹, Brian Fulton-Howard⁴³⁰, Douglas R. Galasko⁴⁰¹, Adriana Gamboa^{431,432}, Marla Gearing^{433,434}, Daniel H. Geschwind⁴¹⁴, Bernardino Ghetti⁴³⁵, John R. Gilbert^{88,154}, Thomas J. Grabowski^{181,436}, Neill R. Graff-Radford^{377,423}, Struan F. A. Grant^{437,438,439}, Robert C. Green⁴⁴⁰, John H. Growdon⁴⁴¹, Jonathan L. Haines^{56,57}, Hakon Hakonarson^{442,443}, James Hall³⁷⁷, Ronald L. Hamilton⁴⁴⁴, Kara L. Hamilton-Nelson¹⁵⁴, Oscar Harari⁴¹⁵, Lindy E. Harrell⁴⁴⁵, Jacob Haut¹⁴, Elizabeth Head⁴⁴⁶, Victor W. Henderson^{447,448}, Michelle Hernandez⁴²⁰, Timothy Hohman^{93,449}, Lawrence S. Honig⁵⁰, Ryan M. Huebinger⁴⁵⁰, Matthew J. Huentelman⁴⁵¹, Christine M. Hulette⁴⁵², Bradley T. Hyman⁴⁴¹, Linda S. Hynan^{370,453,454}, Laura Ibanez^{415,455}, Gail P. Jarvik^{196,456}, Suman Jayadev¹⁸¹, Lee-Way Jin⁴⁵⁷, Kim Johnson⁴²⁰, Leigh Johnson⁴³¹, M. Ilyas Kamboh^{388,458,459}, Anna M. Karydas⁴⁰⁰, Mindy J. Katz⁴⁶⁰, Jeffrey A. Kaye^{461,462}, C. Dirk Keene⁴⁶³, Aisha Khaleeq⁴¹⁶, Ronald Kim⁴⁴⁶, Janice Knebl⁴³¹, Neil W. Kowall^{20,464}, Joel H. Kramer⁴⁶⁵, Pavel P. Kuksa¹⁴, Frank M. LaFerla⁴⁶⁶, James J. Lah⁴⁶⁷, Eric B. Larson⁴⁶⁸, Chien-Yueh Lee¹⁴, Edward B. Lee¹⁴, Alan Lerner⁵⁷, Yuk Yee Leung¹⁴, James B. Leverenz⁴⁶⁹, Allan I. Levey⁴⁶⁷, Mingyao Li¹⁴, Andrew P. Lieberman⁴⁷⁰, Richard B. Lipton⁴⁶⁰, Mark Logue^{248,397,471}, Constantine G. Lyketsos⁴⁷², John Malamon¹⁴, Douglas Mains^{431,432}, Daniel C. Marson⁴⁴⁵, Frank Martiniuk⁴⁷³, Deborah C. Mash⁴⁷⁴, Eliezer Masliah^{401,475}, Paul Massman⁴¹⁶, Arjun Masurkar⁴²⁸, Wayne C. McCormick¹⁹⁶, Susan M. McCurry⁴⁷⁶, Andrew N. McDavid⁴⁰⁶, Stefan McDonough⁴⁷⁷, Ann C. McKee^{20,464}, Marsel Mesulam^{393,394}, Jesse Mez²⁰, Bruce L. Miller⁴⁷⁸, Carol A. Miller⁴⁷⁹, Joshua W. Miller⁴⁵⁷, Thomas J. Montine⁴⁸⁰, Edwin S. Monuki⁴⁴⁶, John C. Morris^{404,415,445,481}, Amanda J. Myers⁴¹³, Trung Nguyen⁴⁵³, Sid O'Bryant⁴⁸², John M. Olichney⁴⁸³, Marcia Ory⁴⁸⁴, Raymond Palmer⁴⁸⁵, Joseph E. Parisi⁴⁸⁶, Henry L. Paulson^{373,375}, Valory Pavlik⁴¹⁶, David Paydarfar³⁷¹, Victoria Perez⁴²⁰, Elaine Peskind⁴⁸⁷, Ronald C. Petersen³⁹⁸, Jennifer E. Phillips-Cremins^{439,488}, Aimee Pierce⁴¹², Marsha Polk⁴⁸⁹, Wayne W. Poon⁴²¹, Huntington Potter⁴⁹⁰, Liming Qu¹⁴, Mary Quiceno^{491,492}, Joseph F. Quinn^{461,462}, Ashok Raj⁴⁰⁵, Murray Raskind⁴⁸⁷, Eric M. Reiman^{451,493,494,495}, Barry Reisberg^{428,489}, Joan S. Reisch⁴¹⁷, John M. Ringman⁴¹⁰, Erik D. Roberson⁴⁴⁵, Monica Rodriguear⁴¹⁶, Ekaterina Rogaeva⁴⁹⁶, Howard J. Rosen⁴⁰⁰, Roger N. Rosenberg⁴⁵³, Donald R. Royall⁴⁸⁵, Mark A. Sager³⁸², Mary Sano¹⁰⁶, Andrew J. Saykin^{119,497}, Julie A. Schneider^{384,386,498}, Lon S. Schneider^{410,499}, William W. Seeley⁴⁰⁰, Jin Sha¹⁴, Susan H. Slifer¹⁵⁴, Scott Small^{50,186}, Amanda G. Smith⁴⁰⁵, Janet P. Smith⁴¹⁷, Yeunjoo E. Song^{56,57}, Joshua A. Sonnen⁴⁶³, Salvatore Spina⁴³⁵, Peter St George-Hyslop^{500,501}, Robert A. Stern²⁰, Alan B. Stevens^{484,502,503}, Stephen M. Strittmatter⁵⁰⁴, David Sultzer⁵⁰⁵, Russell H. Swerdlow⁴⁰³, Rudolph E. Tanzi⁴⁴¹, Jeffrey L. Tilson⁵⁰⁶, John Q. Trojanowski¹⁴, Juan C. Troncoso⁵⁰⁷, Debby W. Tsuang^{395,487}, Otto Valladares¹⁴, Viviana M. Van Deerlin¹⁴, Linda J. van Eldik¹²², Robert Vassar^{393,394}, Harry V. Vinters^{410,508}, Jean-Paul Vonsattel⁵⁰, Sandra Weintraub⁵⁰⁹, Kathleen A. Welsh-Bohmer^{402,510}, Patrice L. Whitehead¹⁵⁴, Ellen M. Wijsman^{196,456,511}, Kirk C. Wilhelmsen⁴⁰⁸, Benjamin Williams⁴¹¹, Jennifer Williamson⁵⁰, Henrik Wilms⁴²⁰, Thomas S. Wingo⁴⁶⁷, Thomas Wisniewski^{512,513}, Randall L. Woltjer⁵¹⁴,

**Martin Woon³⁹², Clinton B. Wright⁵¹⁵, Chuang-Kuo Wu⁴²⁰, Steven G. Younkin^{376,423}, Chang-En Yu¹⁹⁶,
Lei Yu^{384,386}, Yuanchao Zhang⁴⁴², Yi Zhao⁴⁸ and Xiongwei Zhu⁵¹⁶**

