



# HHS Public Access

## Author manuscript

Nat Genet. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

Nat Genet. 2019 March ; 51(3): 414–430. doi:10.1038/s41588-019-0358-2.

\*Correspondence and requests for materials should be addressed to B.W.K. bkunkle@miami.edu, J.-C.L. jean-charles.lambert@pasteur-lille.fr or M.A.P. mpericak@miami.edu.

Author contributions

**ADGC.** *Study design or conception:* A.C.N., A.A.-W., E.R.M., K.H.-N., A.B.K., B.N.V., G.W.B., O.V., M.Butkiewicz, W.B., Y.Song, G.D.S., M.A.P.-V. *Sample contribution:* S.Mukherjee, P.K.C., R.B., P.M.A., M.S.A., D. Beekly, D. Blacker, R.S. Doody, T.J.F., M.P.F., B.Ghetti, R.M.H., M.I.K., M.J.K., C.K., W.K., E.B.L., R.B.L., T.J.M., R.C.P., E.M.R., J.S.R., D.R.R., M. Sano, P.S.G.-H., D.W.T., C.K.W., R.L.A., L.G.A., S.E.A., S.A., C.S.A., C.T.B., L.L.B., S. Barral, T.G.B., J.T.B., E.H.B., T.D.B., B.F.B., J.D.B., A.Boxer, J.R.B., J.M.B., J.D.Buxbaum, N.J.C., C. Cao, C.S.C., C.M.C., R.M.C., H.C.C., D.H.C., E.A.C., C.DeCarli, M.Dick, R.D., N.R.G.-R., D.A.E., K.M.F., K.B.F., D.W.F., M.R.F., S.F., T.M.F., D.R.G., M.Gearing, D.H.G., J.R.G., R.C.G., J.H.G., R.L.H., L.E.H., L.S.H., M.J.H., C.M.H., B.T.H., G.P.J., E.A., L.W.J., G.R.J., A.Karydas, J.A.K., R.K., N.W.K., J.H.K., F.M.L., J.J.L., J.B.L., A.I.L., A.P.L., K.L.L., C.G.L., D.C.M., F.M., D.C.Mash, E.M., W.C.M., S.M.M., A.N.M., A.C.M., M.M., B.L.M., C.A.M., J.W.M., J.C.M., A.J.M., S.O., J.M.O., J.E.P., H.L.P., E.P., A.P., W.W.P., H.P., J.F.Q., A.Raj, M.R., B.R., C.R., J.M.R., E.D.R., E.R., H.J.R., R.N.R., M.A.S., A.J.S., M.L.C., J. Vance, J.A.S., L.S.S., W.W.S., A.G.S., J.A.Sonnen, S. Spina, R.A.S., R.H.S., R.E.T., J.Q.T., J.C.T., V.M.V.D., L.J.V.E., H.V.V., J.P.V., S.W., K.A.W.-B., K.C.W., J.Williamson, T.S.W., R.L.W., C.B.W., C.-E.Y., L.Y., D.B., P.L.D.J., C.Cruchaga, A.M.G., N.E.-T., S.G.Y., D.W.D., H.H., L.A.F., J.Haines, R.Mayeux, L.-S.W., G.D.S., M.A.P.-V. *Data generation:* B.W.K., K.H.-N., A.B.K., O.V., L.Q., Y.Z., W.P., S.Slier, J.Malamon, B.A.D., P.W., L.B.C., M.A., M.Tang, J.R.G., L.-S.W. *Analysis:* B.W.K., A.C.N., A.A.-W., E.R.M., K.H.-N., A.B.K., M.Tang, M.M.C., B.N.V., G.W.B., O.V., M.Butkiewicz, W.B., Y.S., G.D.S., M.A.P.-V. *Manuscript preparation:* B.W.K., G.D.S., M.A.P.-V. *Study supervision/ management:* B.W.K., L.A.F., J.Haines, R.Mayeux, L.-S.W., G.D.S., M.A.P.-V. **EADI.** *Study design or conception:* P.A., J.-C.L. *Sample contribution:* K.S., M.Hiltunen, J.E., M.D.Z., I.M., F.S.-G., M.C.D.N., D.Wallon, S.E., R.V., P.D.D., A.Squassina, E.R.-R., C.M.-F., Y.A.B., H.T., V.Giedraitis, L.Kilander, R.Brundin, L.C., S.Helisalmi, A.M.K., A.Haapasalo, V.S., V.Frisardi, V.Deramecourt, N.F., O.H., C.Dufouil, A.Brice, K.R., B.D., H.Soininen, L.Fratiglioni, L.K., F.Panza, D.H., P.C., F.S., P.B., L.Lannfelt, F.P., M.Engelsson, C.G., P.S.-J., A.L., J.Clarimon, C.Berr, S.D., J.-F.D., A.Pilotto, M.J.B., P.Bosco, E.C., G.N., D.C., C.V.B., P.A., J.-C.L. *Data generation:* R.O., J.-G.G., M.-L.M., D.Bacq, F.G., B.F., S.Meslage *Analysis:* B.G.-B., V.D., C.Bellenguez *Manuscript preparation:* B.G.-B., P.A., J.-C.L. *Study supervision/management:* J.-F.Deleuze, A.Boland, P.A., J.-C.L. **GERAD/PERADES.** *Study design or conception:* R.Sims, M.C.O., M.J.O., A.R., P.A.H., J.W. *Sample contribution:* R.Raybould, T.Morgan, P.Hoffmann, D.Harold, O.P., N.D., N.C.F., J.T.H., Y.P., M.Daniilidou, J.U., D.Galimberti, E.Scarpini, J.Kornhuber, S.Sordon, M.Mayhaus, W.G., A.M.H., S.Lovestone, R.Sussams, C.Holmes, W.M., A.Kawalia, S.Moebus, J.Turton, J.Lord, I.K., A.L., B.L., M.Gill, M.D.-F., I.A., A.Ciaramella, C.Cupidi, R.G.M., R.Cecchetti, M.T., D.Craig, D.A., A.G., M.K., O.G., H.Hampel, D.C.R., L.F., B.M., J.A.J., P.Passmore, J.M.S., J.D.W., M.K.L., P.Poitri, J.Powell, J.S.K.K., M.Mancuso, U.B., A.M., G.Livingston, N.J.B., J.Hardy, J.B., R.Guerreiro, E.F., C.Masullo, G.B., L.M., A.H., M.Scherer, M.Riemenschneider, R.Heun, H.K., M.Leber, I.H., I.G., M.Hull, J.M., K.Mayo, T.F., D.Drichel, T.D.C., P.Hollingworth, R.Marshall, A.Meggy, G.M., G.L., D.G., G.R., F.J., B.V., E.V., K.-H.J., M.Dichgans, D.Mann, S.P.-B., N.K., H.W., K.M., K.Brown, C.Medway, M.M.N., N.M.H., A.Daniele, A.Bayer, J.G., H.V.D.B., C.Brayne, S.R.-H., A.A.-C., C.E.S., J.Wiltfang, V.A., A.B.S., J.C., S.M., M.Rosser, N.S.R., B.N., S.Sorbi, E.S., G.S., C.Caltagirone, M.D.O., R.C., A.D.S., D.W., G.W., A.C.B., M.G., Y.B.-S., P.M., P.P., V.B., N.W., P.D., R.G., P.G.K., S.L., C.C., J.T., R.Munger, A.R., J.W. *Data generation:* R.Sims, R.Raybould, T.Morgan, P.Hoffmann, D.Harold, A.Gerrish, N.D., P.Hollingworth, R.Marshall, A.Meggy, A.R., J.W. *Analysis:* R.Sims, M.V., A.F., N.Badarinarayan, D.Harold, G.M., G.L., D.G., V.E.-P., A.R., J.W., P.A.H. *Manuscript preparation:* R.Sims, T.D.C., P.A.H., J.W. *Study supervision/ management:* R.Sims, L.J., V.E.-P., A.R., P.A.H., J.W. **CHARGE.** *Study design or conception:* A.L.D., C.M.V.D., S.S. *Sample contribution:* J.C.B., A.Ruiz, I.D.R., L.M.R., I.Q., A.C., A.L.F., G.E., J.J.H., A.O., M.E.G., H.L., H.Comic, G.Roschupkin, S.Li, I.Hernández, Q.Y., A.S.B., L.T., T.H.M., W.T.L., F.R., E.Boerwinkle, J.I.R., A.G.U., S.M.-G., O.L.L., M.B., M.F., N.A., L.J.L., M.A.I., H.S., R.S., V.G., B.M.P. *Data generation:* J.C.B., J.Jakobsdottir, A.Ruiz, A.V.S., X.J., S.-H.C., H.H.A., J.A.B., T.A., E.H., C.Sarnowski, D.V., L.A.C. *Analysis:* J.C.B., S.J.v.d.L., V.C., J.Jakobsdottir, Y.C., Y.Saba, S.Ahmad, A.Ruiz, A.V.S., C.C.W., C.M.V.D., S.S. *Manuscript preparation:* S.J.v.d.L., A.Ruiz, B.M.P., C.M.V.D., S.S. *Study supervision/management:* C.M.V.D., S.S.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at <https://doi.org/10.1038/s41588-019-0358-2>.

Competing interests

D. Blacker is a consultant for Biogen, Inc. R.C.P. is a consultant for Roche, Inc.; Merck, Inc.; Genentech, Inc.; Biogen, Inc.; GE Healthcare; and Eisai, Inc. A.R.W. is a former employee and stockholder of Pfizer, Inc., and a current employee of the Perelman School of Medicine at the University of Pennsylvania Orphan Disease Center in partnership with the Loulou. A.M.G. is a member of the scientific advisory board for Denali Therapeutics. N.E.-T. is a consultant for Cytox. J.Hardy holds a collaborative grant with Cytox cofunded by the Department of Business (Biz). F.J. acts as a consultant for Novartis, Eli Lilly, Nutricia, MSD, Roche and Piramal. Neither J.M. nor his family owns stock or has equity interest (outside of mutual funds or other externally directed accounts) in any pharmaceutical or biotechnology company. J.M. is currently participating in clinical trials of antideementia drugs from Eli Lilly and Company, Biogen and Janssen. J.M. serves as a consultant for Lilly USA. He receives research support from Eli Lilly/Avid Radiopharmaceuticals and is funded by NIH grant nos. P50AG005681, P01AG003991, P01AG026276 and UF01AG032438. C.Cruchaga receives research support from Biogen, EISAI, Alector and Parabon. The funders of the study had no role in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. C.Cruchaga is a member of the advisory board of ADx Healthcare. M.R.F. receives grant/research support from AbbVie, Accera, ADCS Posiphene, Biogen, Eisai, Eli Lilly, Genentech, Novartis and Suven Life Sciences, Ltd. He is a consultant/advisory board/DSMB board member for Accera, Avanir, AZTherapies, Cognition Therapeutics, Cortexyme, Eli Lilly & Company, Longeveron, Medavante, Merck and Co. Inc., Otsuka Pharmaceutical, Proclara (formerly Neurophage Pharmaceuticals), Neurotropo Biosciences, Takeda, vTv Therapeutics and Zhejian Hisun Pharmaceuticals. He has a transgenic mouse model patent that is licensed to Elan. R.A.S. receives consulting fees as a member of the Alzheimer's Disease Advisory Board, Biogen; and as member of the Executive Committee for

# Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates A $\beta$ , tau, immunity and lipid processing

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

## Abstract

Risk for late-onset Alzheimer's disease (LOAD), the most prevalent dementia, is partially driven by genetics. To identify LOAD risk loci, we performed a large genome-wide association meta-analysis of clinically diagnosed LOAD (94,437 individuals). We confirm 20 previous LOAD risk loci and identify five new genome-wide loci (*IQCK*, *ACE*, *ADAM10*, *ADAMTS1*, and *WWOX*), two of which (*ADAM10*, *ACE*) were identified in a recent genome-wide association (GWAS)-by-

---

AZD3293 Alzheimer's Disease Studies, Eli Lilly. R.B.L. receives consulting fees from Merck, Inc. E.M.R. receives grant funding from several NIH grant and research contracts with Genentech/Roche, Novartis/ Amgen and Avid/Lilly. He is a compensated scientific advisor to Alkahest, Alzheon, Aural Analytics, Denali, Takeda and Zinfandel. He is an advisor to Roche and Roche Diagnostics, which reimburse his expenses only. T.G.B. has research support/contracts from the National Institutes of Health, State of Arizona, Michael J Fox Foundation, Avid Radiopharmaceuticals, Navida Biopharmaceuticals and Aprinoia Therapeutics. He is an advisory board member with Vivid Genomics and has consultancy work with Roche Diagnostics. A.G.S. conducts multiple industry-funded clinical trials, but all funds go to her academic institution. They have current (within last 12 months) research contracts with Eli Lilly, Novartis, Roche, Janssen, AbbVie, Biogen, NeuroEM, Suven and Merck. She does not receive personal compensations from these organizations. G.D.S. is a consultant for Biogen, Inc. J.M.B. is participating in clinical trials of antementia drugs for Eli Lilly, Toyama Chemical Company, Merck, Biogen, AbbVie, vTv Therapeutics, Janssen and Roche. He has received research grants from Eli Lilly, Avid Radiopharmaceuticals and Astra Zeneca. He is a consultant for Stage 2 Innovations. L.F. is a consultant for Allergan, Eli Lilly, Avraham Pharmaceuticals, Axovant, Biogen, Boehringer Ingelheim, Eisai, Functional Neuromodulation, Lundbeck, MerckSharpe & Dohme, Novartis, Pfizer, Pharnext, Roche and Schwabe Pharma. M.B has consulted as an advisory board member for Araclon, Grifols, Lilly, Nutricia, Roche and Servier. She received fees for lectures and funds for research from Araclon, Grifols, Nutricia, Roche and Servier. She has not received personal compensations from these organizations. A.Ruiz has consulted for Grifols and Landsteiner Genmed. He received fees for lectures or funds for research and/or reimbursement of expenses for congresses attendance from Araclon and Grifols. He has not received personal compensations from these organizations. O.P. acts as a consultant for Roche and Biogen, Inc. He is currently participating in clinical trials of antementia drugs from Novartis, Genentech, Roche and Pharmatrophix. B.T.H. is a consultant for Aztherapy, Biogen, Calico, Ceregene, Genentech, Lilly, Neurophage, Novartis and Takeda, and receives research support from Abbvie, Amgen, Deanli, Fidelity Biosciences, General Electric, Lilly, Merck, Sangamo and Spark therapeutics. BTH owns Novartis stock. H.Hampel serves as Senior Associate Editor for the Journal Alzheimer's & Dementia; he received lecture fees from Biogen and Roche, research grants from Pfizer, Avid and MSD AVENIR (paid to the institution), travel funding from Functional Neuromodulation, Axovant, Eli Lilly and company, Takeda and Zinfandel, GE Healthcare and Oryzon Genomics, consultancy fees from Jung Diagnostics, Cytox Ltd., Axovant, Anavex, Takeda and Zinfandel, GE Healthcare, Oryzon Genomics and Functional Neuromodulation, and participated in scientific advisory boards of Functional Neuromodulation, Axovant, Eli Lilly and company, Cytox Ltd., GE Healthcare, Takeda and Zinfandel, Oryzon Genomics and Roche Diagnostica. Harald Hampel is a co-inventor on numerous patents relating to biomarker measurement but has received no royalties from these patents. A.A.-C. has consultancies for GSK, Cytokinetics, Biogen Idec, Treeway Inc, Chronos Therapeutics, OrionPharma and Mitsubishi-Tanabe Pharma, and was Chief Investigator for commercial clinical trials run by OrionPharma and Cytokinetics.

### Additional information

**Supplementary information** is available for this paper at <https://doi.org/10.1038/s41588-019-0358-2>.

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

### Data availability

Genome-wide summary statistics for the Stage 1 discovery have been deposited in The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS)—a NIA/NIH-sanctioned qualified-access data repository, under accession NG00075. Stage 1 data (individual level) for the GERAD cohort can be accessed by applying directly to Cardiff University. Stage 1 ADGC data are deposited in NIAGADS. Stage 1 CHARGE data are accessible by applying to dbGaP for all US cohorts and to Erasmus University for Rotterdam data. AGES primary data are not available owing to Icelandic laws. Stage 2 and Stage 3 primary data are available upon request.

familial-proxy of Alzheimer's or dementia. Fine-mapping of the human leukocyte antigen (HLA) region confirms the neurological and immune-mediated disease haplotype HLA-DR15 as a risk factor for LOAD. Pathway analysis implicates immunity, lipid metabolism, tau binding proteins, and amyloid precursor protein (APP) metabolism, showing that genetic variants affecting APP and A $\beta$  processing are associated not only with early-onset autosomal dominant Alzheimer's disease but also with LOAD. Analyses of risk genes and pathways show enrichment for rare variants ( $P = 1.32 \times 10^{-7}$ ), indicating that additional rare variants remain to be identified. We also identify important genetic correlations between LOAD and traits such as family history of dementia and education.

Our previous work identified 19 genome-wide-significant common variant signals in addition to *APOE* that influence risk for LOAD (onset age > 65 years)<sup>1</sup>. These signals, combined with 'subthreshold' common variant associations, account for ~31% of the genetic variance of LOAD<sup>2</sup>, leaving the majority of genetic risk uncharacterized<sup>3</sup>. To search for additional signals, we conducted a GWAS meta-analysis of non-Hispanic Whites (NHW) by using a larger Stage 1 discovery sample (17 new, 46 total datasets;  $n = 21,982$  cases, 41,944 cognitively normal controls) from our group, the International Genomics of Alzheimer's Project (IGAP) (composed of four consortia: Alzheimer Disease Genetics Consortium (ADGC), Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE), The European Alzheimer's Disease Initiative (EADI), and Genetic and Environmental Risk in AD/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease Consortium (GERAD/ PERADES) (Supplementary Tables 1 and 2, and Supplementary Note). To sample both common and rare variants (minor allele frequency (MAF)  $> 0.01$  and MAF  $< 0.01$ , respectively), we imputed the discovery datasets by using a 1,000 Genomes reference panel consisting of 36,648,992 single-nucleotide polymorphisms (SNPs), 1,380,736 insertions/deletions, and 13,805 structural variants. After quality control, 9,456,058 common variants and 2,024,574 rare variants were selected for analysis. Genotype dosages were analyzed within each dataset, and then combined with meta-analysis (Supplementary Fig. 1 and Supplementary Tables 1–3).

## Results

### Meta-analysis of Alzheimer's disease GWAS.

The Stage 1 discovery meta-analysis produced 12 loci with genome-wide significance ( $P < 5 \times 10^{-8}$ ) (Table 1), all of which are previously described<sup>1,4–11</sup>. Genomic inflation factors ( $\lambda$ ) were slightly inflated ( $\lambda$  median = 1.05;  $\lambda$  regression = 1.09; see Supplementary Figure 2 for a quantile–quantile (QQ) plot); however, univariate linkage disequilibrium score (LDSC) regression<sup>12,13</sup> estimates indicated that the majority of this inflation was due to a polygenic signal, with the intercept being close to 1 (1.026, s.e.m. = 0.006). The observed heritability ( $H^2$ ) of LOAD was estimated at 0.071 (0.011) using LDSC. Stage 1 meta-analysis was first followed by Stage 2, using the I-select chip we previously developed in Lambert et al.<sup>1</sup> (including 11,632 variants,  $n = 18,845$ ; Supplementary Table 4) and finally Stage 3A ( $n = 11,666$ ) or Stage 3B ( $n = 30,511$ ) (for variants in regions not well captured in the I-select chip) (see Supplementary Figure 1 for the workflow). The final sample was 35,274 clinical and autopsy-documented Alzheimer's disease cases and 59,163 controls.

Meta-analysis of Stages 1 and 2 produced 21 genome-wide-significant associations ( $P = 5 \times 10^{-8}$ ) (Table 1 and Fig. 1), 18 of which were previously reported as genome-wide significant in Lambert et al.<sup>1</sup>. Three other signals were not initially described in the initial IGAP GWAS: the rare R47H *TREM2* coding variant previously reported by others<sup>7,8,14</sup>; *ECHDC3* (rs7920721; NC\_000010.10: g.11720308A>G), which was recently identified as a potential genome-wide-significant Alzheimer's disease risk locus in several studies<sup>15–17</sup>, and *ACE* (rs138190086; NC\_000017.10: g.61538148G>A) (Supplementary Figs. 3 and 4). In addition, seven signals showed suggestive association with  $P < 5 \times 10^{-7}$  (closest genes: *ADAM10*, *ADAMTS1*, *ADAMTS20*, *IQCK*, *MIR142/TspoAPI-AS1*, *NDUFAF6*, and *SPPL2A*) (Supplementary Figs. 5–11). Stage 3A and meta-analysis of all three stages for these nine signals (excluding the *TREM2* signal; see Supplementary Table 5 for the variant list) identified five genome-wide-significant loci. In addition to *ECHDC3*, this included four new genome-wide Alzheimer's disease risk signals at *IQCK*, *ADAMTS1*, *ACE*, and *ADAM10* (Table 2). *ACE* and *ADAM10* were previously reported as Alzheimer's disease candidate genes<sup>18–22</sup> but were not replicated in some subsequent studies<sup>23–25</sup>. A recent GWAS using family history of Alzheimer's disease or dementia as a proxy<sup>26</sup> also identified these two risk loci, suggesting that while use of proxy Alzheimer's disease/dementia cases introduces less sensitivity and specificity for true Alzheimer's disease signals overall in comparison to clinically diagnosed Alzheimer's disease, proxy studies can identify disease-relevant associations. Two of the four other signals approached genome-wide significance: *mIR142/TspoAPI-AS1* ( $P = 5.3 \times 10^{-8}$ ) and *NDUFAF6* ( $P = 9.2 \times 10^{-8}$ ) (Table 2). Stage 3A also extended the analysis of two loci (*NME8* and *MEF2C*) that were previously genome-wide significant in our 2013 meta-analysis. These loci were not genome-wide significant in our current study and will deserve further investigation (*NME8*:  $P = 2.7 \times 10^{-7}$ ; *MEF2C*:  $P = 9.1 \times 10^{-8}$ ; Supplementary Figs. 12 and 13). Of note, GCTA COJO<sup>27</sup> conditional analysis of the genome-wide loci indicates that *TREM2* and three other loci (*BINI*, *ABCA7*, and *PTK2B/CLU*) have multiple independent LOAD association signals (Supplementary Table 6), suggesting that the genetic variance associated with some GWAS loci is probably underestimated.

We also selected 33 variants from Stage 1 (28 common and 5 rare variants in loci not well captured in the I-select chip; see Methods for full selection criteria) for genotyping in Stage 3B (including populations of Stage 2 and Stage 3A). We nominally replicated a rare variant (rs71618613; NC\_000005.9: g.29005985A>C) within an intergenic region near *SUCLG2P4* (MAF = 0.01;  $P = 6.8 \times 10^{-3}$ ; combined  $P = 3.3 \times 10^{-7}$ ) and replicated a low-frequency variant in the *TREM2* region (rs114812713; NC\_000006.11: g.41034000G>C, MAF = 0.03,  $P = 7.2 \times 10^{-3}$ ; combined  $P = 2.1 \times 10^{-13}$ ) in the gene *OARD1* that may represent an independent signal according to our conditional analysis (Table 2, Supplementary Figs. 14 and 15, Supplementary Tables 6 and 7). In addition, rs62039712 (NC\_000016.9: g.79355857G>A) in the *WWOX* locus reached genome-wide significance ( $P = 3.7 \times 10^{-8}$ ), and rs35868327 (NC\_000005.9: g.52665230T>A) in the *FST* locus reached suggestive significance ( $P = 2.6 \times 10^{-7}$ ) (Table 2 and Supplementary Figs. 16 and 17). *WWOX* may play a role in Alzheimer's disease through its interaction with tau<sup>28,29</sup>, and it is worth noting that the sentinel variant (defined as the variant with the lowest  $P$  value) is just 2.4 mega-bases from *PLCG2*, which contains a rare variant that we recently associated with

Alzheimer's disease<sup>14</sup>. Since both rs62039712 and rs35868327 were only analyzed in a restricted number of samples, these loci deserve further attention.

### Candidate gene prioritization at genome-wide loci.

To evaluate the biological significance and attempt to identify the underlying risk genes for the newly identified genome-wide signals (*IQCK*, *ACE*, *ADAM10*, *ADAMTS1*, and *WWOX*) and those found previously, we pursued five strategies: (1) annotation and gene-based testing for deleterious coding, loss-of-function (LOF) and splicing variants; (2) expression-quantitative trait loci (eQTL) analyses; (3) evaluation of transcriptomic expression in LOAD clinical traits (correlation with the BRAAK stage<sup>30</sup> and differential expression in Alzheimer's disease versus control brains<sup>31</sup>); (4) evaluation of transcriptomic expression in Alzheimer's disease-relevant tissues<sup>32–34</sup>; and (5) gene cluster/pathway analyses. For the 24 signals reported here, other evidence indicates that *APOE*<sup>35,36</sup>, *ABCA7* (refs. 37–40), *BIN1* (ref. 41), *TREM2* (refs. 7,8), *SORL1* (refs. 42,43), *ADAM10* (ref. 44), *SPI1* (ref. 45), and *CR1* (ref. 46) are the true Alzheimer's disease risk gene, although there is a possibility that multiple risk genes exist in these regions<sup>47</sup>. Because many GWAS loci are intergenic, and the closest gene to the sentinel variant may not be the actual risk gene, in these analyses we considered all protein-coding genes within  $\pm 500$  kilobases (kb) of the sentinel variant linkage disequilibrium (LD) regions ( $r^2 > 0.5$ ) for each locus as a candidate Alzheimer's disease gene ( $n = 400$  genes) (Supplementary Table 8).

We first annotated all sentinel variants for each locus and variants in LD ( $r^2 > 0.7$ ) with these variants in a search for deleterious coding, LOF or splicing variants. In line with findings that most causal variants for complex disease are non-coding<sup>48</sup>, only 2% of 1,073 variants across the 24 loci (excluding *APOE*) were exonic variants, with a majority (58%) being intronic (Supplementary Fig. 18 and Supplementary Table 9). Potentially deleterious variants include the rare R47H missense variant in *TREM2*, common missense variants in *CR1*, *SPI1*, *MS4A2*, and *IQCK*, and a relatively common (MAF = 0.16) splicing variant in *IQCK*. Using results of a large whole-exome-sequencing study conducted in the ADGC and CHARGE sample<sup>49</sup> ( $n = 5,740$  LOAD cases and 5,096 controls), we also identified ten genes located in our genome-wide loci as having rare deleterious coding, splicing or LOF burden associations with LOAD (false discovery rate (FDR)  $P < 0.01$ ), including previously implicated rare-variant signals in *ABCA7*, *TREM2*, and *SORL1* (refs. 14,49–55), and additional associations with *TREML4* in the *TREM2* locus, *TAP2* and *PSMB8* in the *HLA-DRB1* locus, *PIP* in the *EPHA1* locus, *STYX* in the *FERMT2* locus, *RIN3* in the *SLC24A4* locus, and *KCNH6* in the *ACE* locus (Supplementary Table 10).

For eQTL analyses, we searched existing eQTL databases and studies for cis-acting eQTLs in a prioritized set of variants ( $n = 1,873$ ) with suggestive significance or in LD with the sentinel variant in each locus. Of these variants, 71–99% have regulatory potential when considering all tissues according to RegulomeDB<sup>56</sup> and HaploReg<sup>57</sup>, but restricting to Alzheimer's disease-relevant tissues (via Ensembl Regulatory Build<sup>58</sup> and GWAS4D<sup>59</sup>) appears to aid in regulatory variant prioritization, with probabilities for functional variants increasing substantially when using GWAS4D cell-dependent analyses with brain or monocytes, for instance (these and other annotations are provided in Supplementary Table

11). Focusing specifically on eQTLs, we found overlapping cis-acting eQTLs for 153 of the 400 protein-coding genes, with 136 eQTL-controlled genes in Alzheimer's disease-relevant tissues (that is, brain and blood/immune cell types; see Methods for details) (Supplementary Tables 12 and 13). For our newly identified loci, there were significant eQTLs in Alzheimer's disease-relevant tissue for *ADAM10*, *FAM63B*, and *SSTM* (in the *ADAM10* locus); *ADAMTS1* (*ADAMTS1* locus); and *ACSM1*, *ANKS4B*, *C16orf62*, *GDE1*, *GPRC5B*, *IQCK*, and *KNOP1* (*IQCK* locus). There were no eQTLs in Alzheimer's disease-relevant tissues in the *WWOX* or *ACE* locus, although several eQTLs for *PSMC5* in coronary artery tissue were found for the *ACE* locus. eQTLs for genes in previously identified loci include *BIN1* (*BIN1* locus), *INPP5D* (*INPP5D* locus), *CD2AP* (*CD2AP* locus), and *SLC24A4* (*SLC24A4* locus). Co-localization analysis confirmed evidence of a shared causal variant affecting expression and disease risk in 66 genes over 20 loci, including 31 genes over 13 loci in LOAD-relevant tissue (see Supplementary Table 14 and 15 for complete lists). Genes implicated include *CR1* (*CR1* locus), *ABCA7* (*ABCA7* loci), *BIN1* (*BIN1* locus), *SPI1* and *MYBPC3* (*SPI1* locus), *MS4A2*, *MS4A6A*, and *MS4A4A* (*MS4A2* locus), *KNOP1* (*IQCK* locus), and *HLA-DRB1* (*HLA-DRB1* locus) (Supplementary Table 12).

To study the differential expression of genes in brains of patients with Alzheimer's disease versus controls, we used 13 expression studies<sup>31</sup>. We found that 58% of the 400 protein-coding genes within the genome-wide loci had evidence of differential expression in at least one study (Supplementary Table 16). Additional comparisons to Alzheimer's disease related gene expression sets revealed that 62 genes were correlated with pathogenic stage (BRAAK) in at least one brain tissue<sup>30</sup> (44 genes in prefrontal cortex, the most relevant LOAD tissue; 36 in cerebellum and 1 in visual cortex). Finally, 38 genes were present in a set of 1,054 genes preferentially expressed in aged microglial cells, a gene set shown to be enriched for Alzheimer's disease genes ( $P = 4.1 \times 10^{-5}$ )<sup>34</sup>. We also annotated our list of genes with brain RNA-seq data, which showed that 80% were expressed in at least one type of brain cell, and the genes were most highly expressed in fetal astrocytes (26%), followed by microglia/macrophages (15.8%), neurons (14.8%), astrocytes (11.5%), and oligodendrocytes (6.5%). When not considering fetal astrocytes, mature astrocytes (21%), and microglial cells (20.3%), the resident macrophage cells of the brain thought to play a key role in the pathologic immune response in LOAD<sup>8,14,60</sup>, became the highest expressed cell types in the genome-wide set of genes, with 5.3% of the 400 genes showing high microglial expression (Supplementary Table 17; see Supplementary Table 18 for the highly expressed gene list by cell type).

We conducted pathway analyses (MAGMA<sup>61</sup>) separately for common ( $MAF > 0.01$ ) and rare variants ( $MAF < 0.01$ ). For common variants, we detected four function clusters including (1) APP metabolism/A $\beta$  formation (regulation of A $\beta$  formation:  $P = 4.56 \times 10^{-7}$  and regulation of APP catabolic process:  $P = 3.54 \times 10^{-6}$ ); (2) tau protein binding ( $P = 3.19 \times 10^{-5}$ ); (3) lipid metabolism (four pathways including protein-lipid complex assembly:  $P = 1.45 \times 10^{-7}$ ); and (4) immune response ( $P = 6.32 \times 10^{-5}$ ) (Table 3 and Supplementary Table 19). Enrichment of the four clusters remained after removal of genes in the *APOE* region. When *APOE*-region genes and genes near genome-wide-significant genes were removed, tau showed moderate association ( $P = 0.027$ ), and lipid metabolism and immune-related

Author Manuscript  
Author Manuscript  
Author Manuscript  
Author Manuscript

pathways showed strong associations ( $P < 0.001$ ) (Supplementary Table 20). Genes driving these enrichments (that is, having a gene-wide  $P < 0.05$ ) included *SCNA*, a Parkinson's risk gene that encodes alpha-synuclein, the main component of Lewy bodies, which may play a role in tauopathies<sup>62,63</sup>, for the tau pathway; apolipoprotein genes (*APOM*, *APOA5*) and *ABCA1*, a major regulator of cellular cholesterol, for the lipid metabolism pathways; and 52 immune pathway genes (Supplementary Table 21). While no pathways were significantly enriched for rare variants, lipid and A $\beta$  pathways did reach nominal significance in rare-variant-only analyses. Importantly, we also observed a highly significant correlation between common and rare pathway gene results ( $P = 1.32 \times 10^{-7}$ ), suggesting that risk Alzheimer's disease genes and pathways are enriched for rare variants. In fact, 50 different genes within tau, lipid, immunity and A $\beta$  pathways showed nominal rare-variant driven associations ( $P < 0.05$ ) with LOAD.

To further explore the APP/A $\beta$  pathway enrichment, we analyzed a comprehensive set of 335 APP metabolism genes<sup>64</sup> curated from the literature. We observed significant enrichment of this gene set in common variants ( $P = 2.27 \times 10^{-4}$ ;  $P = 3.19 \times 10^{-4}$  excluding *APOE*), with both *ADAM10* and *ACE* nominally significant drivers of this result (Table 4 and Supplementary Tables 22 and 23). Several 'sub-pathways' were also significantly enriched in the common variants, including 'clearance and degradation of A $\beta$ ', and 'aggregation of A $\beta$ ', along with its subcategory 'microglia', the latter supporting microglial cells suspected role in response to A $\beta$  in LOAD<sup>65</sup>. Nominal enrichment for risk from rare variants was found for the pathway 'aggregation of A $\beta$ : chaperone' and 23 of the 335 genes.

To identify candidate genes for our novel loci, we combined results from our five prioritization strategies in a priority ranking method similar to that of Fritzsche et al.<sup>66</sup> (Fig. 2 and Supplementary Table 24). *ADAM10* was the top ranked gene of the 11 genes within the *ADAM10* locus. *ADAM10*, the most important  $\alpha$ -secretase in the brain, is a component of the non-amyloidogenic pathway of APP metabolism<sup>67</sup> and sheds TREM2 (ref. 68), an innate immunity receptor expressed selectively in microglia. Overexpression of *ADAM10* in mouse models can halt A $\beta$  production and subsequent aggregation<sup>69</sup>. In addition, two rare *ADAM10* alterations segregating with disease in LOAD families increased A $\beta$  plaque load in 'Alzheimer-like' mice, with diminished  $\alpha$ -secretase activity from the alterations probably the causal mechanism<sup>19,44</sup>. For the *IQCK* signal, which is also an obesity locus<sup>70,71</sup>, *IQCK*, a relatively uncharacterized gene, was ranked top, although four of the other 11 genes in the locus have a priority rank = 4, including *KNOP1* and *GPRC5B*, the latter being a regulator of neurogenesis<sup>72,73</sup> and inflammatory signaling in obesity<sup>74</sup>. Of the 22 genes in the *ACE* locus, *PSMC5*, a key regulator of major histocompatibility complex (MHC)<sup>75,76</sup>, has a top score of 4, while *DDX42*, *MAP3K3*, an important regulator of macrophages and innate immunity<sup>77,78</sup>, and *CD79B*, a B lymphocyte antigen receptor subunit, each have a score of 3. Candidate gene studies have associated *ACE* variants with Alzheimer's disease risk<sup>20,22,79</sup>, including a strong association in the Wadi Ara, an Israeli Arab community with high risk of Alzheimer's disease<sup>21</sup>. However, these studies yielded inconsistent results<sup>23</sup>, and our work reports a clear genome-wide association in NHW at this locus. While *ACE* was not prioritized, it should not be rejected as a candidate gene, as its expression in Alzheimer's disease brain tissue is associated with A $\beta$  load and Alzheimer's disease severity<sup>80</sup>. Furthermore, cerebrospinal fluid (CSF) levels of the angiotensin-converting

enzyme (ACE) are associated with A $\beta$  levels<sup>81</sup> and LOAD risk<sup>82</sup>, and studies show ACE can inhibit A $\beta$  toxicity and aggregation<sup>83</sup>. Finally, angiotensin II, a product of ACE function, mediates a number of neuropathological processes in Alzheimer's disease<sup>84</sup> and is now a target for intervention in phase II clinical trials of Alzheimer's disease<sup>85</sup>. Another novel genome-wide locus reported here, *ADAMTS1*, is within 665 kb of *APP* on chromosome 21. Of three genes at this locus, our analyses nominate *ADAMTS1* as the likely risk gene, although we cannot rule out that this signal is a regulatory element for *APP*. *ADAMTS1* is elevated in Down's syndrome with neurodegeneration and Alzheimer's disease<sup>86</sup>, and it is a potential neuroprotective gene<sup>87–89</sup> or a neuroinflammatory gene important to microglial response<sup>90</sup>. Finally, *WWOX* and *MAF*, which surround an intergenic signal in an obesity associated locus<sup>91</sup>, were both prioritized for the *WWOX* locus, with *MAF*, another important regulator of macrophages<sup>92,93</sup>, being highly expressed in microglia in the Brain RNA-seq database, and *WWOX*, a high-density-lipoprotein cholesterol and triglyceride-associated gene<sup>94,95</sup>, being expressed most highly in astrocytes and neurons. *WWOX* has been implicated in several neurological phenotypes<sup>96</sup>; in addition, it binds tau and may play a critical role in regulating tau hyper-phosphorylation, neurofibrillary formation and A $\beta$  aggregation<sup>28,29</sup>. Intriguingly, treatment of mice with its binding partner restores memory deficits<sup>97</sup>, hinting at its potential in neurotherapy.