³⁶⁹Sanders-Brown Center on Aging, Department of Epidemiology, College of Public Health, University of Kentucky, Lexington, KY, USA. ³⁷⁰Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA. ³⁷¹Department of Neurology, Dell Medical School, University of Texas at Austin, Austin, TX, USA. ³⁷²Department of Neurology, Johns Hopkins University, Baltimore, MD, USA. ³⁷³Department of Neurology, University of Michigan, Ann Arbor, MI, USA. ³⁷⁴Geriatric Research, Education and Clinical Center (GRECC), VA Ann Arbor Healthcare System (VAAHS), Ann Arbor, MI, USA. ³⁷⁵Michigan Alzheimer's Disease Center, University of Michigan, Ann Arbor, MI, USA. ³⁷⁶Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA. ³⁷⁷Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, TX, USA. ³⁷⁸Departments of Neurology, Radiology, and Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA. ³⁷⁹Indiana Alzheimer's Disease Research Center, Indiana University School of Medicine, Indianapolis, IN, USA. ³⁸⁰Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ³⁸¹Geriatric Research, Education and Clinical Center (GRECC), University of Wisconsin, Madison, WI, USA. ³⁸²Department of Medicine, University of Wisconsin, Madison, WI, USA. ³⁸³Wisconsin Alzheimer's Disease Research Center, Madison, WI, USA. ³⁸⁴Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA. ³⁸⁵Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL, USA. ³⁸⁶Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA. ³⁸⁷Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Phoenix, AZ, USA. ³⁸⁸Departments of Psychiatry, Neurology, and Psychology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. ³⁸⁹National Alzheimer's Coordinating Center, University of Washington, Seattle, WA, USA. ³⁹⁰Human Genetics Center, Department of Epidemiology, Human Genetics, and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX, USA. ³⁹¹Department of Psychiatry and Hope Center Program on Protein Aggregation and Neurodegeneration, Washington University School of Medicine, St. Louis, MO, USA. ³⁹²Department of Psychiatry, University of Texas at Austin/Dell Medical School, Austin, TX, USA. ³⁹³Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ³⁹⁴Cognitive Neurology and Alzheimer's Disease Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ³⁹⁵VA Puget Sound Health Care System/GRECC, Seattle, WA, USA. ³⁹⁶Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA. ³⁹⁷Department of Psychiatry, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA. ³⁹⁸Department of Neurology, Mayo Clinic, Rochester, MN, USA. ³⁹⁹Swedish Medical Center, Seattle, WA, USA. ⁴⁰⁰Department of Neurology, University of California San Francisco, San Francisco, CA, USA. ⁴⁰¹Department of Neurosciences, University of California San Diego, La Jolla, CA, USA. ⁴⁰²Department of Medicine, Duke University, Durham, NC, USA. ⁴⁰³University of Kansas Alzheimer's Disease Center, University of Kansas Medical Center, Kansas City, KS, USA. ⁴⁰⁴Department of Pathology and Immunology, Washington University, St. Louis, MO, USA. ⁴⁰⁵USF Health Byrd Alzheimer's Institute, University of South Florida, Tampa, FL, USA. ⁴⁰⁶Fred Hutchinson Cancer Research Center, Seattle, WA, USA. ⁴⁰⁷Mental Health and Behavioral Science Service, Bruce W. Carter VA Medical Center, Miami, FL, USA. ⁴⁰⁸Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ⁴⁰⁹Neurogenetics Program, University of California, Los Angeles, Los Angeles, CA, USA. ⁴¹⁰Department of Neurology, University of Southern California, Los Angeles, CA, USA. ⁴¹¹Section of Gerontology and Geriatric Medicine Research, Wake Forest School of Medicine, Winston-Salem, NC, USA. ⁴¹²Department of Neurology, University of California, Irvine, Irvine, CA, USA. ⁴¹³Department of Psychiatry and Behavioral Sciences, Miller School of Medicine, University of Miami, Miami, FL, USA. ⁴¹⁴NeuroGenomics and Informatics, Washington University in St. Louis, St. Louis, MO, USA. ⁴¹⁵Department of Psychiatry, Washington University in St. Louis, St. Louis, MO, USA. ⁴¹⁶Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, Houston, TX, USA. ⁴¹⁷Department of Population and Data Sciences, University of Texas Southwestern Medical Center, Dallas, Texas, USA. ⁴¹⁸Center for Translational and Computational Neuroimmunology, Department of Neurology, Columbia University Medical Center, New York, NY, USA. ⁴¹⁹Department of Neurology, University of California, Davis, Sacramento, CA, USA. ⁴²⁰Departments of Neurology, Pharmacology and Neuroscience, Texas Tech University Health Science Center, Lubbock, TX, USA. ⁴²¹Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA. ⁴²²Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Miami Beach, FL, USA. ⁴²³Department of Neurology, Mayo Clinic, Jacksonville, FL, USA. ⁴²⁴Rush Institute for Healthy Aging, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA. ⁴²⁵Office of Strategy and Measurement, University of North Texas Health Science Center, Fort Worth, TX, USA. ⁴²⁶Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA. ⁴²⁷Department of Neurology, Indiana University, Indianapolis, IN, USA. ⁴²⁸Department of Psychiatry, New York University, New York, NY, USA. ⁴²⁹C.S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital, Charlestown, MA, USA. ⁴³⁰Department of Neuroscience, Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁴³¹Department of Health Behavior and Health Systems, University of North Texas Health Science Center, Fort Worth, TX, USA. ⁴³²Department of Health Management and Policy, School of Public Health, University of North Texas Health Science Center, Fort Worth, TX, USA. ⁴³³Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA. ⁴³⁴Emory Alzheimer's Disease Center, Emory University, Atlanta, GA, USA. ⁴³⁵Department of Pathology and Laboratory Medicine, Indiana University, Indianapolis, IN, USA. ⁴³⁶Department of Radiology, University of Washington, Seattle, WA, USA. ⁴³⁷Center for Spatial and Functional Genomics, Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA. ⁴³⁸Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁴³⁹Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁴⁴⁰Division of Genetics, Department of Medicine and Partners Center for Personalized Genetic Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. ⁴⁴¹Department of Neurology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA. ⁴⁴²Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA, USA. ⁴⁴³Division of Human Genetics, Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁴⁴⁴Department of Pathology (Neuropathology), University of Pittsburgh, Pittsburgh, PA, USA. ⁴⁴⁵Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA. ⁴⁴⁶Department of Pathology and Laboratory Medicine, University of California Irvine, Irvine, CA, USA. ⁴⁴⁷Department of Epidemiology and Population Health, Stanford University, Stanford, CA, USA. ⁴⁴⁸Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA. ⁴⁴⁹Vanderbilt Memory and Alzheimer's Center, Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA. ⁴⁵⁰Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA. ⁴⁵¹Neurogenomics Division, Translational Genomics Research Institute, Phoenix, AZ, USA. ⁴⁵²Department of Pathology, Duke University, Durham, NC, USA. ⁴⁵³Department of Neurology, University of Texas Southwestern Medical Center, Dallas, TX, USA. ⁴⁵⁴Department of Neurological Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA. ⁴⁵⁵Hope Center Program on Protein Aggregation and Neurodegeneration, Washington University School of Medicine, St. Louis, MO, USA. ⁴⁵⁶Department of Genome Sciences, University of Washington, Seattle, WA, USA. ⁴⁵⁷Department of Pathology and Laboratory Medicine, University of California, Davis, Sacramento, CA, USA. ⁴⁵⁸Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA, USA. ⁴⁵⁹Alzheimer's Disease Research Center, University of Pittsburgh, Pittsburgh, PA, USA. ⁴⁶⁰Department of Neurology, Albert Einstein College of Medicine, New York, NY, USA. ⁴⁶¹Department of Neurology, Oregon Health and Science University, Portland, OR, USA. ⁴⁶²Department of Neurology, Portland Veterans Affairs Medical Center, Portland, OR, USA. ⁴⁶³Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA. ⁴⁶⁴Department of Pathology, Boston

University, Boston, MA, USA. ⁴⁶⁵Department of Neuropsychology, University of California San Francisco, San Francisco, CA, USA. ⁴⁶⁶Department of Neurobiology and Behavior, University of California Irvine, Irvine, CA, USA. ⁴⁶⁷Department of Neurology, Emory University, Atlanta, GA, USA. ⁴⁶⁸Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA. ⁴⁶⁹Cleveland Clinic Lou Ruvo Center for Brain Health, Cleveland Clinic, Cleveland, OH, USA. ⁴⁷⁰Department of Pathology, University of Michigan, Ann Arbor, MI, USA. ⁴⁷¹National Center for PTSD at Boston VA Healthcare System, Boston, MA, USA. ⁴⁷²Department of Psychiatry, Johns Hopkins University, Baltimore, MD, USA. ⁴⁷³Department of Medicine (Pulmonary), New York University, New York, NY, USA. ⁴⁷⁴Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA. ⁴⁷⁵Department of Pathology, University of California San Diego, La Jolla, CA, USA. ⁴⁷⁶School of Nursing Northwest Research Group on Aging, University of Washington, Seattle, WA, USA. ⁴⁷⁷Pfizer Worldwide Research and Development, New York, NY, USA. ⁴⁷⁸Weill Institute for Neurosciences, Memory and Aging Center, University of California, San Francisco, San Francisco, CA, USA. ⁴⁷⁹Department of Pathology, University of Southern California, Los Angeles, CA, USA. ⁴⁸⁰Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA. ⁴⁸¹Department of Neurology, Washington University at St. Louis, St. Louis, MO, USA. ⁴⁸²Institute for Translational Research, University of North Texas Health Science Center, Fort Worth, TX, USA. ⁴⁸³Center for Mind and Brain and Department of Neurology, University of California, Davis, Sacramento, CA, USA. ⁴⁸⁴Center for Population Health and Aging, Texas A&M University Health Science Center, Lubbock, TX, USA. ⁴⁸⁵Department of Family and Community Medicine, University of Texas Health Science Center San Antonio, San Antonio, TX, USA. ⁴⁸⁶Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. ⁴⁸⁷Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, USA. ⁴⁸⁸Department of Bioengineering, University of Pennsylvania, Philadelphia, PA, USA. ⁴⁸⁹Alzheimer's Disease Center, New York University, New York, NY, USA. ⁴⁹⁰Department of Neurology, University of Colorado School of Medicine, Aurora, CO, USA. ⁴⁹¹Department of Internal Medicine and Geriatrics, University of North Texas Health Science Center, Fort Worth, TX, USA. ⁴⁹²Department of Medical Education, TCU/UNTHSC School of Medicine, Fort Worth, TX, USA. ⁴⁹³Arizona Alzheimer's Consortium, Phoenix, AZ, USA. ⁴⁹⁴Banner Alzheimer's Institute, Phoenix, AZ, USA. ⁴⁹⁵Department of Psychiatry, University of Arizona, Phoenix, AZ, USA. ⁴⁹⁶Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada. ⁴⁹⁷Department of Radiology and Imaging Sciences, Indiana University, Indianapolis, IN, USA. ⁴⁹⁸Department of Pathology (Neuropathology), Rush University Medical Center, Chicago, IL, USA. ⁴⁹⁹Department of Psychiatry, University of Southern California, Los Angeles, CA, USA. ⁵⁰⁰Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK. ⁵⁰¹Faculty of Medicine, Department of Medicine (Neurology), University of Toronto, Toronto, Ontario, Canada. ⁵⁰²Center for Applied Health Research, Baylor Scott & White Health, Temple, TX, USA. ⁵⁰³College of Medicine, Texas A&M University Health Science Center, College Station, TX, USA. ⁵⁰⁴Program in Cellular Neuroscience, Neurodegeneration and Repair, Yale University School of Medicine, New Haven, CT, USA. ⁵⁰⁵Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, USA. ⁵⁰⁶Renaissance Computing Institute, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ⁵⁰⁷Department of Pathology, Johns Hopkins University, Baltimore, MD, USA. ⁵⁰⁸Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Los Angeles, CA, USA. ⁵⁰⁹Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ⁵¹⁰Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA. ⁵¹¹Department of Biostatistics, University of Washington, Seattle, WA, USA. ⁵¹²Department of Psychiatry, New York University Grossman School of Medicine, New York, NY, USA. ⁵¹³Center for Cognitive Neurology and Departments of Neurology and Pathology, New York University Grossman School of Medicine, New York, NY, USA. ⁵¹⁴Department of Pathology, Oregon Health and Science University, Portland, OR, USA. ⁵¹⁵Evelyn F. McKnight Brain Institute, Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA. ⁵¹⁶Department of Pathology, Case Western Reserve University, Cleveland, OH, USA.

CHARGE

Hieab Adams¹, Rufus O. Akinyemi⁵¹⁷, Muhammad Ali⁵¹⁸, Nicola Armstrong⁵¹⁹, Hugo J. Aparicio¹⁰⁹, Maryam Bahadori¹³⁰, James T. Becker⁵²⁰, Monique Breteler⁵²¹, Daniel Chasman⁵²², Ganesh Chauhan⁵²³, Hata Comic¹², Simon Cox⁵²⁴, Adrienne L. Cupples²¹, Gail Davies⁵²⁵, Charles S. DeCarli⁵²⁶, Marie-Gabrielle Duperron⁵²⁷, Josée Dupuis²¹, Tavia Evans¹², Frank Fan⁵²⁸, Annette Fitzpatrick⁵²⁹, Alison E. Fohner²³, Mary Ganguli⁵²⁸, Mirjam Geerlings⁵³⁰, Stephen J. Glatt⁵³¹, Hector M. Gonzalez⁵³², Monica Goss¹³⁰, Hans Grabe⁵³³, Mohamad Habes⁵³⁴, Susan R. Heckbert⁵³⁵, Edith Hofer⁵³⁶, Elliot Hong⁵³⁷, Timothy Hughes¹³⁰, Xueqiu Jian¹³⁰, Tiffany F. Kautz⁵³⁸, Maria Knol¹², William Kremen¹², Paul Lacaze⁵³⁹, Jari Lahti⁵⁴⁰, Quentin Le Grand⁵²⁷, Elizabeth Litkowski⁵⁴¹, Shuo Li²¹, Dan Liu⁵²¹, Xuan Liu²¹, Marisa Loitfelder⁵⁴², Alisa Manning⁵⁴³, Pauline Maillard⁵⁴⁴, Riccardo Marioni⁵⁴⁵, Bernard Mazoyer⁵⁴⁶, Debora Melo van Lent¹³⁰, Hao Mei⁵⁴⁷, Aniket Mishra⁵²⁷, Paul Nyquist⁵⁴⁸, Jeffrey O'Connell⁵³⁷, Yash Patel⁵⁴⁹, Tomas Paus⁵⁵⁰, Zdenka Pausova⁵⁵¹, Katri Raikonen-Talvitie⁵⁴⁰, Moeen Riaz⁵³⁹, Stephen Rich⁵³⁹, Jerome Rotter⁵⁵², Jose Romero⁵⁵³, Gena Roshchupkin¹², Yasaman Saba⁵⁵⁴, Murali Sargurupremraj⁵⁵⁴, Helena Schmidt⁵⁵⁴, Reinhold Schmidt⁵⁵⁵, Joshua M. Shulman⁵⁵⁶, Jennifer Smith⁵⁵⁷, Hema Sekhar⁵²⁷, Reddy Rajula⁵²⁷, Jean Shin⁵⁵⁸, Jeannette Simino⁵⁵⁹, Eva Sliz⁵⁵⁹, Alexander Teumer⁵⁶⁰, Alvin Thomas⁵⁶¹, Adrienne Tin⁵⁵⁹, Elliot Tucker-Drob⁵⁶², Dina Vojinovic¹², Yanbing Wang⁹, Galit Weinstein⁵⁶³, Dylan Williams⁵⁶⁴, Katharina Wittfeld⁵⁶⁵, Lisa Yanek⁵⁴⁸ and Yunju Yang⁵⁶⁶

⁵¹⁷Centre for Genomic and Precision Medicine, College of Medicine, UI, Ibadan, Nigeria. ⁵¹⁸Washington University at St. Louis, St. Louis, MO, USA.