For previously reported loci, applying the same prioritization approach highlights several genes, as described in Fig. 2, some of which are involved in APP metabolism (*FERMT2*, *PICALM*) or tau toxicity (*BIN1*, *CD2AP*, *FERMT2*, *CASS4*, *PTK2B*)<sup>98–101</sup>. Pathway, tissue and disease trait enrichment analyses support the utility of our prioritization method, as the 53 prioritized genes with a score  $> 5$  are (1) enriched in substantially more Alzheimer's disease-relevant pathways, processes and dementia-related traits; (2) enriched in candidate Alzheimer's disease cell types such as monocytes (adjusted  $P = 9.0 \times 10^{-6}$ ) and macrophages (adjusted  $P = 5.6 \times 10^{-3}$ ); and (3) more strongly associated with dementia-related traits and Alzheimer's disease-relevant pathways (Supplementary Table 25 and 26; see Supplementary Fig. 19 for the interaction network of these prioritized genes). To further investigate the cell types and tissues the prioritized genes are expressed in, we performed differentially expressed gene (DEG) set enrichment analysis of the prioritized genes by using GTEx<sup>102</sup> tissues, and we identified significant differential expression in several potentially relevant Alzheimer's disease tissues including immune-related tissues (upregulation in blood and spleen), obesity-related tissue (upregulation in adipose), heart tissues (upregulation in left ventricle and atrial appendage), and brain tissues (dowregulation in cortex, cerebellum, hippo-campus, basal ganglia, and amygdala). Furthermore, the 53 genes are overexpressed in 'adolescence' and 'young adult' brain tissues in BrainSpan<sup>103</sup>, a transcriptomic atlas of the developing human brain, which is consistent with accumulating evidence suggesting Alzheimer's disease may start decades before the onset of disease<sup>104,105</sup> (Supplementary Fig. 20; see Supplementary Fig. 21 for a tissue expression heat map for the 53 genes).

### Fine-mapping of the HLA region.

The above approach prioritized *HLA-DRB1* as the top candidate gene in the MHC locus, known for its complex genetic organization and highly polymorphic nature (see

Supplementary Fig. 22 for a plot of the region of the Stage 1 results). Previous analyses in the ADGC (5,728 Alzheimer's disease cases and 5,653 controls) have linked both HLA class I and II haplotypes with Alzheimer's disease risk<sup>106</sup>. In order to further investigate this locus in a much larger sample, we used a robust imputation method and fine-mapping association analysis of alleles and haplotypes of HLA class I and II genes in 14,776 cases and 23,047 controls from our datasets (Supplementary Table 27). We found risk effects of *HLA-DQA1*\*01:02 (FDR  $P = 0.014$ ), *HLA-DRB1*\*15:01 (FDR  $P = 0.083$ ), and *HLA-DQB1*\*06:02 (FDR  $P = 0.010$ ) (Supplementary Table 28). After conditioning on the sentinel meta-analysis variant in this region (rs78738018), association signals were lost for the three alleles, suggesting that the signal observed at the variant level is due to the association of these three alleles. These alleles form the *HLA-DQA1*\*01:02~*HLA-DQB1*\*06:02~*HLA-DRB1*\*15:01 (*DR15*) haplotype, which is also associated with Alzheimer's disease in our sample (FDR  $P = 0.013$ ) (Supplementary Table 29). Taken together, these results suggest a central role of the *DR15* haplotype in Alzheimer's disease risk, a finding originally discovered in a small study in the Tunisian population<sup>107</sup> and more recently in a large ADGC analysis<sup>106</sup>. Intriguingly, the *DR15* haplotype and its component alleles also associate with protection against diabetes<sup>108</sup>, a high risk for multiple sclerosis<sup>109,110</sup>, and risk or protective effects with many other immune-mediated diseases (Supplementary Table 30). Moreover, the associated diseases include a large number of traits queried from an HLA-specific Phewas<sup>111</sup>, including neurological diseases (for example, Parkinson's disease<sup>112,113</sup>) and diseases with risk factors for Alzheimer's disease (for example, hyperthyroidism<sup>114</sup>), pointing to potential shared and/or interacting mechanisms and comorbidities, a common paradigm in the MHC locus<sup>115</sup>. Two additional alleles, *HLA-DQA1*\*03:01 and *HLA-DQB1*\*03:02, belonging to another haplotype, show a protective effect on Alzheimer's disease, but their signal was lost after conditioning on *HLA-DQA1*\*01:02, and the *HLA-DQA1*\*03:01~*HLA-DQB1*\*03:02 haplotype is not associated with Alzheimer's disease (FDR  $P = 0.651$ ).

### Genetic correlations with Alzheimer's disease.

As described above, several of our genome-wide loci have potentially interesting co-morbid or pleiotropic associations with traits that may be relevant to the pathology of Alzheimer's disease. To investigate the extent of LOAD's shared genetic architecture with other traits, we performed LD-score regression to estimate the genetic correlation between LOAD and 792 human diseases, traits and behaviors<sup>12,116</sup> (Supplementary Table 31). The common variant genetic architecture of LOAD was positively correlated with a maternal family history of Alzheimer's disease/dementia ( $r_g$  for the genetic correlation of two traits = 0.81; FDR  $P = 2.79 \times 10^{-7}$ ), similar to the Marioni et al. family proxy analyses<sup>26</sup>, which found maternal genetic correlation with Alzheimer's disease to be higher than that for paternal Alzheimer's disease ( $r_g = 0.91$  and 0.66, respectively). There is substantial overlap between these estimates, as the Marioni et al. analyses include the 2013 IGAP summary statistics and employed the same UK Biobank variable that we used for  $r_g$  estimates with maternal history of dementia. We also find significant negative correlation between Alzheimer's disease and multiple measures of educational attainment (for example, college completion,  $r_g = -0.24$ ; years of schooling,  $r_g$  range = -0.19 to -0.24; cognitive scores,  $r_g = -0.24$  and -0.25) (FDR  $P < 0.05$ ), supporting the theory that a greater cognitive reserve could help protect against

development of LOAD<sup>117</sup>. The extent to which socioeconomic, environmental, or cultural factors contribute to the correlation between educational attainment and risk for Alzheimer's disease is unknown, but research shows dementia risk to be associated with lower socio-economic status, independently of education status<sup>118,119</sup>. We also found negative correlations at  $P < 0.05$  with multiple measures of cardiovascular health (that is, family history of high blood pressure and heart disease and vascular/heart problems) and diabetes (that is, fasting proinsulin, basal metabolic rate and fasting insulin), supporting previous research suggesting that use of blood pressure and diabetic medications may reduce the risk of Alzheimer's disease<sup>120</sup>. In fact, use of blood pressure medication does show a negative genetic correlation with Alzheimer's disease in our study ( $r_g = -0.12$ ;  $P = 0.035$ ), although this result does not survive FDR correction. These and other top results from this analysis (for example, body mass index, height; see Supplementary Table 31 for a full list of other nominally significant correlations) have been linked to Alzheimer's disease previously<sup>116,120–127</sup>, either through suggestive or significant genetic or epidemiological associations (see Kuzma et al.<sup>128</sup> for a recent review), but the multiple measures here support and emphasize their genetic correlation with LOAD and highlight the possible genetic pleiotropy or co-morbidity of these traits with pathology of LOAD.

## Discussion

In conclusion, our work identifies five new genome-wide associations for LOAD and shows that GWAS data combined with high-quality imputation panels can reveal rare disease risk variants (for example, *TREM2*). The enrichment of rare variants in pathways associated with Alzheimer's disease indicates that additional rare variants remain to be identified, and larger samples and better imputation panels will facilitate identifying them. While these rare variants may not contribute substantially to the predictive value of genetic findings, they will enhance the understanding of disease mechanisms and potential drug targets. Discovery of the risk genes at genome-wide loci remains challenging, but we demonstrate that converging evidence from existing and new analyses can prioritize risk genes. We also show that APP metabolism is associated with not only early-onset Alzheimer's disease but also LOAD, suggesting that therapies developed by studying early-onset families could also be applicable to the more common late-onset form of the disease. Pathway analysis showing that tau is involved in LOAD supports recent evidence that tau may play an early pathological role in Alzheimer's disease<sup>129–131</sup> and confirms that therapies targeting tangle formation/degradation could potentially affect LOAD. Finally, our fine-mapping analyses of HLA and genetic correlation results point to LOAD's shared genetic architecture with many immunemediated and cognitive traits, suggesting that research and interventions that elucidate mechanisms behind these relationships could also yield fruitful therapeutic strategies for LOAD.

## Methods

### Samples.

All Stage 1 meta-analysis samples are from four consortia: ADGC, CHARGE, EADI, and GERAD/PERADES. Summary demographics of all 46 case-control studies from the four

consortia are described in Supplementary Tables 1 and 2. Written informed consent was obtained from study participants or, for those with substantial cognitive impairment, from a caregiver, legal guardian, or other proxy. Study protocols for all cohorts were reviewed and approved by the appropriate institutional review boards. Further details of all cohorts can be found in the Supplementary Note.

### Pre-imputation genotype chip quality control.

Standard quality control was performed on all datasets individually, including exclusion of individuals with low call rate, individuals with a high degree of relatedness, and variants with low call rate. Individuals with non-European ancestry according to principal components analysis of ancestry-informative markers were excluded from the further analysis.

### Imputation and pre-analysis quality control.

Following genotype chip quality control, each dataset was phased and imputed to the 1,000 Genomes Project (phase 1 integrated release 3, March 2012)<sup>132</sup> using SHAPEIT/IMPUTE2<sup>133,134</sup> or MaCH/Minimac<sup>135,136</sup> software (Supplementary Table 3). All reference population haplotypes were used for the imputation, as this method improves accuracy of imputation for low-frequency variants<sup>137</sup>. Common variants (MAF > 0.01%) with an  $r^2$  or an information measure <0.40 from MaCH and IMPUTE2 were excluded from further analyses. Rare variants (MAF < 0.01%) with a ‘global’ weighted imputation quality score of <0.70 were also excluded from analyses. This score was calculated by weighting each variant’s MACH/IMPUTE2 imputation quality score by study sample size and combining these weighted scores for use as a post-analysis filter. We also required the presence of each variant in 30% of cases and 30% of controls across all datasets.

### Stage 1 association analysis and meta-analysis.

Stage 1 single variant-based association analysis employed an additive genotype model adjusting for age (defined as age-at-onset for cases and age-at-last exam for controls), sex, and population substructure using principal components<sup>138</sup>. The score test was implemented on all case-control datasets. This test is optimal for meta-analysis of rare variants due to its balance between power and control of type 1 error<sup>139</sup>. Family datasets were tested using GWAF<sup>140</sup>, with generalized estimating equations (GEE) implemented for common variants (MAF > 0.01), and a general linear mixed effects model (GLMM) implemented for rare variants (MAF < 0.01), per our preliminary data showing that the behavior of the test statistics for GEE was fine for common variants but inflated for rare variants, while GLMM controlled this rare-variant inflation. Variants with regression coefficient  $|\beta| > 5$  or  $P$  value equal to 0 or 1 were excluded from further analysis.

Within-study results for Stage 1 were meta-analyzed in METAL<sup>141</sup> using an inverse-variance-based model with genomic control. The meta-analysis was split into two separate analyses according to the study sample size, with all studies being included in the analysis of common variants (MAF > 0.01), and only studies with a total sample size of 400 or greater being included in the rare-variant (MAF < 0.01) analysis. See the Supplementary Note for further details of the meta-analyses methods.

### **Stage 1 summary statistics quality control and analysis.**

Genomic inflation was calculated for lambda ( $\lambda$ ) in the GenABEL package<sup>142</sup>. In addition, we performed LDSC regression via LD Hub v.1.9.0 (refs. <sup>12,13</sup>) to calculate the LD score regression intercept and derive a heritability estimate for the inverse-variance weighted meta-analysis summary statistics. The *APOE* region (Chr19:45,116,911–46,318,605) was removed to calculate the intercept. Removal of the *APOE* region reduced the heritability estimate slightly from 0.071 (s.e.m. = 0.011) to 0.0637 (s.e.m. = 0.009).

LDSC was also employed via the LD Hub web server to obtain genetic correlation estimates ( $rg$ )<sup>116</sup> between LOAD and a wide range of other disorders, diseases and human traits, including 518 UK BioBank traits<sup>143</sup>. UK BioBank is a large long-term study (~500,000 volunteers aged 40 to 69) begun in 2006 in the United Kingdom, which is investigating the contributions of genetic predisposition and environmental exposure (that is, nutrition, lifestyle, and medications) to the development of disease. While volunteers in the study are generally healthier than the overall United Kingdom population<sup>144</sup>, its large size and comprehensive data collection make the study an invaluable resource for researchers looking to interrogate the combined effect of genetics and environmental factors on disease. Before analyses in LD Hub, we removed all SNPs with extremely large effect sizes including the MHC (Chr6:26,000,000–34,000,000) and *APOE* region, as outliers can overly influence the regression analyses. A total of 1,180,989 variants were used in the correlation analyses. Statistical significance of the genetic correlations was estimated using 5% Benjamini–Hochberg FDR corrected *P* values.

GCTA COJO<sup>27</sup> was used to conduct conditional analysis of the Stage 1 summary statistics, with 28,730 unrelated individuals from the ADGC as a reference panel for calculation of LD. See URLs for methods for creation of the ‘ADGC reference dataset’.

### **Stage 2 and 3 genotyping, quality control, and analysis.**

Stage 2 genotypes were determined for 8,362 cases and 10,483 controls (Supplementary Table 4). 1,633 variants from the I-select chip were located in the 24 genome-wide loci (defined by the LD blocks of the sentinel variants; excluding the *APOE* region), with an average of 68 variants per locus. The most well-covered loci were *HLA-DRB1*, *M24A2*, and *PICALM* (763, 202, and 156 variants available, respectively); the least were *MAF*, *ADAMTS1*, and *INPP5D* (0, 4, and 5 variants, respectively).

Stage 3A was conducted for variants selected as novel loci from meta-analyses of Stages 1 and 2 with  $P < 5 \times 10^{-7}$  (9 variants) and variants that were previously significant ( $P < 5 \times 10^{-8}$ ) that were not genome-wide significant after Stages 1 and 2 (2 variants) (4,930 cases and 6,736 controls) (Supplementary Table 5). Variants were genotyped using Taqman.

---

**URLs.** ADGC Reference Dataset: [https://kauwelab.byu.edu/Portals/22/adgc\\_combined\\_1000G\\_09192014.pdf](https://kauwelab.byu.edu/Portals/22/adgc_combined_1000G_09192014.pdf); AlzBase: <http://alz.big.ac.cn/alzBase/>; Brain RNA-seq Database: <http://www.brainrnaseq.org/>; Enrichr: <http://amp.pharm.mssm.edu/Enrichr/>; exSNP: <http://www.exsnp.org/>; NESDA eQTL catalog: <https://eqtl.onderzoek.io/index.php?page=info>; FUMA: <http://fuma.ctglab.nl/>; HLA-PheWas catalog: <https://phewascatalog.org/hla>; INFERNO: <http://inferno.lisanwanglab.org/index.php>; LD Hub: <http://ldsc.broadinstitute.org/ldhub/>; STRING: <https://string-db.org/>.

Stage 3B, which combined samples from Stage 2 and 3A, included variants with  $\text{MAF} < 0.05$  and  $P < 1 \times 10^{-5}$  or variants with  $\text{MAF} \geq 0.05$  and  $P < 5 \times 10^{-6}$  in novel loci not covered in the 2013 iSelect genotyping<sup>1</sup> (13,292 cases and 17,219 controls) (Supplementary Table 7). See the Supplementary Note for details on selection of variants for Stage 3B follow-up genotyping. For Stages 1, 2, and 3, samples did not overlap.

Per-sample quality checks for genetic sex and relatedness were performed in PLINK. Sex mismatches or individuals showing a high degree of relatedness (identical-by-descent value of 0.98 or greater) were removed from the analysis. A panel of ancestry-informative markers was used to perform principal component analysis with SMARTPCA from EIGENSOFT 4.2 software<sup>145</sup>, and individuals with non-European ancestry were excluded. Variant quality control was also performed separately in each country including removal of variants missing in more than 10% of individuals, having a Hardy–Weinberg  $P$  value in controls lower than  $1 \times 10^{-6}$  or a  $P$  value for missingness between cases and controls lower than  $1 \times 10^{-6}$ .

Per-study analysis for Stage 2 and Stage 3 followed the same analysis procedures described for Stage 1, except for covariate adjustments per cohort, where all analyses were adjusted on sex and age apart from the Italian, Swedish, and Gr@ACE cohorts, which were also adjusted for principal components. Within-study results were meta-analyzed in METAL<sup>141</sup> using an inverse-variance-based model.

### **Characterization of gene(s) and non-coding features in associated loci.**

We determined the base-pair boundaries of the search space for potential gene(s) and non-coding features in each of the 24 associated loci (excluding *APOE*) using the ‘proxy search’ mechanism in LDLink<sup>146</sup>. LDLink uses 1,000 genomes genotypes to calculate LD for a selected population; in our case all five European populations were selected (population codes CEU, TSI, FIN, GBR, and IBS). The boundaries for all variants in LD ( $r^2 = 0.5$ ) with the top associated variant from the Stage 2 meta-analysis for each region  $\pm 500$  kb of the ends of the LD blocks (as eQTL controlled genes are typically less than 500 kb from their controlling variant<sup>147</sup>) were input into the UCSC genome browser’s ‘Table Browser’ for RefSeq<sup>148</sup> and GENCODEv24lift37<sup>149</sup> genes at each associated locus. The average size of the LD blocks was 123 kb.

### **Identification of potentially causal coding or splicing variants.**

To identify deleterious coding or splicing variants that may represent causal variants for our genome-wide loci, we first used SNIPA<sup>150</sup> to identify variants in high LD (defined as  $r^2 > 0.7$ ) with the sentinel variants of the 24 genome-wide loci (excluding *APOE*) ( $n = 1,073$ ). The sentinel variants were defined as the variants with the lowest  $P$  in each genome-wide locus. We then used Ensembl VEP<sup>151</sup> for annotation of the set of sentinel variants and their proxies. We used BLOSUM62 (ref. <sup>152</sup>), SIFT<sup>153</sup>, Polyphen-2 (ref. <sup>154</sup>), CADD<sup>155</sup>, Condel<sup>156</sup>, MPC<sup>157</sup> and Eigen<sup>158</sup> to predict the pathogenicity of protein-altering exonic variants and MaxEntScan to predict the splicing potential of variants. Splicing variants with high splicing potential according to MaxEntScan<sup>159</sup> and protein-coding variants predicted to be deleterious by two or more programs were considered to be potentially causal variants for

a locus. It should be noted that while we do include rare variants from imputation in our analyses, we may be missing many rare causal variants in this study.

### Identification of genes with rare-variant burden via gene-based testing.

We used the summary statistics results of a large whole-exome sequencing (WES) study of LOAD, the Alzheimer's Disease Sequencing Project (ADSP) case-control study ( $n = 5,740$  LOAD cases and 5,096 cognitively normal controls of NHW ancestry) to identify genes within our genome-wide loci that may contribute to the association signal through rare deleterious coding, splicing or LOF variants. The individuals in the ADSP study largely overlap with individuals in the ADGC and CHARGE cohorts included in our Stage 1 meta-analysis. All 400 protein-coding genes within our LD-defined genome-wide loci were annotated with the gene-based results from this study, and the results were corrected using a 1% FDR  $P$  as a cutoff for significance. Complete details of the analysis can be found in Bis et al.<sup>49</sup> and the Supplementary Note.