⁵¹⁹Mathematics and Statistics, Curtin University, Perth, Western Australia, Australia. ⁵²⁰Departments of Psychiatry, Neurology, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA. ⁵²¹Population Health Sciences, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany. ⁵²²Brigham and Women's Hospital, Harvard University, Boston, MA, USA. ⁵²³INSERM U1219, University of Bordeaux, Bordeaux, France. ⁵²⁴University of Edinburgh,

Edinburgh, UK. ⁵²⁵Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK. ⁵²⁶Department of Neurology and Center for Neuroscience, University of California, Davis, Davis, CA, USA. ⁵²⁷Bordeaux Population Health Research Center, Team VIN-TAGE, UMR 1219, University of Bordeaux, INSERM, Bordeaux, France. ⁵²⁸University of Pittsburgh, Pittsburgh, PA, USA. ⁵²⁹Department of Family Medicine, University of Washington, Seattle, WA, USA. ⁵³⁰University Medical Center Utrecht, Utrecht, the Netherlands. ⁵³¹Psychiatric Genetic Epidemiology & Neurobiology Laboratory (PsychGENe Lab), Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA. ⁵³²University of California, San Diego, San Diego, CA, USA. ⁵³³Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany. ⁵³⁴Department of Radiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA. ⁵³⁵School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA. ⁵³⁶Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria. ⁵³⁷University of Maryland, College Park, MD, USA. ⁵³⁸Department of General Medicine, University of Texas Health Science Center, San Antonio, TX, USA. ⁵³⁹Monash University Clayton Campus, Melbourne, Victoria, Australia. ⁵⁴⁰University of Helsinki, Helsinki, Finland. ⁵⁴¹University of Colorado Anschutz Medical Center, Aurora, CO, USA. ⁵⁴²Medical University of Graz, Graz, Austria. ⁵⁴³Massachusetts General Hospital, Harvard University, Cambridge, MA, USA. ⁵⁴⁴Imaging of Dementia and Aging (IDeA) Laboratory, Department of Neurology, University of California, Davis, Davis, CA, USA. ⁵⁴⁵University of Staffmail, Edinburgh, UK. ⁵⁴⁶University of Bordeaux, IMN, Bordeaux, France. ⁵⁴⁷University of Mississippi Medical Center, Jackson, MS, USA. ⁵⁴⁸GeneSTAR Research Program, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA. ⁵⁴⁹University of Toronto, Toronto, Ontario, Canada. ⁵⁵⁰Departments of Psychiatry & Neuroscience, Centre Hospitalier Universitaire Saint-Justine, University of Montreal, Montreal, Quebec, Canada. ⁵⁵¹Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada. ⁵⁵²Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute and Pediatrics at Harbor-UCLA Medical Center, Torrance, CA, USA. ⁵⁵³Boston Medical Center, Boston, MA, USA. ⁵⁵⁴Gottfried Schatz Research Center, Department of Molecular Biology and Biochemistry, Medical University of Graz, Graz, Austria. ⁵⁵⁵Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria. ⁵⁵⁶Departments of Neurology, Molecular & Human Genetics, and Neuroscience and Program in Developmental Biology, Baylor College of Medicine, Houston, TX, USA. ⁵⁵⁷Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA. ⁵⁵⁸Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada. ⁵⁵⁹University of Mississippi Medical Center, Jackson, MS, USA. ⁵⁶⁰Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany. ⁵⁶¹University of North Carolina, Chapel Hill, NC, USA. ⁵⁶²University of Texas, Austin, TX, USA. ⁵⁶³Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria. ⁵⁶⁴Karolinska Institute, Stockholm, Sweden. ⁵⁶⁵German Center for Neurodegenerative Diseases (DZNE), Site Rostock/Greifswald, Greifswald, Germany. ⁵⁶⁶Institute of Molecular Medicine, University of Texas Health Science Center at Houston McGovern Medical School, Houston, TX, USA.

Methods

Samples. All of our stage I meta-analysis samples came from the following consortia/datasets: EADB, GR@ACE, EADI, GERAD/PERADES, DemGene, Bonn, the Rotterdam study, the CCHS study, NxC and the UKBB. In the UKBB, individuals who did not report dementia or any family history of dementia were used as controls; the analysis included 2,447 diagnosed cases, 46,828 proxy cases of dementia and 338,440 controls. All individuals included in stage I are of European ancestry; demographic data on these case-control studies are summarized in Supplementary Table 1, and more detailed descriptions are available in the Supplementary Note. Stage II samples are from the ADGC, CHARGE and FinnGen consortia (Supplementary Table 1 and Supplementary Note) and are described in detail elsewhere^{5,6,9,10,54–56}. Written informed consent was obtained from study participants or, for those with substantial cognitive impairment, a caregiver, legal guardian or other proxy. Study protocols for all cohorts were reviewed and approved by the appropriate institutional review boards.

Quality control and imputation. A standard quality control was performed on variants and samples from all datasets individually. The samples were then imputed with the TOPMed reference panel^{57,58}. The Haplotype Reference Consortium (HRC) panel⁵⁹ was also used for some datasets (Supplementary Table 2). For the UKBB, we used the provided imputed data generated from a combination of the 1000 Genomes, HRC and UK10K reference panels (Supplementary Note).

Stage I analyses. Tests of the association between clinical or proxy-ADD status and autosomal genetic variants were conducted separately in each dataset by using logistic regression and an additive genetic model, as implemented in SNPTEST 2.5.4-beta3 (ref. ⁶⁰) or PLINK v1.90 (ref. ⁴). However, a logistic mixed model (as implemented in SAIGE v0.36.4 (ref. ⁶¹)) was considered for the UKBB data. We analyzed the genotype probabilities in SNPTEST (using the newml method) and dosages in PLINK and SAIGE. Analyses were adjusted for PCs and genotyping centers, when necessary (Supplementary Table 2). For the UKBB dataset, only variants with a MAF above 0.01% and a minor allele count (MAC) above 3 were analyzed, and effect sizes and standard errors were corrected by a factor of two, because proxy cases were analyzed. This approach is appropriate for variants with a moderate-to-high frequency and a small effect size. For all datasets, we filtered out duplicated variants and variants with (1) missing data on the effect size, standard error or *P* value; (2) an absolute effect size above 5; (3) an imputation quality below 0.3; and (4) a value below 20 for the product of the MAC and the imputation quality (MAC-info score). For datasets not imputed with the TOPMed reference panel, we also excluded (1) variants for which conversion of position or alleles from the GRCh37 assembly to the GRCh38 assembly was not possible or problematic or (2) variants with very large difference of frequency between the TOPMed reference panel and the reference panels used to perform imputation.

Results were then combined across studies in a fixed-effect meta-analysis with an inverse-variance weighted approach, as implemented in METAL v2011-03-25 software⁶². We filtered out (1) variants with a heterogeneity *P* value below 5×10^{-8} , (2) variants analyzed in less than 20% of the total number of cases and (3) variants with frequency amplitude above 0.4 (defined as the difference between the maximum and minimum frequencies across all the studies). We also excluded variants not analyzed in the EADB-TOPMed dataset.