### Regulatory variant and eQTL analysis.

To identify potential functional risk variants and genes at each associated locus, we first annotated a list of prioritized variants from the 24 associated loci (excluding *APOE*) ( $n = 1,873$ ). This variant list combined variants in LD with the sentinel variants ( $r^2 > 0.5$ ) using INFERNO<sup>160</sup> LD expansion ( $n = 1,339$ ) and variants with suggestive significance ( $P < 10^{-5}$ ) and LD ( $r^2 > 0.5$ ) with the sentinel variants for the 24 associated loci (excluding *APOE*) ( $n = 1,421$  variants). We then identified variants with regulatory potential in this set of variants using four programs that incorporate various annotations to identify likely regulatory variants: RegulomeDB<sup>56</sup>, HaploReg v.4.1 (refs. 57,161), GWAS4D<sup>59</sup>, and the Ensembl Regulatory Build<sup>58</sup>. We used the ChromHMM (core 15-state model) as 'source epigenomes' for the HaploReg analyses. We used immune (Monocytes-CD14<sup>+</sup>, GM12878 lymphoblastoid, HSMM myoblast) and brain (NH-A astrocytes) for the Ensembl Regulatory Build analyses. We then used the list of 1,873 prioritized variants to search for genes functionally linked via eQTLs in LOAD relevant tissues including various brain and blood tissue types, including all immune-related cell types, most specifically myeloid cells (macrophages and monocytes) and B-lymphoid cells, which are cell types implicated in LOAD and neurodegeneration by a number of recent studies<sup>14,45,162,163</sup>. While their specificity may be lower for identifying Alzheimer's disease risk eQTLs, we included whole blood cell studies in our Alzheimer's disease-relevant tissue class due to their high correlation of eQTLs with Alzheimer's disease-relevant tissues (70% with brain<sup>164</sup>, 51–70% for monocytes and lymphoblastoid cell lines<sup>165</sup>) and their large sample sizes that allow for increased discovery power. See the Supplementary Note for details on the eQTL databases and studies searched, and Supplementary Table 13 for sample sizes of each database/study.

Formal co-localization testing of our summary Stage 1 results was conducted using (1) COLOC<sup>166</sup> via INFERNO and (2) Summary Mendelian Randomization (SMR)-Heidi analysis<sup>167</sup>. The approximate Bayes factor (ABF), which was used to assess significance in the INFERNO COLOC analysis, is a summary measure that provides an alternative to the  $P$  value for the identification of associations as significant. SMR-Heidi analysis, which employs a heterogeneity test (HEIDI test) to distinguish pleiotropy or causality (a single

genetic variant affecting both gene expression and the trait) from linkage (two distinct genetic variants in LD, one affecting gene expression and one affecting trait), was also employed for co-localization analysis. Genes located less than 1 Mb from the GWAS sentinel variants that pass a 5% Benjamini–Hochberg FDR-corrected SMR *P*-value significance threshold and a HEIDI *P*-value > 0.05 threshold were considered significant. The Westra eQTL<sup>168</sup> summary data and Consortium for the Architecture of Gene Expression (CAGE) eQTL summary data were used for analysis. These datasets, conducted in whole blood, are large eQTL studies (Westra: discovery phase *n* = 5,311, replication phase *n* = 2,775; CAGE: *n* = 2,765), and while there is some overlap in samples between the two datasets, CAGE provides finer coverage. The ADGC reference panel dataset referenced above for GCTA COJO analysis was used for LD calculations.

### Human brain gene expression analyses.

We also evaluated gene expression of all candidate genes in the associated loci (see Supplementary Table 8 for a complete list of genes searched), using differential Alzheimer's disease gene expression results from AlzBase<sup>31</sup>, brain tissue expression from the Brain RNA-seq Database<sup>32,33</sup> (see URLs), and the HuMi\_Aged gene set<sup>34</sup>, a set of genes preferentially expressed in aged human microglia established through RNA-seq expression analysis of aged human microglial cells from ten post-mortem brains. AlzBase includes transcription data from brain and blood from aging, non-dementia, mild cognitive impairment, early-stage Alzheimer's disease, and late-stage Alzheimer's disease. See ALZBase (see URLs) for a complete list of studies included in the search. Correlation values for the BRAAK stage expression were taken from the Zhang et al.<sup>30</sup> study of 1,647 post-mortem brain tissues from LOAD patients and non-demented subjects.

### Pathway analysis.

Pathway analyses were performed with MAGMA<sup>61</sup>, which performs SNP-wise gene analysis of summary statistics with correction for LD between variants and genes to test whether sets of genes are jointly associated with a phenotype (that is, LOAD), compared to other genes across the genome. Adaptive permutation was used to produce an empirical *P* value and an FDR-corrected *q* value. Gene sets used in the analyses were from GO<sup>169,170</sup>, KEGG<sup>171,172</sup>, REACTOME<sup>173,174</sup>, BIOCARTA, and MGI<sup>175</sup> pathways. Analyses were restricted to gene sets containing between 10 and 500 genes, a total of 10,861 sets. Variants were restricted to common variants (MAF > 0.01) and rare variants (MAF < 0.01) only for each analysis, and separate analyses for each model included and excluded the *APOE* region. Analyses were also performed after removal of all genome-wide-significant genes. Primary analyses used a 35-kb upstream/10-kb downstream window around each gene in order to capture potential regulatory variants for each gene, while secondary analyses were run using a 0-kb window<sup>176</sup>. To test for significant correlation between common and rare-variant gene results, we performed a gene property analysis in MAGMA, regressing the gene-wide association statistics from rare variants on the corresponding statistics from common variants, correcting for LD between variants and genes using the ADGC reference panel. The Aβ-centered network pathway analysis used a curated list of 32 Aβ-related gene sets and all 335 genes combined (see Campion et al.<sup>64</sup> for details). The combined dataset of

28,730 unrelated individuals from the ADGC referenced in the GCTA COJO analysis was used as a reference set for LD calculations in these analyses.

### Validation of prioritization method.

Evaluation of the prioritization of the risk genes in genome-wide loci was done using STRING<sup>177</sup>, and Jensen Diseases<sup>178</sup>, Jensen Tissues<sup>179</sup>, dbGAP gene sets, and the ARCHS4<sup>180</sup> resource via the EnrichR<sup>181</sup> tool. We evaluated both the 400 genes set list and a list of 53 genes with priority score  $\geq 5$  (adding in *APOE* to both lists as the top gene in the *APOE* locus) using the standard settings for both STRING and EnrichR. We used the  $q$  value, which is the adjusted  $P$  value using the Benjamini–Hochberg FDR method with a 5% cutoff for correction for multiple hypotheses testing. We also performed ‘differentially expressed gene (DEG)’ sets analysis via FUMA<sup>182</sup>. These analyses were performed in order to assess whether our 53 prioritized genes were significantly differentially expressed in certain GTEx v.7 (ref. <sup>102</sup>; 30 general tissues and 53 specific tissues) or BrainSpan tissues (11 tissue developmental periods with distinct DEG sets ranging from early prenatal to middle adulthood)<sup>103</sup>. FUMA defines DEG sets by calculating a two-sided  $t$ -test per tissue versus all remaining tissue types or developmental periods. Genes with a Bonferroni-corrected  $P < 0.05$  and absolute log(fold change)  $> 0.58$  were considered DEGs. Input genes were tested against each of the DEG sets using the hypergeometric test. Significant enrichment was defined by Bonferroni-corrected  $P < 0.05$ .

### HLA region analysis.

Non-familial datasets from the ADGC, EADI and GERAD consortiums were used for HLA analysis. After imputation quality control, a total of 14,776 cases and 23,047 controls were available for analysis (Supplementary Table 27). Within ADGC, GenADA, ROSMAP, TARC1, TGEN2, and a subset of the UMCWRMSSM datasets were not imputed as Affymetrix genotyping arrays are not supported by the imputation software.

**Imputation of HLA alleles.**—Two-field resolution HLA alleles were imputed using the R package HIBAG v.1.4 (ref. <sup>183</sup>) and the NHW-specific training set. This software uses specific combinations of variants to predict HLA alleles. Alleles with an imputation posterior probability lower than 0.5 were considered as undetermined as recommended by HIBAG developers. *HLA-A*, *HLA-B*, *HLA-C* class I genes, and *HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, and *HLA-DRB1* class II genes were imputed. Individuals with more than two undetermined HLA alleles were excluded.

**Statistical analysis.**—All analyses were performed in R<sup>184</sup>. Associations of HLA alleles with disease were tested using logistic regressions, adjusting for age, sex, and principal components as specified above for single variant association analysis. Only HLA alleles with a frequency higher than 1% were analyzed. Haplotype estimations and association analyses with disease were performed using the ‘haplo.glm’ function from the haplo.stats R package<sup>185</sup> with age, sex, and principal components as covariates. Analysis was performed on two-loci and three-loci haplotypes of *HLA-DQA1*, *HLA-DQB1*, and *HLA-DRB1* genes. Haplotypes with a frequency below 1% were excluded from the analysis. Considering the high LD in the MHC region, only haplotypes predicted with posterior probabilities higher

than 0.2 were considered for analysis. Meta-analysis *P* values were computed using an inverse-variance-based model as implemented in METAL software<sup>141</sup>. For haplotypes analysis, only individuals with no undetermined HLA alleles and only datasets with more than 100 cases or controls were included. Adjustments on HLA significant variants and HLA alleles were performed by introducing the variant or alleles as covariates in the regression models. Adjusted *P* values were computed using the FDR method and the R ‘p.adjust’ function, and applied to the meta-analysis *P* values. The FDR threshold was set to 10%.

### Reporting Summary.

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

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Authors

Brian W. Kunkle<sup>1,310,\*</sup>, Benjamin Grenier-Boley<sup>2,3,4,310</sup>, Rebecca Sims<sup>5,6</sup>, Joshua C. Bis<sup>7</sup>, Vincent Damotte<sup>2,3,4</sup>, Adam C. Naj<sup>8</sup>, Anne Boland<sup>9</sup>, Maria Vronskaya<sup>5</sup>, Sven J. van der Lee<sup>10</sup>, Alexandre Amlie-Wolf<sup>11</sup>, Céline Bellenguez<sup>2,3,4</sup>, Aura Frizatti<sup>5</sup>, Vincent Chouraki<sup>2,3,4,12,13</sup>, Eden R. Martin<sup>1</sup>, Kristel Sleegers<sup>14,15</sup>, Nandini Badarinarayanan<sup>5</sup>, Johanna Jakobsdottir<sup>16</sup>, Kara L. Hamilton-Nelson<sup>1</sup>, Sonia Moreno-Grau<sup>17,18</sup>, Robert Olaso<sup>9</sup>, Rachel Raybould<sup>5,6</sup>, Yuning Chen<sup>19</sup>, Amanda B. Kuzma<sup>11</sup>, Mikko Hiltunen<sup>20,21</sup>, Tanesha Morgan<sup>5</sup>, Shahzad Ahmad<sup>10</sup>, Badri N. Vardarajan<sup>22,23,24</sup>, Jacques Epelbaum<sup>25</sup>, Per Hoffmann<sup>26,27,28</sup>, Merce Boada<sup>17,18</sup>, Gary W. Beecham<sup>1</sup>, Jean-Guillaume Garnier<sup>9</sup>, Denise Harold<sup>29</sup>, Annette L. Fitzpatrick<sup>30,31</sup>, Otto Valladares<sup>11</sup>, Marie-Laure Moutet<sup>9</sup>, Amy Gerrish<sup>32</sup>, Albert V. Smith<sup>33,34</sup>, Liming Qu<sup>11</sup>, Delphine Bacq<sup>9</sup>, Nicola Denning<sup>5,6</sup>, Xueqiu Jian<sup>35</sup>, Yi Zhao<sup>11</sup>, Maria Del Zompo<sup>36</sup>, Nick C. Fox<sup>32,37</sup>, Seung-Hoan Choi<sup>17</sup>, Ignacio Mateo<sup>38</sup>, Joseph T. Hughes<sup>39</sup>, Hieab H. Adams<sup>10</sup>, John Malamont<sup>11</sup>, Florentino Sanchez-Garcia<sup>40</sup>, Yogen Patel<sup>39</sup>, Jennifer A. Brody<sup>7</sup>, Beth A. Dombroski<sup>11</sup>, Maria Candida Deniz Naranjo<sup>40</sup>, Makrina Daniilidou<sup>41</sup>, Gudny Eiriksdottir<sup>16</sup>, Shubhabrata Mukherjee<sup>42</sup>, David Wallon<sup>43</sup>, James Uphill<sup>44</sup>, Thor Aspelund<sup>16,45</sup>, Laura B. Cantwell<sup>11</sup>, Fabienne Garzia<sup>9</sup>, Daniela Galimberti<sup>46,47</sup>, Edith Hofer<sup>48,49</sup>, Mariusz Butkiewicz<sup>50</sup>, Bertrand Fin<sup>9</sup>, Elio Scarpini<sup>46,47</sup>, Chloe Sarnowski<sup>19</sup>, Will S. Bush<sup>50</sup>, Stéphane Meslage<sup>9</sup>, Johannes Kornhuber<sup>51</sup>, Charles C. White<sup>52</sup>, Yuenjoo Song<sup>50</sup>, Robert C. Barber<sup>53</sup>, Sebastiaan Engelborghs<sup>54,55</sup>, Sabrina Sordon<sup>56</sup>, Dina Voijnovic<sup>10</sup>, Perrie M. Adams<sup>57</sup>, Rik Vandenberghe<sup>58</sup>, Manuel Mayhaus<sup>56</sup>, L. Adrienne Cupples<sup>12,19</sup>, Marilyn S. Albert<sup>59</sup>, Peter P. De Deyn<sup>54,55</sup>, Wei Gu<sup>56</sup>, Jayanadra J. Himali<sup>12,13,19</sup>, Duane Beekly<sup>60</sup>, Alessio Squassina<sup>36</sup>, Annette M. Hartmann<sup>61</sup>, Adelina Orellana<sup>17</sup>, Deborah Blacker<sup>62,63</sup>, Eloy Rodriguez-Rodriguez<sup>38</sup>, Simon Lovestone<sup>64</sup>, Melissa E. Garcia<sup>65</sup>, Rachelle S. Doody<sup>66</sup>, Carmen Munoz-Fernandez<sup>40</sup>, Rebecca Sussams<sup>67</sup>, Honghuang Lin<sup>68</sup>, Thomas J. Fairchild<sup>69</sup>, Yolanda A. Benito<sup>40</sup>, Clive Holmes<sup>67</sup>, Hata Karamuji - omi<sup>10</sup>, Matthew

P. Frosch<sup>70</sup>, Hakan Thonberg<sup>71,72</sup>, Wolfgang Maier<sup>73,74</sup>, Gennady Roshchupkin<sup>10</sup>, Bernardino Ghetti<sup>75</sup>, Vilmantas Giedraitis<sup>76</sup>, Amit Kawalia<sup>77</sup>, Shuo Li<sup>19</sup>, Ryan M. Huebinger<sup>78</sup>, Lena Kilander<sup>76</sup>, Susanne Moebus<sup>79</sup>, Isabel Hernández<sup>17,18</sup>, M. Ilyas Kamboh<sup>80,81,82</sup>, RoseMarie Brundin<sup>76</sup>, James Turton<sup>83</sup>, Qiong Yang<sup>19</sup>, Mindy J. Katz<sup>84</sup>, Letizia Concari<sup>85,86</sup>, Jenny Lord<sup>83</sup>, Alexa S. Beiser<sup>12,13,19</sup>, C. Dirk Keene<sup>87</sup>, Seppo Helisalmi<sup>20,21</sup>, Iwona Kloszewska<sup>88</sup>, Walter A. Kukull<sup>31</sup>, Anne Maria Koivisto<sup>20,21</sup>, Aoibhinn Lynch<sup>89,90</sup>, Lluís Tarraga<sup>17,18</sup>, Eric B. Larson<sup>91</sup>, Annakaisa Haapasalo<sup>92</sup>, Brian Lawlor<sup>89,90</sup>, Thomas H. Mosley<sup>93</sup>, Richard B. Lipton<sup>84</sup>, Vincenzo Solfrizzi<sup>94</sup>, Michael Gill<sup>89,90</sup>, W. T. Longstreth Jr<sup>31,95</sup>, Thomas J. Montine<sup>87</sup>, Vincenza Frisardi<sup>96</sup>, Monica Diez-Fairen<sup>97,98</sup>, Fernando Rivadeneira<sup>10,99,100</sup>, Ronald C. Petersen<sup>101</sup>, Vincent Deramecourt<sup>102</sup>, Ignacio Alvarez<sup>97,98</sup>, Francesca Salani<sup>103</sup>, Antonio Ciaramella<sup>103</sup>, Eric Boerwinkle<sup>104,105</sup>, Eric M. Reiman<sup>106,107,108,109</sup>, Nathalie Fievet<sup>2,3,4</sup>, Jerome I. Rotter<sup>110</sup>, Joan S. Reisch<sup>111</sup>, Olivier Hanon<sup>112</sup>, Chiara Cupidi<sup>113</sup>, A. G. Andre Uitterlinden<sup>10,99,100</sup>, Donald R. Royal<sup>114</sup>, Carole Dufouil<sup>115,116</sup>, Raffaele Giovanni Maletta<sup>113</sup>, Itziar de Rojas<sup>17,18</sup>, Mary Sano<sup>117</sup>, Alexis Brice<sup>118,119</sup>, Roberta Cecchetti<sup>120</sup>, Peter St George-Hyslop<sup>121,122</sup>, Karen Ritchie<sup>123,124,125</sup>, Magda Tsolaki<sup>41</sup>, Debby W. Tsuang<sup>126,127</sup>, Bruno Dubois<sup>128,129,130,131</sup>, David Craig<sup>132</sup>, Chuang-Kuo Wu<sup>133</sup>, Hilkka Soininen<sup>20,21</sup>, Despoina Avramidou<sup>41</sup>, Roger L. Albin<sup>134,135,136</sup>, Laura Fratiglioni<sup>137</sup>, Antonia Germanou<sup>41</sup>, Liana G. Apostolova<sup>138,139,140,141</sup>, Lina Keller<sup>137</sup>, Maria Koutroumani<sup>41</sup>, Steven E. Arnold<sup>142</sup>, Francesco Panza<sup>96</sup>, Olympia Gkatzima<sup>41</sup>, Sanjay Asthana<sup>143,144,145</sup>, Didier Hannequin<sup>39</sup>, Patrice Whitehead<sup>1</sup>, Craig S. Atwood<sup>139,140,141</sup>, Paolo Caffarra<sup>82,83</sup>, Harald Hampel<sup>146,147,148,149</sup>, Inés Quintela<sup>150</sup>, Ángel Carracedo<sup>150</sup>, Lars Lannfelt<sup>76</sup>, David C. Rubinsztein<sup>121,151</sup>, Lisa L. Barnes<sup>152,153,154</sup>, Florence Pasquier<sup>102</sup>, Lutz Frölich<sup>155</sup>, Sandra Barra<sup>22,23,24</sup>, Bernadette McGuinness<sup>132</sup>, Thomas G. Beach<sup>156</sup>, Janet A. Johnston<sup>132</sup>, James T. Becker<sup>80,157,158</sup>, Peter Passmore<sup>132</sup>, Eileen H. Bigio<sup>159,160</sup>, Jonathan M. Schott<sup>32</sup>, Thomas D. Bird<sup>95,126</sup>, Jason D. Warren<sup>32</sup>, Bradley F. Boeve<sup>101</sup>, Michelle K. Lupton<sup>39,161</sup>, James D. Bowen<sup>162</sup>, Petra Proitsi<sup>39</sup>, Adam Boxer<sup>163</sup>, John F. Powell<sup>39</sup>, James R. Burke<sup>164</sup>, John S. K. Kauwe<sup>165</sup>, Jeffrey M. Burns<sup>166</sup>, Michelangelo Mancuso<sup>167</sup>, Joseph D. Buxbaum<sup>117,168,169</sup>, Ubaldo Bonuccelli<sup>167</sup>, Nigel J. Cairns<sup>170</sup>, Andrew McQuillin<sup>171</sup>, Chuanhai Cao<sup>172</sup>, Gill Livingston<sup>171</sup>, Chris S. Carlson<sup>144,145</sup>, Nicholas J. Bass<sup>171</sup>, Cynthia M. Carlsson<sup>173</sup>, John Hardy<sup>174</sup>, Regina M. Carney<sup>175</sup>, Jose Bras<sup>37,176</sup>, Minerva M. Carrasquillo<sup>177</sup>, Rita Guerreiro<sup>37,176</sup>, Mariet Allen<sup>177</sup>, Helena C. Chui<sup>178</sup>, Elizabeth Fisher<sup>176</sup>, Carlo Masullo<sup>179</sup>, Elizabeth A. Crocco<sup>180</sup>, Charles DeCarli<sup>181</sup>, Gina Biscegllo<sup>177</sup>, Malcolm Dick<sup>182</sup>, Li Ma<sup>177</sup>, Ranjan Duara<sup>183</sup>, Neill R. Graff-Radford<sup>177</sup>, Denis A. Evans<sup>184</sup>, Angela Hodges<sup>185</sup>, Kelley M. Faber<sup>138</sup>, Martin Scherer<sup>186</sup>, Kenneth B. Fallon<sup>187</sup>, Matthias Riemenschneider<sup>56</sup>, David W. Fardo<sup>188</sup>, Reinhard Heun<sup>74</sup>, Martin R. Farlow<sup>140</sup>, Heike Kölsch<sup>74</sup>, Steven Ferris<sup>189</sup>, Markus Leber<sup>190</sup>, Tatiana M. Foroud<sup>138</sup>, Isabella Heuser<sup>191</sup>, Douglas R. Galasko<sup>192</sup>, Ina Giegling<sup>61</sup>, Marla Gearing<sup>193,194</sup>, Michael Hüll<sup>195</sup>, Daniel H. Geschwind<sup>196</sup>, John R. Gilbert<sup>1</sup>, John Morris<sup>197,198</sup>, Robert C. Green<sup>199</sup>, Kevin Mayo<sup>197,200,201</sup>, John H. Growdon<sup>202</sup>, Thomas Feulner<sup>56</sup>, Ronald L. Hamilton<sup>203</sup>, Lindy E. Harrell<sup>204</sup>, Dmitriy Drichel<sup>205</sup>, Lawrence S. Honig<sup>22</sup>, Thomas D. Cushion<sup>5,6</sup>, Matthew J. Huentelman<sup>106</sup>, Paul

Hollingworth<sup>5</sup>, Christine M. Hulette<sup>206</sup>, Bradley T. Hyman<sup>202</sup>, Rachel Marshall<sup>5</sup>, Gail P. Jarvik<sup>207,208</sup>, Alun Meggy<sup>5</sup>, Erin Abner<sup>209</sup>, Georgina E. Menzies<sup>5,6</sup>, Lee-Way Jin<sup>210</sup>, Ganna Leonenko<sup>5</sup>, Luis M. Real<sup>210</sup>, Gyungah R. Jun<sup>211</sup>, Clinton T. Baldwin<sup>211</sup>, Detelina Grozeva<sup>5</sup>, Anna Karydas<sup>162</sup>, Giancarlo Russo<sup>212</sup>, Jeffrey A. Kaye<sup>213,214</sup>, Ronald Kim<sup>215</sup>, Frank Jessen<sup>73,74,190</sup>, Neil W. Kowall<sup>13,216</sup>, Bruno Vellas<sup>217</sup>, Joel H. Kramer<sup>218</sup>, Emma Vardy<sup>219</sup>, Frank M. LaFerla<sup>220</sup>, Karl-Heinz Jöckel<sup>79</sup>, James J. Lah<sup>221</sup>, Martin Dichgans<sup>222,223</sup>, James B. Leverenz<sup>224</sup>, David Mann<sup>225</sup>, Allan I. Levey<sup>221</sup>, Stuart Pickering-Brown<sup>225</sup>, Andrew P. Lieberman<sup>226</sup>, Norman Klopp<sup>227</sup>, Kathryn L. Lunetta<sup>19</sup>, H-Erich Wichmann<sup>228,229,230</sup>, Constantine G. Lyketsos<sup>231</sup>, Kevin Morgan<sup>232</sup>, Daniel C. Marson<sup>204</sup>, Kristelle Brown<sup>83</sup>, Frank Martiniuk<sup>233</sup>, Christopher Medway<sup>83</sup>, Deborah C. Mash<sup>234</sup>, Markus M. Nöthen<sup>26,27</sup>, Eliezer Masliah<sup>192,235</sup>, Nigel M. Hooper<sup>225</sup>, Wayne C. McCormick<sup>42</sup>, Antonio Daniele<sup>236</sup>, Susan M. McCurry<sup>237</sup>, Anthony Bayer<sup>238</sup>, Andrew N. McDavid<sup>172</sup>, John Gallacher<sup>64</sup>, Ann C. McKee<sup>13,216</sup>, Hendrik van den Bussche<sup>186</sup>, Marsel Mesulam<sup>160,239</sup>, Carol Brayne<sup>240</sup>, Bruce L. Miller<sup>241</sup>, Steffi Riedel-Heller<sup>242</sup>, Carol A. Miller<sup>243</sup>, Joshua W. Miller<sup>244</sup>, Ammar Al-Chalabi<sup>245</sup>, John C. Morris<sup>170,200</sup>, Christopher E. Shaw<sup>245,246</sup>, Amanda J. Myers<sup>180</sup>, Jens Wiltfang<sup>247,248,249</sup>, Sid O'Bryant<sup>53</sup>, John M. Olichney<sup>181</sup>, Victoria Alvarez<sup>250</sup>, Joseph E. Parisi<sup>251</sup>, Andrew B. Singleton<sup>252</sup>, Henry L. Paulson<sup>134,136</sup>, John Collinge<sup>44</sup>, William R. Perry<sup>1</sup>, Simon Mead<sup>44</sup>, Elaine Peskind<sup>127</sup>, David H. Cribbs<sup>253</sup>, Martin Rossor<sup>32</sup>, Aimee Pierce<sup>253</sup>, Natalie S. Ryan<sup>44</sup>, Wayne W. Poon<sup>182</sup>, Benedetta Naemias<sup>254,255</sup>, Huntington Potter<sup>256</sup>, Sandro Sorbi<sup>254,257</sup>, Joseph F. Quinn<sup>186,187</sup>, Eleonora Sacchinelli<sup>103</sup>, Ashok Raj<sup>172</sup>, Gianfranco Spalletta<sup>258,259</sup>, Murray Raskind<sup>127</sup>, Carlo Caltagirone<sup>258</sup>, Paola Bossù<sup>103</sup>, Maria Donata Orfei<sup>258</sup>, Barry Reisberg<sup>189,260</sup>, Robert Clarke<sup>261</sup>, Christiane Reitz<sup>22,23,262</sup>, A David Smith<sup>263</sup>, John M. Ringman<sup>264</sup>, Donald Warden<sup>263</sup>, Erik D. Roberson<sup>204</sup>, Gordon Wilcock<sup>263</sup>, Ekaterina Rogaea<sup>122</sup>, Amalia Cecilia Bruni<sup>113</sup>, Howard J. Rosen<sup>163</sup>, Maura Gallo<sup>113</sup>, Roger N. Rosenberg<sup>265</sup>, Yoav Ben-Shlomo<sup>266</sup>, Mark A. Sager<sup>144</sup>, Patrizia Mecocci<sup>120</sup>, Andrew J. Saykin<sup>138,140</sup>, Pau Pastor<sup>97,98</sup>, Michael L. Cuccaro<sup>1</sup>, Jeffery M. Vance<sup>1</sup>, Julie A. Schneider<sup>152,154,267</sup>, Lori S. Schneider<sup>178,268</sup>, Susan Slifer<sup>1</sup>, William W. Seeley<sup>163</sup>, Amanda G. Smith<sup>172</sup>, Joshua A. Sonnen<sup>87</sup>, Salvatore Spina<sup>75</sup>, Robert A. Stern<sup>13</sup>, Russell H. Swerdlow<sup>166</sup>, Mitchell Tang<sup>11</sup>, Rudolph E. Tanzi<sup>202</sup>, John Q. Trojanowski<sup>269</sup>, Juan C. Troncoso<sup>270</sup>, Vivianna M. Van Deerlin<sup>269</sup>, Linda J. Van Eldik<sup>271</sup>, Harry V. Vinters<sup>272,273</sup>, Jean Paul Vonsattel<sup>274</sup>, Sandra Weintraub<sup>160,275</sup>, Kathleen A. Welsh-Bohmer<sup>164,276</sup>, Kirk C. Wilhelmsen<sup>277</sup>, Jennifer Williamson<sup>22</sup>, Thomas S. Wingo<sup>221,278</sup>, Randall L. Wolter<sup>279</sup>, Clinton B. Wright<sup>280</sup>, Chang-En Yu<sup>42</sup>, Lei Yu<sup>152,154</sup>, Yasaman Saba<sup>281</sup>, Alzheimer Disease Genetics Consortium (ADGC)<sup>282</sup>, The European Alzheimer's Disease Initiative (EADI)<sup>282</sup>, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE)<sup>282</sup>, Genetic and Environmental Risk in AD/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease Consortium (GERAD/PERADES)<sup>282</sup>, Alberto Pilotto<sup>283,284</sup>, Maria J. Bullido<sup>18,285,286</sup>, Oliver Peters<sup>191,287</sup>, Paul K. Crane<sup>42</sup>, David Bennett<sup>152,154</sup>, Paola Bosco<sup>288</sup>, Eliecer Coto<sup>250</sup>, Virginia Boccardi<sup>120</sup>, Phil L. De Jager<sup>289</sup>, Alberto Lleo<sup>18,290</sup>, Nick Warner<sup>291</sup>, Oscar L. Lopez<sup>80,82,157</sup>, Martin Ingelsson<sup>76</sup>, Panagiotis Deloukas<sup>292</sup>, Carlos

Cruchaga<sup>197,198</sup>, Caroline Graff<sup>71,72</sup>, Rhian Gwilliam<sup>292</sup>, Myriam Fornage<sup>35</sup>, Alison M. Goate<sup>168,293</sup>, Pascual Sanchez-Juan<sup>38</sup>, Patrick G. Kehoe<sup>294</sup>, Najaf Amin<sup>10</sup>, Nilifur Ertekin-Taner<sup>177,295</sup>, Claudine Berr<sup>123,124</sup>, Stéphanie Debette<sup>118,119</sup>, Seth Love<sup>294</sup>, Lenore J. Launer<sup>65</sup>, Steven G. Younkin<sup>177,295</sup>, Jean-Francois Dartigues<sup>296</sup>, Chris Corcoran<sup>297</sup>, M. Arfan Ikram<sup>10,298,299</sup>, Dennis W. Dickson<sup>177</sup>, Gael Nicolas<sup>43</sup>, Dominique Campion<sup>43,300</sup>, JoAnn Tschanz<sup>297</sup>, Helena Schmidt<sup>281,301</sup>, Hakon Hakonarson<sup>302,303</sup>, Jordi Clarimon<sup>18,290</sup>, Ron Munger<sup>297</sup>, Reinhold Schmidt<sup>48</sup>, Lindsay A. Farrer<sup>13,19,211,304,305</sup>, Christine Van Broeckhoven<sup>14,15</sup>, Michael C. O'Donovan<sup>5</sup>, Anita L. Destefano<sup>13,19</sup>, Lesley Jones<sup>5,6</sup>, Jonathan L. Haines<sup>50</sup>, Jean-Francois Deleuze<sup>9</sup>, Michael J. Owen<sup>5</sup>, Vilmundur Gudnason<sup>16,34</sup>, Richard Mayeux<sup>22,23,24</sup>, Valentina Escott-Price<sup>5,6</sup>, Bruce M. Psaty<sup>7,31,306,307</sup>, Alfredo Ramirez<sup>77,190</sup>, Li-San Wang<sup>11</sup>, Agustin Ruiz<sup>17,18,311</sup>, Cornelia M. van Duijn<sup>10,311</sup>, Peter A. Holmans<sup>5,311</sup>, Sudha Seshadri<sup>12,13,308,311</sup>, Julie Williams<sup>5,6,311</sup>, Phillippe Amouyel<sup>2,3,4,309,311</sup>, Gerard D. Schellenberg<sup>11,310</sup>, Jean-Charles Lambert<sup>2,3,4,310,311,\*</sup>, Margaret A. Pericak-Vance<sup>1,310,311,\*</sup>

## Affiliations

- <sup>1</sup>John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA. <sup>2</sup>Inserm, U1167, RID-AGE-Risk Factors and Molecular Determinants of Aging-Related Diseases, Lille, France. <sup>3</sup>Institut Pasteur de Lille, Lille, France. <sup>4</sup>Univ. Lille, U1167-Excellence Laboratory LabEx DISTALZ, Lille, France. <sup>5</sup>Division of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK. <sup>6</sup>UK Dementia Research Institute at Cardiff, Cardiff University, Cardiff, UK. <sup>7</sup>Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA. <sup>8</sup>Department of Biostatistics and Epidemiology/ Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. <sup>9</sup>Centre National de Recherche en Génomique Humaine, Institut de Biologie François Jacob, CEA, Université Paris-Saclay, and LabEx GENMED, Evry, France. <sup>10</sup>Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands. <sup>11</sup>Penn Neurodegeneration Genomics Center, Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. <sup>12</sup>Framingham Heart Study, Framingham, MA, USA. <sup>13</sup>Department of Neurology, Boston University School of Medicine, Boston, MA, USA. <sup>14</sup>Neurodegenerative Brain Diseases Group, Center for Molecular Neurology, VIB, Antwerp, Belgium. <sup>15</sup>Laboratory for Neurogenetics, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium. <sup>16</sup>Icelandic Heart Association, Kopavogur, Iceland. <sup>17</sup>Research Center and Memory Clinic of Fundació ACE, Institut Català de Neurociències Aplicades-Universitat Internacional de Catalunya, Barcelona, Spain. <sup>18</sup>Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas, Instituto de Salud Carlos III, Madrid, Spain. <sup>19</sup>Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA. <sup>20</sup>Institute of Biomedicine, University of Eastern Finland, Kuopio, Finland. <sup>21</sup>Department of Neurology, Kuopio University Hospital, Kuopio, Finland. <sup>22</sup>Taub

Institute on Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University, New York, NY, USA. <sup>23</sup>Gertrude H. Sergievsky Center, Columbia University, New York, NY, USA. <sup>24</sup>Department of Neurology, Columbia University, New York, NY, USA. <sup>25</sup>UMR 894, Center for Psychiatry and Neuroscience, Inserm, Université Paris Descartes, Paris, France. <sup>26</sup>Institute of Human Genetics, University of Bonn, Bonn, Germany. <sup>27</sup>Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany. <sup>28</sup>Division of Medical Genetics, University Hospital and Department of Biomedicine, University of Basel, Basel, Switzerland. <sup>29</sup>School of Biotechnology, Dublin City University, Dublin, Ireland. <sup>30</sup>Department of Family Medicine, University of Washington, Seattle, WA, USA. <sup>31</sup>Department of Epidemiology, University of Washington, Seattle, WA, USA. <sup>32</sup>Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK. <sup>33</sup>Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA. <sup>34</sup>Faculty of Medicine, University of Iceland, Reykjavik, Iceland. <sup>35</sup>Brown Foundation Institute of Molecular Medicine, University of Texas Health Sciences Center at Houston, Houston, TX, USA. <sup>36</sup>Section of Neuroscience and Clinical Pharmacology, Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy. <sup>37</sup>UK Dementia Research Institute at UCL, Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK. <sup>38</sup>Neurology Service and CIBERNED, 'Marqués de Valdecilla' University Hospital (University of Cantabria and IDIVAL), Santander, Spain. <sup>39</sup>Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. <sup>40</sup>Department of Immunology, Hospital Universitario Doctor Negrín, Las Palmas de Gran Canaria, Spain. <sup>41</sup>Department of Neurology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece. <sup>42</sup>Department of Medicine, University of Washington, Seattle, WA, USA. <sup>43</sup>Normandie University, UNIROUEN, Inserm U1245, and Rouen University Hospital, Department of Neurology, Department of Genetics and CNR-MAJ, Normandy Center for Genomic and Personalized Medicine, Rouen, France. <sup>44</sup>Department of Neurodegenerative Disease, MRC Prion Unit at UCL, Institute of Prion Diseases, London, UK. <sup>45</sup>Centre for Public Health, University of Iceland, Reykjavik, Iceland. <sup>46</sup>Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy. <sup>47</sup>University of Milan, Centro Dino Ferrari, Milan, Italy. <sup>48</sup>Clinical Division of Neurogeriatrics, Department of Neurology, Medical University Graz, Graz, Austria. <sup>49</sup>Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria. <sup>50</sup>Institute for Computational Biology, Department of Population & Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA. <sup>51</sup>Department of Psychiatry and Psychotherapy, University of Erlangen-Nuremberg, Erlangen, Germany. <sup>52</sup>Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA. <sup>53</sup>Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, TX, USA. <sup>54</sup>Laboratory for Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium. <sup>55</sup>Department of Neurology and Memory

Clinic, Hospital Network Antwerp, Antwerp, Belgium.<sup>56</sup>Department of Psychiatry and Psychotherapy, University Hospital, Saarland, Germany.<sup>57</sup>Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA.<sup>58</sup>Laboratory for Cognitive Neurology, Department of Neurology, University Hospital and University of Leuven, Leuven, Belgium.<sup>59</sup>Department of Neurology, Johns Hopkins University, Baltimore, MD, USA.<sup>60</sup>National Alzheimer's Coordinating Center, University of Washington, Seattle, WA, USA.<sup>61</sup>Department of Psychiatry, Martin Luther University Halle-Wittenberg, Halle, Germany.<sup>62</sup>Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA.<sup>63</sup>Department of Psychiatry, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA.<sup>64</sup>Department of Psychiatry, University of Oxford, Oxford, UK.<sup>65</sup>Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Bethesda, MD, USA.<sup>66</sup>Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, Houston, TX, USA.<sup>67</sup>Division of Clinical Neurosciences, School of Medicine, University of Southampton, Southampton, UK.<sup>68</sup>Section of Computational Biomedicine, Department of Medicine, Boston University School of Medicine, Boston, MA, USA.<sup>69</sup>Office of Strategy and Measurement, University of North Texas Health Science Center, Fort Worth, TX, USA.<sup>70</sup>C.S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital, Charlestown, MA, USA.<sup>71</sup>Theme Aging, Unit for Hereditary Dementias, Karolinska University Hospital-Solna, Stockholm, Sweden.<sup>72</sup>Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Alzheimer Research Center, Division of Neurogeriatrics, Solna, Sweden.<sup>73</sup>German Center for Neurodegenerative Diseases, Bonn, Germany.<sup>74</sup>Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany.<sup>75</sup>Department of Pathology and Laboratory Medicine, Indiana University, Indianapolis, IN, USA.<sup>76</sup>Department of Public Health and Caring Sciences/Geriatrics, Uppsala University, Uppsala, Sweden.<sup>77</sup>Department for Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, Bonn, Germany.<sup>78</sup>Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA.<sup>79</sup>Institute for Medical Informatics, Biometry and Epidemiology, University Hospital of Essen, University Duisburg-Essen, Essen, Germany.<sup>80</sup>Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA.<sup>81</sup>Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA, USA.<sup>82</sup>Alzheimer's Disease Research Center, University of Pittsburgh, Pittsburgh, PA, USA.<sup>83</sup>Institute of Genetics, Queen's Medical Centre, University of Nottingham, Nottingham, UK.<sup>84</sup>Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA.<sup>85</sup>Section of Neuroscience, DIMEC-University of Parma, Parma, Italy.<sup>86</sup>FERB-Alzheimer Center, Gazzaniga (Bergamo), Italy.<sup>87</sup>Department of Pathology, University of Washington, Seattle, WA, USA.<sup>88</sup>Elderly and Psychiatric Disorders Department, Medical University of Lodz, Lodz, Poland.<sup>89</sup>Mercer's Institute for Research on Aging, St. James's Hospital and Trinity College, Dublin, Ireland.<sup>90</sup>St. James's Hospital and Trinity College, Dublin, Ireland.<sup>91</sup>Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA.<sup>92</sup>A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland,