The genomic inflation factor lambda was computed with the GenABEL 1.8-0 R package⁶³ and a median approach after exclusion of the *APOE* region (44–46 Mb on chromosome 19 in GRCh38). The LD score regression intercept was computed with LDSC v1.0.1 software using the ‘baselineLD’ LD scores built from 1000 Genomes phase 3 (ref. ⁶⁴). The analysis was restricted to HapMap 3 variants and excluded multiallelic variants, variants without an rs ID and variants in the *APOE* region.

Definition of associated loci. A region of ± 500 kb was defined around each variant with a stage I *P* value below 1×10^{-5} . These regions were then merged (using bedtools v2.27.0 software; <https://bedtools.readthedocs.io/en/latest/>) to define nonoverlapping regions. The region corresponding to the *APOE* locus was excluded. We then used the PLINK clumping procedure to define independent hits in each region. An iterative clumping procedure was applied to all variants with a stage I *P* value below 1×10^{-5} , starting with the variant with the lowest *P* value (referred to as the index variant). Variants with a stage I *P* value below 1×10^{-5} , located within 500 kb of this index variant and in LD with the index variant (r^2 above 0.001) were assigned to the index variant’s clump. The clumping procedure was then applied until all the variants had been clumped. LD in the EADB-TOPMed dataset was computed using high-quality (probability ≥ 0.8) imputed genotypes.

Stage II analyses. Variants with a stage I *P* value below 1×10^{-5} were followed up (Supplementary Note). Results were combined across all stage I and II studies in a fixed-effect meta-analysis with an inverse variance weighted approach, as implemented in METAL. In each clump, we then reported the variants with positive follow-up results (i.e., the same direction of effect in stage I and stage II, and a stage II *P* value below 0.05) and the lowest *P* value in the meta-analysis. Those variants were considered to be associated at the genome-wide significance

level if they had a *P* value below 5×10^{-8} in the stage I and II meta-analysis. However, we excluded the chr6:32657066:G:A variant, because its frequency amplitude was high.

Pathway analysis. A total of 10,271 gene sets were considered for analysis (Supplementary Note). Gene set enrichment analyses were performed in MAGMA v1.08 (refs. ^{65,66}), with correction for the number of variants in each gene, LD between variants and LD between genes. LD was computed from the EADB-TOPMed dataset using high-quality (probability ≥ 0.9) imputed genotypes. 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 by De Leeuw et al.⁶⁷. We used the ‘mean’ test statistic, which uses the sum of $-\log(\text{variant } P \text{ value})$ across all genes. The primary analysis assigned variants to genes if they lay within the gene boundaries, although a secondary analysis used a window of 35 kb upstream and 10 kb downstream to assign variants to genes (as in Kunkle et al.⁵). The primary analysis included all variants with an imputation quality above 0.8. We used *q* values⁶⁸ to account for multiple testing.

Expression in various cell types. The expression of genes was assigned to specific cell classes of the adult brain, as described previously⁶⁹. Briefly, middle temporal gyrus single-nucleus transcriptomes from the Allen Brain Atlas dataset (49,555 total nuclei derived from 8 human tissue donors aged 24–66 years) were used to annotate and select six main cell classes using Seurat 3.1.1 (ref. ⁷⁰): glutamatergic neurons, GABAergic neurons, astrocytes, oligodendrocytes, microglia and endothelial cells. Enrichment analyses were performed by using the mean gene expression per nucleus for each cell type relative to the total expression summed across cell types as a quantitative covariate in a MAGMA gene property analysis.

Functional interpretation of GWAS signals and gene prioritization. To prioritize candidate genes in the new loci, we systematically searched for evidence for these genes in seven different domains: (1) variant annotation, (2) eQTL-GWAS integration, (3) sQTL-GWAS integration, (4) protein QTL (pQTL)-GWAS integration, (5) mQTL-GWAS integration, (6) histone acetylation QTL (haQTL)-GWAS integration and (7) APP metabolism. On the basis of this evidence, we then defined a gene prioritization score of between 0 and 100 for each candidate gene (Supplementary Fig. 34). Detailed information on the domains, categories (e.g., the tissue or cell type for QTL-GWAS integration domains) and subcategories (for the type of evidence) is given in Supplementary Table 19. A brief summary of how evidence was assessed in each domain is provided below, together with a detailed description of the gene prioritization strategy.

Candidate genes. We considered protein-coding candidate genes within a ± 1 -Mb window of the new lead variants. The genes in overlapping loci (i.e., L28, L30 and L37) were assigned to their respective loci based on proximity to the lead variants, and the distal genes were not considered for gene prioritization in the investigated loci. Moreover, we did not perform gene prioritization in the complex IGH gene cluster locus (L27), as this telomeric region contains complex splicing events (spanning a high number of IGH genes) that probably result from known fusion events⁶⁸.

The variant annotation domain. In this domain, we determined whether the candidate gene was the nearest protein-coding gene to the lead variant and/or whether the lead variant was a rare variant (MAF < 1%) and/or protein-altering variant of the investigated candidate gene.

Molecular QTL-GWAS integration domains. To study the downstream effects of new ADD-associated variants on molecular phenotypes (i.e., expression, splicing, protein expression, methylation and histone acetylation) in various AD-relevant tissues, cell types and brain regions, molecular *cis*-QTL information (i.e., the genetic variants that regulate these molecular phenotypes) was integrated with the stage I ADD GWAS results in genetic colocalization analyses, TWASs and a genetically driven DNA methylation scan. These molecular QTLs include eQTLs, sQTLs, pQTLs, mQTLs and haQTLs. We mapped and prepared eQTL/sQTL catalogs in AD-relevant bulk brain regions from AMP-AD cohorts^{51–74} and in LCLs from the EADB Belgian cohort. We used additional eQTL/sQTL information in AD-relevant bulk brain regions from GTEx⁷⁵ and microglia from the MiGA study⁷⁶. Furthermore, eQTLs in monocytes and macrophages from various datasets^{77–82} (as prepared by eQTL Catalogue⁸³) were included in the analyses. Data on pQTLs⁸⁴, mQTLs⁸⁵ and haQTLs⁸⁵ were available for DLPCF. Using each molecular QTL catalogue, the effect of the lead variants was queried and significant associations were reported. Moreover, genetic colocalization studies were conducted by comparing ADD association signals with the eQTL/sQTL signals from AMP-AD bulk brain, MiGA microglia and EADB LCL cohorts. We also conducted eTWASs and splicing TWASs (sTWAS) of the ADD risk, along with fine mapping of the eTWAS results. To this end, we trained functional expression and splicing reference panels based on the AMP-AD bulk brain and EADB LCL cohorts, and we leveraged precalculated reference panel weights⁸⁶ for the GTEx dataset⁷⁵ in tissues and cells of interest. Lastly, for the mQTL-GWAS integration

domain, we also tested for associations between ADD and genetically driven DNA methylation (MetaMeth analysis) in blood (with blood–brain methylation correlation estimates obtained from BECON⁸⁷) using the procedures described by Freytag et al.⁸⁸ and Barbeira et al.⁸⁹. A detailed description of the datasets and methods used for each of these analyses is given in the Supplementary Note.

APP metabolism domain. We assessed the functional impact of gene underexpression on APP metabolism for all candidate genes based on a genome-wide high-content short interfering RNA screen¹⁷ (Supplementary Note).