Kuopio, Finland. <sup>93</sup>Departments of Medicine, Geriatrics, Gerontology and Neurology, University of Mississippi Medical Center, Jackson, MS, USA. <sup>94</sup>Interdisciplinary Department of Medicine, Geriatric Medicine and Memory Unity, University of Bari, Bari, Italy. <sup>95</sup>Department of Neurology, University of Washington, Seattle, WA, USA. <sup>96</sup>Department of Geriatrics, Center for Aging Brain, University of Bari, Bari, Italy. <sup>97</sup>Fundació per la Recerca Biomèdica i Social Mútua Terrassa, Terrassa, Barcelona, Spain. <sup>98</sup>Memory Disorders Unit, Department of Neurology, Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain. <sup>99</sup>Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands. <sup>100</sup>Netherlands Consortium on Health Aging and National Genomics Initiative, Leiden, the Netherlands. <sup>101</sup>Department of Neurology, Mayo Clinic, Rochester, MN, USA. <sup>102</sup>CHU Lille, Memory Center of Lille (Centre Mémoire de Ressources et de Recherche), Lille, France. <sup>103</sup>Department of Clinical and Behavioral Neurology, Experimental Neuropsychobiology Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy. <sup>104</sup>School of Public Health, Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX, USA. <sup>105</sup>Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA. <sup>106</sup>Neurogenomics Division, Translational Genomics Research Institute, Phoenix, AZ, USA. <sup>107</sup>Arizona Alzheimer's Consortium, Phoenix, AZ, USA. <sup>108</sup>Banner Alzheimer's Institute, Phoenix, AZ, USA. <sup>109</sup>Department of Psychiatry, University of Arizona, Phoenix, AZ, USA. <sup>110</sup>Institute for Translational Genomics and Population Sciences, Departments of Pediatrics and Medicine, Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA. <sup>111</sup>Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX, USA. <sup>112</sup>University Paris Descartes, EA 4468, AP-HP, Geriatrics Department, Hôpital Broca, Paris, France. <sup>113</sup>Regional Neurogenetic Centre (CRN), ASP Catanzaro, Lamezia Terme, Italy. <sup>114</sup>Departments of Psychiatry, Medicine, Family & Community Medicine, South Texas Veterans Health Administration Geriatric Research Education & Clinical Center (GRECC), UT Health Science Center at San Antonio, San Antonio, TX, USA. <sup>115</sup>University of Bordeaux, Inserm 1219, Bordeaux, France. <sup>116</sup>Department of Neurology, Bordeaux University Hospital / CHU de Bordeaux, Bordeaux, France. <sup>117</sup>Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. <sup>118</sup>Inserm U1127, CNRS UMR 7225, Sorbonne Universités, UPMC Université Paris 06, UMRS 1127, Institut du Cerveau et de la Moelle Épinière, Paris, France. <sup>119</sup>AP-HP, Department of Genetics, Pitié-Salpêtrière Hospital, Paris, France. <sup>120</sup>Section of Gerontology and Geriatrics, Department of Medicine, University of Perugia, Perugia, Italy. <sup>121</sup>Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK. <sup>122</sup>Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada. <sup>123</sup>Inserm U1061 Neuropsychiatry, La Colombière Hospital, Montpellier, France. <sup>124</sup>Montpellier University, Montpellier, France. <sup>125</sup>Department of Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK. <sup>126</sup>VA Puget Sound Health Care System/>GRECC, Seattle, WA, USA. <sup>127</sup>Department of Psychiatry and Behavioral Sciences, University of

Washington School of Medicine, Seattle, WA, USA. <sup>128</sup>Institut de la Mémoire et de la Maladie d'Alzheimer and Institut du Cerveau et de la Moelle Épinière, Département de Neurologie, Hôpital de la Pitié-Salpêtrière, Paris, France. <sup>129</sup>Institut des Neurosciences Translationnelles de Paris, Institut du Cerveau et de la Moelle Épinière, Paris, France. <sup>130</sup>Inserm, CNRS, UMR-S975, Institut du Cerveau et de la Moelle Epinière, Paris, France. <sup>131</sup>Sorbonne Universités, Université Pierre et Marie Curie, Hôpital de la Pitié-Salpêtrière, AP-HP, Paris, France. <sup>132</sup>Ageing Group, Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK. <sup>133</sup>Departments of Neurology, Pharmacology & Neuroscience, Texas Tech University Health Science Center, Lubbock, TX, USA. <sup>134</sup>Department of Neurology, University of Michigan, Ann Arbor, MI, USA. <sup>135</sup>Geriatric Research, Education and Clinical Center (GRECC), VA Ann Arbor Healthcare System (VAAAHS), Ann Arbor, MI, USA. <sup>136</sup>Michigan Alzheimer Disease Center, Ann Arbor, MI, USA. <sup>137</sup>Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden. <sup>138</sup>Indiana Alzheimer's Disease Center, Indiana University School of Medicine, Indianapolis, IN, USA. <sup>139</sup>Department of Medical and Molecular Genetics, Indiana University, Indianapolis, IN, USA. <sup>140</sup>Department of Neurology, Indiana University, Indianapolis, IN, USA. <sup>141</sup>Department of Radiology and Imaging Sciences, Indiana University, Indianapolis, IN, USA. <sup>142</sup>Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. <sup>143</sup>Geriatric Research, Education and Clinical Center (GRECC), University of Wisconsin, Madison, WI, USA. <sup>144</sup>Department of Medicine, University of Wisconsin, Madison, WI, USA. <sup>145</sup>Wisconsin Alzheimer's Disease Research Center, Madison, WI, USA. <sup>146</sup>AXA Research Fund & Sorbonne University Chair, Paris, France. <sup>147</sup>Sorbonne University, GRC n° 21, Alzheimer Precision Medicine (APM), AP-HP, Pitié-Salpêtrière Hospital, Paris, France. <sup>148</sup>Brain & Spine Institute, Inserm U 1127, CNRS UMR 7225, Paris, France. <sup>149</sup>Institute of Memory and Alzheimer's Disease, Department of Neurology, Pitié-Salpêtrière Hospital, AP-HP, Paris, France. <sup>150</sup>Grupo de Medicina Xenómica, Universidade de Santiago de Compostela, Centro Nacional de Genotipado, Centro de Investigación Biomédica en Red de Enfermedades Raras, Santiago de Compostela, Spain. <sup>151</sup>UK Dementia Research Institute, University of Cambridge, Cambridge, UK. <sup>152</sup>Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA. <sup>153</sup>Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL, USA. <sup>154</sup>Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA. <sup>155</sup>Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany. <sup>156</sup>Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Phoenix, AZ, USA. <sup>157</sup>Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA. <sup>158</sup>Department of Psychology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. <sup>159</sup>Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. <sup>160</sup>Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. <sup>161</sup>Genetic Epidemiology,

QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia.  
<sup>162</sup>Swedish Medical Center, Seattle, WA, USA. <sup>163</sup>Department of Neurology, University of California, San Francisco, San Francisco, CA, USA. <sup>164</sup>Department of Neurology, Duke University, Durham, NC, USA. <sup>165</sup>Departments of Biology, Brigham Young University, Provo, UT, USA. <sup>166</sup>University of Kansas Alzheimer's Disease Center, University of Kansas Medical Center, Kansas City, KS, USA. <sup>167</sup>Department of Experimental and Clinical Medicine, Neurological Institute, University of Pisa, Pisa, Italy. <sup>168</sup>Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. <sup>169</sup>Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA. <sup>170</sup>Department of Pathology and Immunology, Washington University, St. Louis, MO, USA. <sup>171</sup>Division of Psychiatry, University College London, London, UK. <sup>172</sup>USF Health Byrd Alzheimer's Institute, University of South Florida, Tampa, FL, USA. <sup>173</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA. <sup>174</sup>Department of Molecular Neuroscience, UCL, Institute of Neurology, London, UK. <sup>175</sup>Mental Health & Behavioral Science Service, Bruce W. Carter VA Medical Center, Miami, FL, USA. <sup>176</sup>Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK. <sup>177</sup>Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA. <sup>178</sup>Department of Neurology, University of Southern California, Los Angeles, CA, USA. <sup>179</sup>Department of Neurology, Catholic University of Rome, Rome, Italy. <sup>180</sup>Department of Psychiatry and Behavioral Sciences, Miller School of Medicine, University of Miami, Miami, FL, USA. <sup>181</sup>Department of Neurology, University of California, Davis, Sacramento, CA, USA. <sup>182</sup>Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA. <sup>183</sup>Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Miami Beach, FL, USA. <sup>184</sup>Rush Institute for Healthy Aging, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA. <sup>185</sup>Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. <sup>186</sup>Department of Primary Medical Care, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany. <sup>187</sup>Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA. <sup>188</sup>Sanders-Brown Center on Aging, Department of Biostatistics, University of Kentucky, Lexington, KY, USA. <sup>189</sup>Department of Psychiatry, New York University, New York, NY, USA. <sup>190</sup>Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany. <sup>191</sup>Department of Psychiatry and Psychotherapy, Charité University Medicine, Berlin, Germany. <sup>192</sup>Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA. <sup>193</sup>Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA. <sup>194</sup>Emory Alzheimer's Disease Center, Emory University, Atlanta, GA, USA. <sup>195</sup>Department of Psychiatry, University of Freiburg, Freiburg, Germany. <sup>196</sup>Neurogenetics Program, University of California, Los Angeles, Los Angeles, CA, USA. <sup>197</sup>Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA. <sup>198</sup>Hope Center Program on Protein Aggregation and Neurodegeneration, Washington University School of Medicine, St. Louis, MO, USA. <sup>199</sup>Division of Genetics,

Department of Medicine and Partners Center for Personalized Genetic Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.  
<sup>200</sup>Department of Neurology, Washington University, St. Louis, MO, USA.  
<sup>201</sup>Department of Genetics, Washington University, St. Louis, MO, USA.  
<sup>202</sup>Department of Neurology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA. <sup>203</sup>Department of Pathology (Neuropathology), University of Pittsburgh, Pittsburgh, PA, USA. <sup>204</sup>Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA. <sup>205</sup>Cologne Center for Genomics, University of Cologne, Cologne, Germany. <sup>206</sup>Department of Pathology, Duke University, Durham, NC, USA. <sup>207</sup>Department of Genome Sciences, University of Washington, Seattle, WA, USA. <sup>208</sup>Department of Medicine (Medical Genetics), University of Washington, Seattle, WA, USA. <sup>209</sup>Sanders-Brown Center on Aging, College of Public Health, Department of Epidemiology, University of Kentucky, Lexington, KY, USA. <sup>210</sup>Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario de Valme, Sevilla, Spain. <sup>211</sup>Department of Medicine (Biomedical Genetics), Boston University School of Medicine, Boston, MA, USA. <sup>212</sup>Functional Genomics Center Zurich, ETH/University of Zurich, Zurich, Switzerland. <sup>213</sup>Department of Neurology, Oregon Health & Science University, Portland, OR, USA. <sup>214</sup>Department of Neurology, Portland Veterans Affairs Medical Center, Portland, OR, USA. <sup>215</sup>Department of Pathology and Laboratory Medicine, University of California, Irvine, Irvine, CA, USA. <sup>216</sup>Department of Pathology, Boston University School of Medicine, Boston University, Boston, MA, USA. <sup>217</sup>Inserm U558, University of Toulouse, Toulouse, France. <sup>218</sup>Department of Neuropsychology, University of California San Francisco, San Francisco, CA, USA. <sup>219</sup>Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK. <sup>220</sup>Department of Neurobiology and Behavior, University of California, Irvine, Irvine, CA, USA. <sup>221</sup>Department of Neurology, Emory University, Atlanta, GA, USA. <sup>222</sup>Institute for Stroke and Dementia Research, Klinikum der Universität München, Munich, Germany. <sup>223</sup>German Center for Neurodegenerative Diseases, Munich, Germany. <sup>224</sup>Cleveland Clinic Lou Ruvo Center for Brain Health, Cleveland Clinic, Cleveland, OH, USA. <sup>225</sup>Division 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. <sup>226</sup>Department of Pathology, University of Michigan, Ann Arbor, MI, USA. <sup>227</sup>Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Munich, Germany. <sup>228</sup>Helmholtz Center Munich, Institute of Epidemiology, Neuherberg, Munich, Germany. <sup>229</sup>Ludwig-Maximilians University Chair of Epidemiology, Munich, Germany. <sup>230</sup>Joint Biobank Munich and KORA Biobank, Baltimore, MD, USA. <sup>231</sup>Department of Psychiatry, Johns Hopkins University, Baltimore, MD, USA. <sup>232</sup>Human Genetics, Schools of Life Sciences and Medicine, University of Nottingham, Nottingham, UK. <sup>233</sup>Department of Medicine-Pulmonary, New York University, New York, NY, USA. <sup>234</sup>Department of Neurology, University of Miami, Miami, FL, USA. <sup>235</sup>Department of Pathology, University of California, San Diego, La Jolla, CA, USA. <sup>236</sup>Institute of Neurology, Catholic

University of Sacred Heart, Rome, Italy.<sup>237</sup>School of Nursing Northwest Research Group on Aging, University of Washington, Seattle, WA, USA.<sup>238</sup>Institute of Primary Care and Public Health, Cardiff University, University Hospital of Wales, Cardiff, UK.<sup>239</sup>Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA.<sup>240</sup>Cambridge Institute of Public Health, University of Cambridge School of Clinical Medicine, Cambridge, UK.<sup>241</sup>Weill Institute for Neurosciences, Memory and Aging Center, University of California, San Francisco, San Francisco, CA, USA.<sup>242</sup>Institute of Social Medicine, Occupational Health and Public Health, University of Leipzig, Leipzig, Germany.<sup>243</sup>Department of Pathology, University of Southern California, Los Angeles, CA, USA.<sup>244</sup>Department of Pathology and Laboratory Medicine, University of California, Davis, Sacramento, CA, USA.<sup>245</sup>Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.<sup>246</sup>UK Dementia Research Institute, King's College London, London, UK.<sup>247</sup>Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, Goettingen, Germany.<sup>248</sup>German Center for Neurodegenerative Diseases, Goettingen, Germany.<sup>249</sup>IBiMED, Medical Sciences Department, University of Aveiro, Aveiro, Portugal.<sup>250</sup>Molecular Genetics Laboratory-Hospital, University of Central Asturias, Oviedo, Spain.<sup>251</sup>Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA.<sup>252</sup>Molecular Genetics Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA.<sup>253</sup>Department of Neurology, University of California, Irvine, Irvine, CA, USA.<sup>254</sup>Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy.<sup>255</sup>Centro di Ricerca, Trasferimento e Alta Formazione DENOTHE, University of Florence, Florence, Italy.<sup>256</sup>Department of Neurology, University of Colorado School of Medicine, Aurora, CO, USA.<sup>257</sup>IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy.<sup>258</sup>Laboratory of Neuropsychiatry, IRCCS Santa Lucia Foundation, Rome, Italy.<sup>259</sup>Division of Neuropsychiatry, Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA.<sup>260</sup>Alzheimer's Disease Center, New York University, New York, NY, USA.<sup>261</sup>Oxford Healthy Aging Project, Clinical Trial Service Unit, University of Oxford, Oxford, UK.<sup>262</sup>Department of Epidemiology, Columbia University, New York, NY, USA.<sup>263</sup>Oxford Project to Investigate Memory and Ageing, University of Oxford, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK.<sup>264</sup>Department of Neurology, Keck School of Medicine at the University of Southern California, Los Angeles, Los Angeles, CA, USA.<sup>265</sup>Department of Neurology, University of Texas Southwestern Medical Center, Dallas, TX, USA.<sup>266</sup>Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.<sup>267</sup>Department of Pathology (Neuropathology), Rush University Medical Center, Chicago, IL, USA.<sup>268</sup>Department of Psychiatry, University of Southern California, Los Angeles, CA, USA.<sup>269</sup>Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.<sup>270</sup>Department of Pathology, Johns Hopkins University, Baltimore, MD, USA.<sup>271</sup>Sanders-Brown Center on Aging, Department of Neuroscience, University of Kentucky, Lexington, KY, USA.<sup>272</sup>Department of

Author Manuscript  
Author Manuscript  
Author Manuscript  
Author Manuscript

Neurology, University of California, Los Angeles, Los Angeles, CA, USA.  
<sup>273</sup>Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Los Angeles, CA, USA. <sup>274</sup>Taub Institute on Alzheimer's Disease and the Aging Brain, Department of Pathology, Columbia University, New York, NY, USA.  
<sup>275</sup>Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. <sup>276</sup>Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA. <sup>277</sup>Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.  
<sup>278</sup>Department of Human Genetics, Emory University, Atlanta, GA, USA.  
<sup>279</sup>Department of Pathology, Oregon Health & Science University, Portland, OR, USA. <sup>280</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA. <sup>281</sup>Gottfried Schatz Research Center for Cell Signaling, Metabolism and Aging, Division of Molecular Biology and Biochemistry, Medical University Graz, Graz, Austria. <sup>282</sup>A list of members and affiliations appears in the Supplementary Note. <sup>283</sup>Gerontology and Geriatrics Research Laboratory, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy. <sup>284</sup>Department Geriatric Care, Orthogeriatrics and Rehabilitation, Galliera Hospital, Genova, Italy. <sup>285</sup>IidiPAZ, Instituto de Investigación Sanitaria la Paz, Madrid, Spain. <sup>286</sup>Centro de Biología Molecular Severo Ochoa (CSIC-UAM), Madrid, Spain. <sup>287</sup>German Center for Neurodegenerative Diseases, Berlin, Germany. <sup>288</sup>Instituto di Ricovero e Cura a Carattere Scientifico, Associazione Oasi Maria Santissima Srl, Troina, Italy.  
<sup>289</sup>Center for Translational and Computational Neuroimmunology, Department of Neurology, Columbia University Medical Center, New York, NY, USA. <sup>290</sup>Memory Unit, Neurology Department and Sant Pau Biomedical Research Institute, Hospital de la Santa Creu i Sant Pau, Autonomous University Barcelona, Barcelona, Spain.  
<sup>291</sup>Somerset Partnership NHS Trust, Somerset, UK. <sup>292</sup>The Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK. <sup>293</sup>Ronald M. Loeb Center for Alzheimer's Disease, Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA. <sup>294</sup>University of Bristol Medical School, Learning & Research level 2, Southmead Hospital, Bristol, UK. <sup>295</sup>Department of Neurology, Mayo Clinic, Jacksonville, FL, USA. <sup>296</sup>Memory Research and Resources Center, CMRR de Bordeaux, Bordeaux, France. <sup>297</sup>Utah State University, Logan, UT, USA.  
<sup>298</sup>Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands. <sup>299</sup>Departments of Radiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands. <sup>300</sup>Department of Research Rouvray Psychiatric Hospital, Sotteville-lès-Rouen, France. <sup>301</sup>Department of Neurology, Medical University Graz, Graz, Austria. <sup>302</sup>Center for Applied Genomics, Children's Hospital of Philadelphia, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. <sup>303</sup>Division of Human Genetics, Department of Pediatrics, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. <sup>304</sup>Department of Ophthalmology, Boston University School of Medicine, Boston University, Boston, MA, USA. <sup>305</sup>Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA. <sup>306</sup>Department of Health Services, University of Washington, Seattle, WA, USA. <sup>307</sup>Kaiser

Permanente, Washington Health Research Institute, Seattle, WA, USA.<sup>308</sup>Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, San Antonio, TX, USA.<sup>309</sup>Centre Hospitalier Universitaire de Lille, Lille, France.<sup>310</sup>These authors contributed equally: Brian W. Kunkle, Benjamin Grenier-Boley, Jean Charles-Lambert, Margaret A. Pericak-Vance.<sup>311</sup>These authors jointly supervised this work: Agustin Ruiz, Cornelia M. van Duijn, Peter A. Holmans, Sudha Seshadri, Julie Williams, Phillippe Amouyel, Gerard D. Schellenberg, Jean-Charles Lambert, Margaret A. Pericak-Vance.