Gene prioritization score. We computed a gene prioritization score for each candidate gene as the weighted sum of the evidence identified in the seven domains. We specified a weight for each type of evidence, as detailed in Supplementary Table 19. For the molecular QTL–GWAS integration domains, we gave more weight to replicated hits (i.e., evidence in several datasets) than to single hits. We also gave more weight to hits observed in brain (the bulk brain and microglia datasets) than to hits observed in other tissues/cell types (LCLs, monocytes, macrophages and blood). To avoid score inflation, several specific rules were applied: (1) for the results of sQTL- and mQTL-based analyses, multiple splice junctions or CpGs annotated for the same genes were aggregated prior to weighting due to correlated data; (2) if we observed a fine-mapped eTwas association for a gene, its other significant (but not fine-mapped) eTwas associations were not considered; (3) for genes having several significant CpGs (prior to aggregation) in MetaMeth analyses, the associated CpGs with a low (<75% percentile) blood–brain methylation correlation estimate were not considered if the gene also had associated CpGs with a high (≥75% percentile) blood–brain methylation correlation estimate.

Gene prioritization strategy. After obtaining a total weighted score per gene, we ranked genes per locus according to their prioritization scores and compared the relative score differences between the highest ranked gene and other genes in the investigated locus. If this relative difference was at least 20% and the gene prioritization score for the highest ranked gene was ≥4, then we classified this gene as a tier 1 prioritized gene in the investigated locus (i.e., a greater likelihood of being the true risk gene responsible for the ADD signal). If this absolute threshold was not met, then the highest ranked gene was classified as a tier 2 prioritized gene (i.e., a lower level of confidence and absence of the minimum level of evidence for a true risk gene). Furthermore, other genes in a locus harboring a tier 1 gene were classified as tier 2 prioritized genes if the relative score difference versus the highest ranked (tier 1) gene was between 20% and 50%. Lastly, when the relative score difference between the highest ranked gene and other genes in the same locus was <20%, then both the highest ranked gene and all genes with a score difference <20% were classified as tier 2 prioritized genes in the investigated locus; based on the current evidence, it is difficult to prioritize two or more similarly scored genes. The gene prioritization strategy is summarized in Supplementary Fig. 34. Detailed descriptions and discussions of prioritized genes and tier levels in each investigated new locus can be found in the Supplementary Note.

GRS analysis. Eight longitudinal MCI cohorts and seven population-based studies were included in the analysis and are fully described in the Supplementary Note and Supplementary Table 33. The GRSs were calculated as previously described⁹⁰. Briefly, we considered variants with genome-wide significant evidence of association with ADD in our study. We did not include any APOE variants in the GRS. Variants were directly genotyped or imputed ($R^2 \geq 0.3$). Imputation was performed using the HRC panel⁵⁹ for subcohorts from the Rotterdam study and the TOPMed panel for the other cohorts⁵⁷. For HRC-imputed data, LD proxies were considered for variants that were not available in this reference panel. The GRS was calculated as the weighted average of the number of risk-increasing alleles for each variant, using dosages. Weights were based on the respective log(OR) obtained in stage II. The GRS was then multiplied by the number of included variants. Thus, the HR measured the effect of carrying one additional average risk allele.

To assess whether the new variants in this study contribute to the risk of conversion to AD (in addition to known AD genes), we calculated two GRSs: one based solely on variants known before this study (GRS_{known}, $n = 39$; Table 1) and another based on variants identified in the present study (GRS_{novel}, $n = 44$; Table 2). These GRSs were calculated in the same way as the GRS encompassing all the variants.

The association between the GRS and the risk of progression to dementia in individuals from population-based cohorts or patients with MCI from memory clinics was tested statistically using Cox proportional hazards models. The models were adjusted for age, sex, the first four PCs (to correct for potential population stratification) and the number of APOE-ε4 and APOE-ε2 alleles (assuming an additive effect). In the FHS study, the generation was used as an additional covariate. In the 3C study, the analysis was adjusted for age, sex, the number of APOE alleles, the two first PCs and center. The PCs used were generated for each cohort, using the same variants as in the case/control study's PC analysis. The number of APOE-ε4 alleles was obtained from direct genotyping or, if missing, the genotypes (with probability >0.8) derived from the TOPMed imputations. The interaction between the GRS and the number of APOE-ε4 alleles was tested on

the multiplicative scale. In the primary analysis, conversion to AD was used as the outcome (conversions to non-AD dementias were coded as being censored at time of conversion), but analyses were repeated using all-cause dementia as the outcome.

To quantify the effect size of the potential association between the GRS and conversion to dementia regarding predictive performance, we computed three different indices measuring different aspects of the predictive performance of the GRS in our prospective, longitudinal cohort studies⁹¹: the continuous version of the C-index^{92,93}, the continuous NRI⁹⁴ and IPA⁹⁵ (Supplementary Note). For all indices, we provide point estimates and 95% CIs.

In the main analysis, indices were computed at the time point for which all cohorts in a specific setting (i.e., population-based studies or memory clinics, respectively) provided follow-up observations (that is 5 years for population-based cohorts and 3 years for MCI cohorts). In a sensitivity analysis, indices for longer or shorter follow-up periods were also derived (that is 3 years and 10 years for population-based cohorts and 5 years for MCI cohorts). Standard errors for indices were derived by non-parametric bootstrapping with 1,000 samples.

To determine the average effect of the GRS across the various cohorts examined, individual cohort results were subjected to both inverse-variance weighted meta-analyses (primary analyses) and random effects meta-analysis (Supplementary Note). To facilitate comparisons of results for different time points, cohorts with longer follow-up periods were meta-analyzed separately. Furthermore, two memory clinic cohorts with a limited sample size ($N < 50$) were excluded to assess their impact on the final meta-analysis results. Meta-analyses were performed using the 'metafor' (3.0.2) R package⁹⁶.

To further illustrate the clinical relevance of the GRS, we pooled computed GRSs across four population-based cohorts (3C, AgeCoDe, VITA and MAS) and computed deciles of the GRS distribution for use as a common reference for all cohorts. We then computed the increase in risk when augmenting the GRS value from the first decile (GRS = 50.76) to the ninth decile (GRS = 59.74) of the distribution. To represent this risk increase in the HR, we rescaled the HR derived from our meta-analyses results using the equation $e^{\log(\text{HR}) * (\text{GRS}_{9\text{thdecile}} - \text{GRS}_{1\text{stdecile}})}$. Importantly, this approach yields exactly the same results as transforming the GRS so that a one unit increment corresponds to the increase from the lowest decile to the highest decile.

Furthermore, we approximated the probability of conversion to AD at 3 and 5 years in memory clinic patients with MCI by using Cox models implemented in the 'PredictCox' function from the 'riskRegression' (2020.12.8) R package⁹⁷. We did not derive AD conversion probabilities for two cohorts with very small sample sizes ($N < 50$). Predicted AD conversion probabilities were derived and averaged for all patients in each of the groups formed by the decile of the GRS distribution in each cohort. The difference between the groups with the highest and lowest GRSs was computed in each cohort. We report the median (range) results in each group formed by the GRS deciles.

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

Data Availability

Genome-wide summary statistics have been deposited to the European Bioinformatics Institute GWAS Catalog (<https://www.ebi.ac.uk/gwas/>) under accession no. GCST90027158.

The significant eQTLs/sQTLs mapped and eTwas/sTwas functional reference panel weights generated for this study (in AD-relevant bulk brain regions from AMP-AD cohorts and in LCLs from the EADB Belgian cohort) are publicly available at <https://doi.org/10.5281/zenodo.5745927> and <https://doi.org/10.5281/zenodo.5745929>.

Anonymized aligned reads of the amplicon-based long-read Nanopore cDNA sequencing experiment conducted for the TSPAN14 splicing analysis are available through the European Nucleotide Archive under accession PRJEB49234.

Moreover, the following data used in the gene prioritization are publicly available: AMP-AD rnaSeqReprocessing Study (<https://www.synapse.org/#!Synapse:syn9702085>);

MayoRNAseq whole-genome sequencing variant call formats (WGS VCFs) (<https://www.synapse.org/#!Synapse:syn11724002>);

ROSMAP WGS VCFs (<https://www.synapse.org/#!Synapse:syn11724057>);

MSBB WGS VCFs (<https://www.synapse.org/#!Synapse:syn11723899>);

eQTLGen (<https://www.eqtlgen.org/>);

eQTL Catalogue database (<https://www.ebi.ac.uk/eqtl/>);

Brain xQTL serve (<http://mostafavilab.stat.ubc.ca/xqtl/>);

GTEx v8 eQTL and sQTL catalogs (<https://www.gtexportal.org/>);

GTEx v8 expression and splicing prediction models (<http://predictdb.org/>);

MiGA eQTLs (<https://doi.org/10.5281/zenodo.4118605>);

MiGA sQTLs (<https://doi.org/10.5281/zenodo.4118403>);

MiGA meta-analysis (<https://doi.org/10.5281/zenodo.4118676>); and

Wingo et al.⁸⁴ pQTL data (<https://www.synapse.org/#!Synapse:syn23627957>).

Code availability

We used publicly available software for all analyses. The software are listed in the Supplementary Note with their appropriate citations and/or URLs.

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Author contributions

EADB coordination: K. Mather, F.J., M.T., R.F.-S., J. Clarimon, J.-F. Deleuze, O.A.A., M.I., M. Hiltunen, K.S., C.M.v.d., R.S., W.M.v.d.F., A. Ruiz, A. Ramirez and J.-C.L. Data analyses: C. Bellenguez, F.K., I.E.J., L.K., S.M.-G., N.A., R.C., B.G.-B., V. Andrade, P.A.H., R.C.-M., V.D., S.J.v.d.L., M.R.C., T.K., I.R., J. Chapuis and P.G.-G. ADGC analysis and coordination: A.C.N., W.S.B., L.A.F., J.L.H., K.L.H.-N., P.P.K., B.W.K., C.-Y.L. and E.R.M., R. Mayeux, M.A.P.-V., J.S., L.-S.W., Y.Z. and G.D.S. Charge analysis and coordination: Q.Y., J.C.B., A.D.S., C.S., B.M.P., R.W., O. Lopez, and S. Seshadri. FinnGen analysis: T.K. and M. Hiltunen. Rotterdam analysis: A.Y., I.P.-N., M. Ghanbari and M.A.I. Sample contribution: S. Ahmad, V. Giedraitis, D. Aarsland, P.V.Á., D.G.-G., C. Abdelnour, E.A.-M., D. Alcolea, M. Alegret, I. Alvarez, V. Alvarez, N.J.A., A. Tsolaki, C. Antúnez, I. Appollonio, M. Arcaro, S. Archetti, A.A.P., B.A., L.A., H. Bailly, N.B., M. Baquero, S. Barral, A. Beiser, A.B.P., J.E.B., P. Benček, L.B., C. Berr, C. Besse, V. Bessi, G. Binetti, A. Bizarro, R.B., M. Boada, E.B., B.B., S. Boschi, P. Bossù, G. Bråthen, J.B., C. Bresner, H. Brodaty, K.J.B., L.I.B., D.B.-R., K.B., V. Burholt, W.S.B., M.C., L.B.C., G.C., J. Chung, M.L.C., Á.C., R.C., L.C.-C., C. Charbonnier, H.-H.C., C. Chilotti, S.C., J.A.C., C. Clark, E. Conti, A.C.-G., E. Costantini, C. Custodero, D.D., M.C.D., A. Daniele, E. Dardiotis, J.-F. Dartigues, P.P.D., K.d.P.L., L.D.d.W., S. Debette, J.D., T.d.S., N.D., A. DeStefano, M.D., J.D.-S., M.D.-F., P.D.R., S. Djurovic, E. Duron, E. Duzel, C.D., G.E., S.E., V.E.-P., A.E., M.E., K.M.F., T. Fabrizio, S.F.N., D.W.F., L. Farotti, C.F., M.F.-F., R.F., C.B.F., E.F., B. Fin, P.F., T. Fladby, K.F., B. Fongang, M.F., J.F., T.M.F., S.F., N.C.F., E.F.-M., M.J.B., A.F.-G., L. Froelich, B.F.-H., D.G., J.M.G.-A., S.G.-M., G.G.-R., R.G., I.G., G. Giorgio, A.M.G., O.G., D.G.-F., A.G.-P., C.G., G. Grande, E. Green, T.G., E. Grunblatt, M. Grunin, V. Gudnason, T.G.-B., A.H., G.H., J.L.H., K.L.H.-N., H. Hampel, O.H., J. Hardy, A.M.H., L.H., J. Harwood, S.H.-H., S.H., M.T.H., I.H., M.J.H., P.H., C.H., H. Holstege, R.H.V., M. Hulsman, J. Humphrey, G.J.B., X.J., C.J., G.R.J., Y.K., J. Kauwe, P.G.K., L. Kilander, A.K.S., M.K., A.K., J. Kornhuber, M.H.K., W.A.K., P.P.K., B.W.K., A.B.K., C.L., E.J.L., L. Launer, A. Lauria, C.-Y.L., J.L., O.Ler., A. Lleó, W.L.J., O. Lopez, A.L.d.M., S.L., M.L., L. Luckcuck, K.L.L., Y.M., J.M., C.A.M., W.M., F. Mangialasche, M. Spalazzi, M. Marquie, R. Marshall, E.R.M., A.M.M., C.M.R., C. Masullo, R. Mayeux, S. Mead, P. Mecocci,

M. Menéndez-González, A.M., S. Mehrabian, S. Mendoza, M.M.-G., P. Mir, S. Moebus, M. Mol, L.M.-P., L. Monttreal, L. Morelli, F. Moreno, K. Morgan, T. Mosley, M.M.N., C. Muchnik, S. Mukherjee, B.N., T.N., G.N., B.G.N., R.O., A.O., M.O., G.O., A.P., C. Paollo, G. Papenberg, L.P., F.P., P. Pastor, G. Peloso, A.P.-C., J.P.-T., P. Pericard, O.P., Y.A.P., J.A.P., G.P.-R., C. Pisanu, T.P., J. Popp, D.P., J. Priller, R.P., O.Q., I.Q., J.Q.T., A. Rábano, I. Rainero, F.R., I. Ramakers, L.M.R., M.J.R., C.R., D.R.-D., P. Ridge, S.R.-H., P. Riederer, N.R., E.R.-R., A. Rongve, I.R.A., M.R.-R., J.L.R., E.R., D.R., M.E.S., P. Sakka, I.S., Á.S., M.B.S.-A., F.S.-G., P.S.J., R.S.-V., S.B.S., C.S., C.L.S., M. Scamosci, N. Scarneas, E. Scarpini, P. Scheltens, N. Scherbaum, M. Scherer, M. Schmid, A. Schneider, J.M.S., G. Selbæk, D.S., M. Serrano, J.S., A.A.S., O.S., S. Slifer, G.J.L.S., H.S., V.S., A. Solomon, Y.S., S. Sorbi, O.S.-G., G. Spalletta, A. Spottke, A. Squassina, E. Stordal, J.P.T., L. Tárraga, N.T., A. Thalamuthu, T.T., G.T., L. Traykov, L. Tremolizzo, A.T.-H., A. Uitterlinden, A. Ullgren, I.U., S.V., O.V., C.V.B., J. Vance, B.N.V., A.v.d.L., J.V.D., J.v.R., J.v.S., R.V., F.V., J.-S.V., J. Vogelgsang, M.V., M.W., D.W., L.-S.W., R.W., L.W., J. Wiltfnag, G.W., B.W., M.Y., H.Z., Y.Z., X.Z., C.Z., M.Z., L.A.F., B.M.P., M. Ghanbari, T.R., P. Sachdev, K. Mather, F.J., M.A.I., A.d.M., J. Hort, M.T. and M.A.P.-V. Core writing group: C. Bellenguez, F.K., V. Andrade, B.G.-B., P.A.H., R.C.-M., L.K., S.J.v.d.L., K.S., A. Ruiz, A. Ramirez and J.-C.L.