## Acknowledgements

We thank all the participants of this study for their contributions. Additional acknowledgements and detailed acknowledgments of funding sources for the study are provided in the Supplementary Note.

## References

1. Lambert JC et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat. Genet* 45, 1452–1458 (2013). [PubMed: 24162737]
2. Adams PM et al. Assessment of the genetic variance of late-onset Alzheimer's disease. *Neurobiol. Aging* 41, 1–8 (2016). [PubMed: 27103513]
3. Gatz M et al. Role of genes and environments for explaining Alzheimer disease. *Arch. Gen. Psychiatry* 63, 168–174 (2006). [PubMed: 16461860]
4. Naj AC et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat. Genet* 43, 436–441 (2011). [PubMed: 21460841]
5. Seshadri S et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA* 303, 1832–1840 (2010). [PubMed: 20460622]
6. Hollingworth P et al. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat. Genet* 43, 429–435 (2011). [PubMed: 21460840]
7. Jonsson T et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *N. Engl. J. Med* 368, 107–116 (2013). [PubMed: 23150908]
8. Guerreiro R et al. TREM2 variants in Alzheimer's disease. *N. Engl. J. Med* 368, 117–127 (2013). [PubMed: 23150934]
9. Jun G et al. Meta-analysis confirms CR1, CLU, and PICALM as alzheimer disease risk loci and reveals interactions with APOE genotypes. *Arch. Neurol* 67, 1473–1484 (2010). [PubMed: 20697030]
10. Harold D et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat. Genet* 41, 1088–1093 (2009). [PubMed: 19734902]
11. Lambert JC et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat. Genet* 41, 1094–1099 (2009). [PubMed: 19734903]
12. Zheng J et al. LD Hub: A centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics* 33, 051094 (2017).
13. Bulik-Sullivan BK et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet* 47, 291–295 (2015). [PubMed: 25642630]
14. Sims RC et al. Novel rare coding variants in PLCG2, ABI3 and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. *Nat. Genet* 49, 1373–1387 (2017). [PubMed: 28714976]
15. Liu JZ et al. Case-control association mapping by proxy using family history of disease. *Nat. Genet* 49, 325–331 (2017). [PubMed: 28092683]

16. Desikan RS et al. Polygenic overlap between c-reactive protein, plasma lipids, and Alzheimer's disease. *Circulation* 131, 2061–2069 (2015). [PubMed: 25862742]
17. Jun GR et al. Transthectic genome-wide scan identifies novel Alzheimer's disease loci. *Alzheimers Dement* 13, 727–738 (2017). [PubMed: 28183528]
18. Vassar R ADAM10 prodomain mutations cause late-onset Alzheimer's disease: not just the latest FAD. *Neuron* 80, 250–253 (2013). [PubMed: 24139026]
19. Kim M et al. Potential late-onset Alzheimer's disease-associated mutations in the ADAM10 gene attenuate alpha-secretase activity. *Hum. Mol. Genet* 18, 3987–3996 (2009). [PubMed: 19608551]
20. Kehoe PG et al. Variation in DCP1, encoding ACE, is associated with susceptibility to Alzheimer disease. *Nat. Genet* 21, 71–72 (1999). [PubMed: 9916793]
21. Meng Y et al. Association of polymorphisms in the Angiotensin-converting enzyme gene with Alzheimer disease in an Israeli Arab community. *Am. J. Hum. Genet* 78, 871–877 (2006). [PubMed: 16642441]
22. Lehmann DJ et al. Large meta-analysis establishes the ACE insertion-deletion polymorphism as a marker of Alzheimer's disease. *Am. J. Epidemiol* 162, 305–317 (2005). [PubMed: 16033878]
23. Wang X-B et al. Angiotensin-converting enzyme insertion/deletion polymorphism is not a major determining factor in the development of sporadic Alzheimer disease: evidence from an updated meta-analysis. *PLoS ONE* 9, e111406 (2014). [PubMed: 25360660]
24. Cai G et al. Evidence against a role for rare ADAM10 mutations in sporadic Alzheimer disease. *Neurobiol. Aging* 33, 416–417.e3 (2012). [PubMed: 20381196]
25. Belbin O et al. A multi-center study of ACE and the risk of late-onset Alzheimer's disease. *J. Alzheimers. Dis* 24, 587–597 (2011). [PubMed: 21297258]
26. Marioni RE et al. GWAS on family history of Alzheimer disease. *Transl. Psychiatry* 8, 99 (2018). [PubMed: 29777097]
27. Yang J et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat. Genet* 44, 369–375 (2012). [PubMed: 22426310]
28. Chang J-Y & Chang N-S WWOX dysfunction induces sequential aggregation of TRAPP6A , TIAF1, tau and amyloid  $\beta$ , and causes apoptosis. *Cell Death Discov* 1, 15003 (2015). [PubMed: 27551439]
29. Sze CI et al. Down-regulation of WW domain-containing oxidoreductase induces tau phosphorylation in vitro: a potential role in Alzheimer's disease. *J. Biol. Chem* 279, 30498–30506 (2004). [PubMed: 15126504]
30. Zhang B et al. Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell* 153, 707–720 (2013). [PubMed: 23622250]
31. Bai Z et al. AlzBase: an integrative database for gene dysregulation in Alzheimer's disease. *Mol. Neurobiol* 53, 310–319 (2016). [PubMed: 25432889]
32. Zhang Y et al. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J. Neurosci* 34, 11929–11947 (2014). [PubMed: 25186741]
33. Zhang Y et al. Purification and characterization of progenitor and mature human astrocytes reveals transcriptional and functional differences with mouse. *Neuron* 89, 37–53 (2016). [PubMed: 26687838]
34. Olah M et al. A transcriptomic atlas of aged human microglia. *Nat. Commun* 9, 539 (2018). [PubMed: 29416036]
35. Corder EH et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat. Genet* 7, 180–184 (1994). [PubMed: 7920638]
36. Kim J, Basak JM & Holtzman DM The role of apolipoprotein E in Alzheimer's disease. *Neuron* 63, 287–303 (2009). [PubMed: 19679070]
37. Steinberg S et al. Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. *Nat. Genet* 47, 445–447 (2015). [PubMed: 25807283]
38. Vasquez JB, Fardo DW & Estus S ABCA7 expression is associated with Alzheimer's disease polymorphism and disease status. *Neurosci. Lett* 556, 58–62 (2013). [PubMed: 24141082]

39. De Roeck A et al. An intronic VNTR affects splicing of ABCA7 and increases risk of Alzheimer's disease. *Acta Neuropathol* 135, 827–837 (2018). [PubMed: 29589097]
40. De Roeck A et al. deleterious ABCA7 mutations and transcript rescue mechanisms in early onset Alzheimer's disease. *Acta Neuropathol* 134, 475–487 (2017). [PubMed: 28447221]
41. Chapuis J et al. Increased expression of BIN1 mediates Alzheimer genetic risk by modulating tau pathology. *Mol. Psychiatry* 18, 1225–1234 (2013). [PubMed: 23399914]
42. Rogeava E et al. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nat. Genet* 39, 168–177 (2007). [PubMed: 17220890]
43. Vardarajan BN et al. Coding mutations in SORL1 and Alzheimer disease. *Ann. Neurol* 77, 215–227 (2015). [PubMed: 25382023]
44. Suh J et al. ADAM10 missense mutations potentiate beta-amyloid accumulation by impairing prodomain chaperone function. *Neuron* 80, 385–401 (2013). [PubMed: 24055016]
45. Huang K et al. A common haplotype lowers PU.1 expression in myeloid cells and delays onset of Alzheimer's disease. *Nat. Neurosci* 20, 1052–1061 (2017). [PubMed: 28628103]
46. Brouwers N et al. Alzheimer risk associated with a copy number variation in the complement receptor 1 increasing C3b/C4b binding sites. *Mol. Psychiatry* 17, 223–233 (2012). [PubMed: 21403675]
47. Flister MJ et al. Identifying multiple causative genes at a single GWAS locus. *Genome Res* 23, 1996–2002 (2013). [PubMed: 24006081]
48. Farh KK-H et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature* 518, 337–343 (2014). [PubMed: 25363779]
49. Bis JC et al. Whole exome sequencing study identifies novel rare and common Alzheimer's-associated variants involved in immune response and transcriptional regulation. *Mol. Psychiatry* 10.1038/s41380-018-0112-7 (2018).
50. Vardarajan BN et al. Coding mutations in SORL1 and Alzheimer disease. *Ann. Neurol* 77, 215–227 (2015). [PubMed: 25382023]
51. Verheijen J et al. A comprehensive study of the genetic impact of rare variants in SORL1 in European early-onset Alzheimer's disease. *Acta Neuropathol* 132, 213–224 (2016). [PubMed: 27026413]
52. Bellenguez C et al. Contribution to Alzheimer's disease risk of rare variants in TREM2, SORL1, and ABCA7 in 1779 cases and 1273 controls. *Neurobiol. Aging* 59, 220e1–220.e9 (2017).
53. Kunkle BW et al. Targeted sequencing of ABCA7 identifies splicing, stop-gain and intronic risk variants for Alzheimer disease. *Neurosci. Lett* 649, 124–129 (2017). [PubMed: 28400126]
54. May P et al. Rare ABCA7 variants in 2 German families with Alzheimer disease. *Neurol. Genet* 4, e224 (2018). [PubMed: 29577078]
55. Guennec K. Le et al. ABCA7 rare variants and Alzheimer disease risk. *Neurology* 86, 1–4 (2016).
56. Boyle AP et al. Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res* 22, 1790–1797 (2012). [PubMed: 22955989]
57. Ward LD & Kellis M HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. *Nucleic Acids Res* 40, D930–D934 (2012). [PubMed: 22064851]
58. Zerbino DR, Wilder SP, Johnson N, Juettemann T & Flieck PR The Ensembl Regulatory Build. *Genome. Biol* 16, 56 (2015). [PubMed: 25887522]
59. Huang D et al. GWAS4D: multidimensional analysis of context-specific regulatory variant for human complex diseases and traits. *Nucleic Acids Res* 46, W114–W120 (2018). [PubMed: 29771388]
60. Gjoneska E et al. Conserved epigenomic signals in mice and humans reveal immune basis of Alzheimer's disease. *Nature* 518, 365–369 (2015). [PubMed: 25693568]
61. de Leeuw CA, Mooij JM, Heskes T & Posthuma D MAGMA: Generalized Gene-Set Analysis of GWAS Data. *PLoS Comput. Biol* 11, 1–19 (2015).
62. Stefanis L alpha-Synuclein in Parkinson's disease. *Cold Spring Harb. Perspect. Med* 2, 1–23 (2012).

63. Takeda A et al. C-terminal alpha-synuclein immunoreactivity in structures other than Lewy bodies in neurodegenerative disorders. *Acta Neuropathol* 99, 296–304 (2000). [PubMed: 10663973]
64. Campion D, Pottier C, Nicolas G, Le Guennec K & Rovelet-Leroux A Alzheimer disease: modeling an A $\beta$ -centered biological network. *Mol. Psychiatry* 7, 861–871 (2016).
65. Yeh FL, Wang Y, Tom I, Gonzalez LC & Sheng M TREM2 binds to apolipoproteins, including APOE and CLU/APOJ, and thereby facilitates uptake of amyloid-beta by microglia. *Neuron* 91, 328–340 (2016). [PubMed: 27477018]
66. Fritzsche LG et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat. Genet* 48, 134–143 (2015). [PubMed: 26691988]
67. Haass C, Kaether C, Thinakaran G & Sisodia S Trafficking and proteolytic processing of APP. *Cold Spring Harb. Perspect. Med* 2, a006270 (2012). [PubMed: 22553493]
68. Kleinberger G et al. TREM2 mutations implicated in neurodegeneration impair cell surface transport and phagocytosis. *Sci. Transl. Med* 6, 243ra86 (2014).
69. Postina R et al. A disintegrin-metalloproteinase prevents amyloid plaque formation and hippocampal defects in an Alzheimer disease mouse model. *J. Clin. Invest* 113, 1456–1464 (2004). [PubMed: 15146243]
70. Hinney A et al. Genetic variation at the CELF1 (CUGBP, elav-like family member 1 gene) locus is genome-wide associated with Alzheimer's disease and obesity. *Am. J. Med. Genet. B* 165B, 283–293 (2014).
71. Speliotes EK et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat. Genet* 42, 937–948 (2010). [PubMed: 20935630]
72. Kurabayashi N, Nguyen MD & Sanada K The G protein-coupled receptor GPRC5B contributes to neurogenesis in the developing mouse neocortex. *Development* 140, 4335–4346 (2013). [PubMed: 24089469]
73. Cool BH et al. A flanking gene problem leads to the discovery of a Gprc5b splice variant predominantly expressed in C57BL/6J mouse brain and in maturing neurons. *PLoS ONE* 5, e10351 (2010). [PubMed: 20436672]
74. Kim Y-J, Sano T, Nabetani T, Asano Y & Hirabayashi Y GPRC5B activates obesity-associated inflammatory signaling in adipocytes. *Sci. Signal* 5, ra85–ra85 (2012). [PubMed: 23169819]
75. Bhat K et al. The 19S proteasome ATPase Sug1 plays a critical role in regulating MHC class II transcription. *Mol. Immunol* 45, 2214–2224 (2008). [PubMed: 18215421]
76. Inostroza-Nieves Y, Venkatraman P & Zavala-Ruiz Z Role of Sug1, a 19S proteasome ATPase, in the transcription of MHC I and the atypical MHC II molecules, HLA-DM and HLA-DO. *Immunol. Lett* 147, 67–74 (2012). [PubMed: 22771340]
77. Kim K, Duramad O, Qin XF & Su B MEKK3 is essential for lipopolysaccharide-induced interleukin-6 and granulocyte-macrophage colony-stimulating factor production in macrophages. *Immunology* 120, 242–250 (2007). [PubMed: 17116170]
78. Yamazaki K et al. Two mechanistically and temporally distinct NF- $\kappa$ B activation pathways in IL-1 signaling. *Sci. Signal* 2, 1–12 (2009).
79. Farrer LA et al. Association between angiotensin-converting enzyme and Alzheimer disease. *New Engl. J. Med* 357, 210–214 (2000).
80. Miners JS et al. Angiotensin-converting enzyme levels and activity in Alzheimer's disease: differences in brain and CSF ACE and association with ACE1 genotypes. *Am. J. Transl. Res* 1, 163–177 (2009). [PubMed: 19956428]
81. Jochemsen HM et al. The association of angiotensin-converting enzyme with biomarkers for Alzheimer's disease. *Alzheimers Res. Ther* 6, 1–10 (2014). [PubMed: 24382028]
82. Kauwe JSK et al. Genome-wide association study of CSFI Levels of 59 Alzheimer's disease candidate proteins: significant associations with proteins involved in amyloid processing and inflammation. *PLoS Genet* 10, e1004758 (2014). [PubMed: 25340798]
83. Baranello RJ et al. Amyloid-beta protein clearance and degradation (ABCD) pathways and their role in Alzheimer's disease. *Curr. Alzheimers Res* 12, 32–46 (2015).