Competing interests

H. Hampel is an employee of Eisai. The present article was initiated and prepared as part of his academic position at Sorbonne University (Paris, France), and it reflects entirely

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Additional information

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Correspondence and requests for materials should be addressed to Céline Bellenguez or Jean-Charles Lambert.

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| <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> 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) |
| <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
<i>Give P values as exact values whenever suitable.</i> |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> 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.
Data analysis	Bedtools 2.27.0 bcftools 1.9 bwa 0.7.17 coloc 4.0.4 Eagle 2.4; 2.0.5 EIGENSOFT 7.2.1 EIGENSTRAT Enhanced FastQTL 2.184_gtex EstiMeth 1.1 FlashPCA 2.0 FOCUS 0.7 GCTA-COJO from gcta 1.93.2beta GENESIS 2.14.4 GenomeStudio 2.0.3 Gentrain 3.0 ggplot2 3.3.3 Guppy 3.2.4 GWAF 2.2 GWASTools 1.30.1 HIBAG 1.4 IGV 2.4.17

LDSC 1.0.1
 Ldstore 2.0
 Leafcutter 0.2.9
 Liftover
 MAGMA 1.08
 METAL v2011-03-25
 MetaXcan 0.6.12
 Michigan Imputation Server 1.2.4
 Minimac 3 and 4-1.0.2
 minimap 2.17
 mosdepth 0.2.9
 NanoStat 1.1.2
 NCBI remap
 PBWT 3.1
 Picard 2.22.6
 PLINK 1.9 and 2.0
 pygenometracks 3.5
 qcat 1.0.1
 R 3.6.0, 3.6.1 and 3.6.3
 RegTools 0.5.1
 RNASeQC 2.3.5
 R package GenABEL 1.8-0
 R package haplo.stats 1.8.6
 R package ieugwasr 0.1.5
 R package metafor 3.0.2
 R package pec 2020.11.17
 R package riskRegression 2020.12.8
 R package stats 3.6.2
 R package survIDINRI 1.1.1
 R package survival 3.2.11
 SAIGE 0.36.3.2 and 0.36.4
 SamJdk 9750c96
 Samtools 1.9
 SeqMeta 1.6.7
 SNPRelate 1.18.1
 SNPTTEST 2.5.3, 2.5.4-beta3 and 2.5.6
 STAR 2.7.3a
 STRING v11
 vcffilterjdk v9750c96

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 Research [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 list of figures that have associated raw data
- A description of any restrictions on data availability

Genome-wide summary statistics have been deposited to the European Bioinformatics Institute GWAS Catalog (<https://www.ebi.ac.uk/gwas/>) under accession no. GCST90027158.

The significant e/sQTLs mapped and e/sTwas functional reference panel weights generated for this study (in AD-relevant bulk brain regions from AMP-AD cohorts and in LCLs from the EADB Belgian cohort) are publicly available at <https://doi.org/10.5281/zenodo.5745927> and <https://doi.org/10.5281/zenodo.5745929>.

Anonymized aligned reads of the amplicon-based long-read nanopore cDNA sequencing experiment conducted for the TSPAN14 splicing analysis are available through ENA under accession PRJEB49234.

Moreover, the following data used in the gene prioritization are publicly available:

AMP-AD rnaSeqReprocessing Study: <https://www.synapse.org/#!Synapse:syn9702085>

MayoRNAseq WGS VCFs: <https://www.synapse.org/#!Synapse:syn11724002>

ROSMAP WGS VCFs: <https://www.synapse.org/#!Synapse:syn11724057>

MSBB WGS VCFs: <https://www.synapse.org/#!Synapse:syn11723899>

eQTLGen: <https://www.eqtlgen.org/>

eQTL Catalogue database: <https://www.ebi.ac.uk/eqtl/>

Brain xQTL serve: <http://mostafavilab.stat.ubc.ca/xqtl/>

GTEx v8 eQTL and sQTL catalogues: <https://www.gtexportal.org/>

GTEx v8 expression and splicing prediction models: <http://predictdb.org/>

MiGA eQTLs: <https://doi.org/10.5281/zenodo.4118605>

MiGA sQTLs: <https://doi.org/10.5281/zenodo.4118403>

MiGA Meta-analysis: <https://doi.org/10.5281/zenodo.4118676>

Wingo et al. pQTL data: <https://www.synapse.org/#!Synapse:syn23627957>

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](https://www.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	Raw data used in this study was collected by the EADB consortia and summary statistics were recruited by external sources used for meta-analysis. Sample size was not pre-determined and was chosen based on all known available cohorts with relevant data collected to date, after quality control steps were performed in each cohort (described in detail in Supplementary Information) in particular to avoid any sample duplications. The sample size was calculated as the number of individuals summed across all studies in the meta-analysis, N=487,511.
Data exclusions	We excluded samples and variants based on standard quality control procedures for GWAS (Samples: Heterozygosity and missingness, Population outliers, Sex-check, Relatedness, Possibly problematic chips batch; Variants: Missingness and Hardy-Weinberg equilibrium, Frequency checks, Ambiguous variants, Duplicated variants). Complete details of our quality control procedures are provided in the methods and supplementary information section of the manuscript.
Replication	The meta-analysis strategy includes replication by default, as it weights the reported test statistics by the evidence of association across multiple samples. Further, SNP-based replication was carried out for the top GWAS association signals in an independent sample (N= 25,392 Alzheimer's disease cases and 276,086 controls; see Methods and supplementary information).
Randomization	Samples were randomized by case and control status on plates during genotyping at their independent study sites.
Blinding	genotyping was done blind without knowing the status of the individuals. The analysts were not blinded to the status of the individuals because QC procedures require knowing case and 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

Methods

n/a	Involved in the study	n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies	<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines	<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology	<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms		
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants		
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data		
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern		

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	We used multiple independent sets of participants in this study. We adjusted the analysis for principal components. Sample sizes, age and gender characteristics for our sample can be found per cohort and overall in Supplementary Tables 1 and Supplementary Information.
Recruitment	Participants from case-control studies were primarily recruited from clinics, nursing homes, disease registries, and hospitals, with controls being drawn from various ongoing studies and screened to exclude dementia/cognitive decline (see description of the samples in the supplementary information). Cases were recruited according to clinical diagnosis and defined as probable AD cases with a potential risk of misdiagnosis (estimated between 10 and 20% in the literature). Controls included in the study were free of cognitive decline but a large part of them did not have any follow-up with the possibility that they developed dementia years later. The UK Biobank recruited adult volunteers from national health registration records. UK Biobank participants are healthier than the general population, but since the data used in this study referred to parental diagnoses, the impact of selection bias should be minor.

Ethics oversight

Written informed consent was obtained from study participants or, for those with substantial cognitive impairment, from a caregiver, legal guardian, or other proxy, and the study protocols for all populations were reviewed and approved by the appropriate local Institutional review boards (see description of the samples in the supplementary information).

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