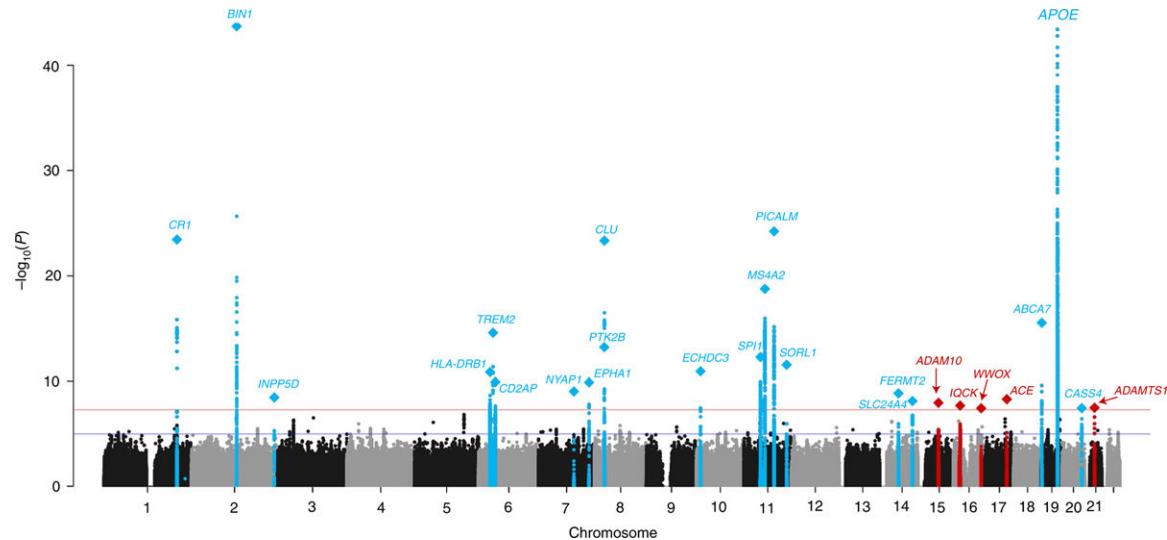
84. Kehoe PG The coming of age of the angiotensin hypothesis in Alzheimer's disease: progress toward disease prevention and treatment? *J. Alzheimers. Dis* 62, 1443–1466 (2018). [PubMed: 29562545]
85. Kehoe PG et al. The rationale and design of the reducing pathology in Alzheimer's disease through Angiotensin TaRgeting (RADAR) Trial. *J. Alzheimers. Dis* 61, 803–814 (2017).
86. Miguel RF, Pollak A & Lubec G Metalloproteinase ADAMTS-1 but not ADAMTS-5 is manifold overexpressed in neurodegenerative disorders as Down syndrome, Alzheimer's and Pick's disease. *Brain. Res. Mol. Brain. Res* 133, 1–5 (2005). [PubMed: 15661359]
87. Suttkus A et al. Aggrecan, link protein and tenascin-R are essential components of the perineuronal net to protect neurons against iron-induced oxidative stress. *Cell Death Dis* 5, e1119 (2014). [PubMed: 24625978]
88. Végh MJ et al. Reducing hippocampal extracellular matrix reverses early memory deficits in a mouse model of Alzheimer's disease. *Acta Neuropathol. Commun* 2, 76 (2014). [PubMed: 24974208]
89. Morawski M, Filippov M, Tzinia A, Tsilibary E & Vargova L ECM in brain aging and dementia. *Prog. Brain. Res* 214, 207–227 (2014). [PubMed: 25410360]
90. Wilcock DM Neuroinflammation in the aging down syndrome brain; lessons from Alzheimer's disease. *Curr. Gerontol. Geriatr. Res* 2012, 170276 (2012).
91. Wang K et al. A genome-wide association study on obesity and obesity-related traits. *PLoS ONE* 6, 3–8 (2011).
92. Kang K et al. Interferon- $\gamma$  represses M2 gene expression in human macrophages by disassembling enhancers bound by the transcription factor MAF. *Immunity* 47, 235–250.e4 (2017). [PubMed: 28813657]
93. Cao S, Liu J, Song L & Ma X The protooncogene c-Maf Is an essential transcription factor for IL-10 gene expression in macrophages. *J. Immunol* 174, 3484–3492 (2005). [PubMed: 15749884]
94. Lee JC et al. WW-domain-containing oxidoreductase is associated with low plasma HDL-C levels. *Am. J. Hum. Genet* 83, 180–192 (2008). [PubMed: 18674750]
95. Saez ME et al. WWOX gene is associated with HDL cholesterol and triglyceride levels. *BMC. Med. Genet* 11, 148 (2010). [PubMed: 20942981]
96. Chang HT et al. WW domain-containing oxidoreductase in neuronal injury and neurological diseases. *Oncotarget* 5, 11792–11799 (2014). [PubMed: 25537520]
97. Lee MH et al. Zfra restores memory deficits in Alzheimer's disease triple-transgenic mice by blocking aggregation of TRAPP/C6A $\beta$ , SH3GLB2, tau, and amyloid  $\beta$ , and inflammatory NF- $\kappa$ B activation. *Alzheimers Dement. Transl. Res. Clin. Interv* 3, 189–204 (2017).
98. Dourlen P et al. Functional screening of Alzheimer risk loci identifies PTK2B as an in vivo modulator and early marker of Tau pathology. *Mol. Psychiatry* 22, 874–883 (2017). [PubMed: 27113998]
99. Chapuis J et al. Genome-wide, high-content siRNA screening identifies the Alzheimer's genetic risk factor FERMT2 as a major modulator of APP metabolism. *Acta Neuropathol* 133, 955–966 (2017). [PubMed: 27933404]
100. Shulman JM et al. Functional screening in *Drosophila* identifies Alzheimer's disease susceptibility genes and implicates tau-mediated mechanisms. *Hum. Mol. Genet* 23, 870–877 (2014). [PubMed: 24067533]
101. Zhao Z et al. Central role for PICALM in amyloid- $\beta$  blood-brain barrier transcytosis and clearance. *Nat. Neurosci* 18, 978–987 (2015). [PubMed: 26005850]
102. Aguet F et al. Genetic effects on gene expression across human tissues. *Nature* 550, 204–213 (2017). [PubMed: 29022597]
103. Miller JA et al. Transcriptional landscape of the prenatal human brain. *Nature* 508, 199–206 (2014). [PubMed: 24695229]
104. Knickmeyer RC & Ross ME Imaging and rare APOE alleles. *Neurology* 87, 558–559 (2016). [PubMed: 27412139]
105. Douaud G et al. A common brain network links development, aging, and vulnerability to disease. *Proc. Natl Acad. Sci. USA* 111, 17648–17653 (2014). [PubMed: 25422429]

106. Steele NZ et al. Fine-mapping of the human leukocyte antigen locus as a risk factor for Alzheimer disease: a case-control study. *PLoS Med* 14, 1–25 (2017).
107. Fekih Mrissa N et al. Association of HLA-DR-DQ polymorphisms with diabetes in Tunisian patients. *Transfus. Apher. Sci* 49, 200–204 (2013). [PubMed: 23402837]
108. Pugliese A et al. HLA-DRB1 15:01-DQA1 01:02-DQB1 06:02 haplotype protects autoantibody-positive relatives from type 1 diabetes throughout the stages of disease progression. *Diabetes* 65, 1109–1119 (2016). [PubMed: 26822082]
109. Patsopoulos Na et al. Fine-mapping the genetic association of the major histocompatibility complex in multiple sclerosis: HLA and non-HLA effects. *PLoS Genet* 9, e1003926 (2013). [PubMed: 24278027]
110. Schmidt H, Williamson D & Ashley-Koch A HLA-DR15 haplotype and multiple sclerosis: a HuGE review. *Am. J. Epidemiol* 165, 1097–1109 (2007). [PubMed: 17329717]
111. Karnes JH et al. Phenome-wide scanning identifies multiple diseases and disease severity phenotypes associated with HLA variants. *Sci. Transl. Med* 9, 1–14 (2017).
112. Wissemann WT et al. Association of Parkinson disease with structural and regulatory variants in the HLA region. *Am. J. Hum. Genet* 93, 984–993 (2013). [PubMed: 24183452]
113. Misra MK, Damotte V & Hollenbach JA The immunogenetics of neurological disease. *Immunology* 153, 399–414 (2018). [PubMed: 29159928]
114. Tan ZS Thyroid function and the risk of Alzheimer disease: the Framingham study. *Arch. Intern. Med* 168, 1514 (2008). [PubMed: 18663163]
115. Dendrou CA, Petersen J, Rossjohn J & Fugger L HLA variation and disease. *Nat. Rev. Immunol* 18, 325–339 (2018). [PubMed: 29292391]
116. Bulik-Sullivan B et al. An atlas of genetic correlations across human diseases and traits. *Nat. Genet* 47, 1236–1241 (2015). [PubMed: 26414676]
117. Stern Y Cognitive reserve in ageing and Alzheimer's disease. *Lancet. Neurol* 11, 1006–1012 (2012). [PubMed: 23079557]
118. Cadar D et al. Individual and area-based socioeconomic factors associated with dementia incidence in England: evidence from a 12-year follow-up in the English longitudinal study of ageing. *JAMA Psychiatry* 75, 723–732 (2018). [PubMed: 29799983]
119. Marden JR, Tchetgen Tchetgen EJ, Kawachi I & Glymour MM Contribution of socioeconomic status at 3 life-course periods to late-life memory function and decline: early and late predictors of dementia risk. *Am. J. Epidemiol* 186, 805–814 (2017). [PubMed: 28541410]
120. Østergaard SDSD et al. Associations between potentially modifiable risk factors and Alzheimer disease: a Mendelian randomization study. *PLoS Med* 12, e1001841 (2015). [PubMed: 26079503]
121. Zhu Z et al. Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat. Commun* 9, 224 (2018). [PubMed: 29335400]
122. Baumgart M et al. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement* 11, 1–9 (2015). [PubMed: 25443857]
123. Larsson SC, Traylor M, Burgess S & Markus HS Genetically-predicted adult height and Alzheimer's disease. *J. Alzheimers. Dis* 60, 691–698 (2017). [PubMed: 28869480]
124. Helzner EP et al. Contribution of vascular risk factors to the progression in Alzheimer disease. *Arch. Neurol* 66, 343–348 (2009). [PubMed: 19273753]
125. Reitz C et al. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer disease. *Arch. Neurol* 67, 1491–1497 (2010). [PubMed: 21149810]
126. Mukherjee S et al. Genetically predicted body mass index and Alzheimer's disease-related phenotypes in three large samples: Mendelian randomization analyses. *Alzheimers Dement* 11, (2015).
127. Arvanitakis Z et al. Late-life blood pressure association with cerebrovascular and Alzheimer disease pathology. *Neurology* 91, e517–e525 (2018). [PubMed: 29997190]

128. Ku ma E et al. Which risk factors causally influence dementia? A systematic review of mendelian randomization studies. *J. Alzheimers. Dis* 36, 215–221 (2018).
129. Murray ME et al. Clinicopathologic and 11C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum. *Brain* 138, 1370–1381 (2015). [PubMed: 25805643]
130. Shi Y et al. ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. *Nature* 549, 523–527 (2017). [PubMed: 28959956]
131. Brier MRMR et al. Tau and A $\beta$  imaging, CSF measures, and cognition in Alzheimer's disease. *Sci. Transl. Med* 8, 338ra66 (2016).
132. Genomes Project, C.. et al. An integrated map of genetic variation from 1,092 human genomes. *Nature* 491, 56–65 (2012). [PubMed: 23128226]
133. Howie BN, Donnelly P & Marchini J A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* 5, e1000529 (2009). [PubMed: 19543373]
134. Delaneau O, Marchini J & Zagury JF A linear complexity phasing method for thousands of genomes. *Nat. Methods* 9, 179–181 (2012).
135. Li Y, Willer CJ, Ding J, Scheet P & Abecasis GR MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes.. *Genet. Epidemiol* 34, 816–834 (2010). [PubMed: 21058334]
136. Howie B, Fuchsberger C, Stephens M, Marchini J & Abecasis GR Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat. Genet* 44, 955–959 (2012). [PubMed: 22820512]
137. Howie B, Marchini J & Stephens M Genotype imputation with thousands of genomes. *G3* 1, 457–470 (2011). [PubMed: 22384356]
138. Price AL et al. Principal components analysis corrects for stratification in genome-wide association studies. *Nat. Genet* 38, 904–909 (2006). [PubMed: 16862161]
139. Ma C et al. Recommended joint and meta-analysis strategies for case-control association testing of single low-count variants. *Genet. Epidemiol* 37, 539–550 (2013). [PubMed: 23788246]
140. Chen M-HH & Yang Q GWAF: an R package for genome-wide association analyses with family data. *Bioinformatics* 26, 580–581 (2010). [PubMed: 20040588]
141. Willer CJ, Li Y & Abecasis GR METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* 26, 2190–2191 (2010). [PubMed: 20616382]
142. Aulchenko YS, Ripke S, Isaacs A & van Duijn CM GenABEL: an R library for genome-wide association analysis. *Bioinformatics* 23, 1294–1296 (2007). [PubMed: 17384015]
143. Sudlow C et al. UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 12, 1–10 (2015).
144. Fry A et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am. J. Epidemiol* 186, 1026–1034 (2017). [PubMed: 28641372]
145. Patterson N, Price AL & Reich D Population structure and eigenanalysis. *PLoS Genet* 2, e190 (2006). [PubMed: 17194218]
146. Machiela MJ & Chanock SJ LDlink: A web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics* 31, 3555–3557 (2015). [PubMed: 26139635]
147. Zhang X et al. Synthesis of 53 tissue and cell line expression QTL datasets reveals master eQTLs. *BMC Genomics* 15, 532 (2014). [PubMed: 24973796]
148. Pruitt KD, Tatusova T, Brown GR & Maglott DR NCBI Reference Sequences (RefSeq): current status, new features and genome annotation policy. *Nucleic Acids Res* 40, D130–D135 (2012). [PubMed: 22121212]
149. Harrow J et al. GENCODE: the reference human genome annotation for The ENCODE Project. *Genome Res* 22, 1760–1774 (2012). [PubMed: 22955987]
150. Arnold M, Raffler J, Pfeuffer a, Suhre K & Kastenmuller G. SNiPA: an interactive, genetic variant-centered annotation browser. *Bioinformatics* 31, 1334–1336 (2014). [PubMed: 25431330]

151. McLaren W et al. The Ensembl variant effect predictor. *Genome Biol* 17, 122 (2016). [PubMed: 27268795]
152. Cargill M et al. Characterization of single-nucleotide polymorphisms in coding regions of human genes. *Nat. Genet* 22, 231–238 (1999). [PubMed: 10391209]
153. Ng PC & Henikoff S SIFT: Predicting amino acid changes that affect protein function. *Nucleic Acids Res* 31, 3812–3814 (2003). [PubMed: 12824425]
154. Adzhubei IA et al. A method and server for predicting damaging missense mutations. *Nat. Methods* 7, 248–249 (2010). [PubMed: 20354512]
155. Kircher M et al. A general framework for estimating the relative pathogenicity of human genetic variants. *Nat. Genet* 46, 310–315 (2014). [PubMed: 24487276]
156. Gonzalez-Perez A & Lopez-Bigas N Improving the assessment of the outcome of nonsynonymous SNVs with a consensus deleteriousness score, Condel. *Am. J. Hum. Genet* 88, 440–449 (2011). [PubMed: 21457909]
157. Samocha KE et al. Regional missense constraint improves variant deleteriousness prediction Preprint at 10.1101/148353 (2017).
158. Ionita-Laza I, McCallum K, Xu B & Buxbaum JD A spectral approach integrating functional genomic annotations for coding and noncoding variants. *Nat. Genet* 48, 214–220 (2016). [PubMed: 26727659]
159. Yeo G & Burge CB Maximum entropy modeling of short sequence motifs with applications to RNA splicing signals. *J. Comput. Biol* 11, 377–394 (2004). [PubMed: 15285897]
160. Amlie-Wolf A et al. INFERNO—INFERring the molecular mechanisms of NOncoding genetic variants. *Nucleic Acids Res* 46, 8740–8753 (2018). [PubMed: 30113658]
161. Ward LD & Kellis M HaploRegv4: systematic mining of putative causal variants, cell types, regulators and target genes for human complex traits and disease. *Nucleic Acids Res* 44, D877–D881 (2015). [PubMed: 26657631]
162. Thériault P, ElAli A & Rivest S The dynamics of monocytes and microglia in Alzheimer’s disease. *Alzheimers Res. Ther* 7, 41 (2015). [PubMed: 25878730]
163. Raj T et al. Polarization of the effects of autoimmune and neurodegenerative risk alleles in leukocytes. *Science* 344, 519–523 (2014). [PubMed: 24786080]
164. Qi T et al. Identifying gene targets for brain-related traits using transcriptomic and methylomic data from blood. *Nat. Commun* 9, 2282 (2018). [PubMed: 29891976]
165. Schramm K et al. Mapping the genetic architecture of gene regulation in whole blood. *PLoS ONE* 9, e93844 (2014). [PubMed: 24740359]
166. Giambartolomei C et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet* 10, e1004383 (2014). [PubMed: 24830394]
167. Zhu Z et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet* 48, 481–489 (2016). [PubMed: 27019110]
168. Westra H-J et al. Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nat. Genet* 45, 1238–1243 (2013). [PubMed: 24013639]
169. Ashburner M et al. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat. Genet* 25, 25–29 (2000). [PubMed: 10802651]
170. Blake JA et al. Gene ontology consortium: going forward. *Nucleic Acids Res* 43, D1049–D1056 (2015). [PubMed: 25428369]
171. Kanehisa M, Sato Y, Kawashima M, Furumichi M & Tanabe M KEGG as a reference resource for gene and protein annotation. *Nucleic Acids Res* 44, D457–D462 (2016). [PubMed: 26476454]
172. Ogata H et al. KEGG: Kyoto encyclopedia of genes and genomes. *Nucleic Acids Res* 27, 29–34 (1999). [PubMed: 9847135]
173. Fabregat A et al. The reactome pathway knowledgebase. *Nucleic Acids Res* 44, D481–D487 (2016). [PubMed: 26656494]
174. Croft D et al. Reactome: a database of reactions, pathways and biological processes. *Nucleic Acids Res* 39, D691–D697 (2011). [PubMed: 21067998]

175. Eppig JT, Blake Ja, Bult CJ, Kadin Ja & Richardson JE. The Mouse Genome Database (MGD): facilitating mouse as a model for human biology and disease. *Nucleic Acids Res* 43, D726–D736 (2014). [PubMed: 25348401]
176. O'Dushlaine C et al. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat. Neurosci* 18, 199–209 (2015). [PubMed: 25599223]
177. Szklarczyk D et al. STRINGv10: protein–protein interaction networks, integrated over the tree of life. *Nucleic Acids Res* 43, D447–D452 (2015). [PubMed: 25352553]
178. Pletscher-Frankild S, Pallejà A, Tsafou K, Binder JX & Jensen LJ. DISEASES: text mining and data integration of disease-gene associations. *Methods* 74, 83–89 (2015). [PubMed: 25484339]
179. Santos A et al. Comprehensive comparison of large-scale tissue expression datasets. *PeerJ* 3, e1054 (2015). [PubMed: 26157623]
180. Lachmann A et al. Massive mining of publicly available RNA-seq data from human and mouse. *Nat. Commun* 9, 1366 (2018). [PubMed: 29636450]
181. Kuleshov MV et al. Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. *Nucleic Acids Res* 44, W90–W97 (2016). [PubMed: 27141961]
182. Watanabe K, Taskesen E, Van Bochoven A & Posthuma D. Functional mapping and annotation of genetic associations with FUMA. *Nat. Commun* 8, 1826 (2017). [PubMed: 29184056]
183. Zheng X et al. HIBAG—HLA genotype imputation with attribute bagging. *Pharmacogenomics. J* 14, 192–200 (2014). [PubMed: 23712092]
184. R v.3.4.3 (R Development Core Team, 2017). 185.
185. haplo.stats v.1.7.9 (2018).



**Fig. 1 |. Manhattan plot of meta-analysis of stage 1, 2, and 3 results for genome-wide association with Alzheimer's disease.**

The threshold for genomewide significance ( $P < 5 \times 10^{-8}$ ) is indicated by the red line, while the blue line represents the suggestive threshold ( $P < 1 \times 10^{-5}$ ). Loci previously identified by the Lambert et al.<sup>1</sup> IGAP GWAS are shown in blue and newly associated loci are shown in red. Loci are named for the closest gene to the sentinel variant for each locus. Diamonds represent variants with the smallest  $P$  values for each genome-wide locus.

Evidence type		Exonic		Tissue expression		eQTL		Pathway		Clinical expression			
Locus	Number of genes in locus	Prioritized gene(s)	Priority score	Coding or splicing change	Rare variant burden	LOAD tissue expression	Microglia-enriched gene	AD-relevant tissue eQTL	eQTL in any tissue type	Evidence of colocalization	Enriched pathway	BRAAK stage association	DEG evidence
Novel genome-wide loci													
<i>ADAM10</i>	11	<i>ADAM10</i>	5										
<i>IQCK</i>	12	<i>IQCK</i>	6										
<i>ACE</i>	22	<i>PSMC5</i>	4										
<i>ADAMTS1</i>	3	<i>ADAMTS1</i>	4										
<i>WWOX</i>	3	<i>MAF</i> <i>WWOX</i>	2										
Known genome-wide loci													
<i>CR1</i>	12	<i>CR1</i> <i>CD55</i> <i>YOD1</i>	7 6 5										
<i>BIN1</i>	9	<i>BIN1</i>	6										
<i>INPP5D</i>	11	<i>INPP5D</i>	7										
<i>HLA-DRB1</i> <sup>a</sup>	46	<i>HLA-DRB1</i> <i>PSMC8</i> <i>C4A</i> <i>GPM3</i> <i>HLA-DPA1</i> <i>HLA-DQA1</i> <i>HLA-DRA</i> <i>HLA-DRB5</i> <i>PSMB9</i>	7 7 6 6 6 6 6 6 6										
<i>TREM2</i>	21	<i>TREM2</i>	6										
<i>CD2AP</i>	8	<i>CD2AP</i>	5										
<i>NYAP1</i>	53	<i>AGFG2</i> <i>PILRA</i> <i>EPHB4</i> <i>C7orf43</i> <i>GAL3ST4</i> <i>ZKSCAN1</i>	6 6 5 5 5 5										
<i>EPHA1</i>	23	<i>FAM131B</i>	5										
<i>PTK2B</i>	6	<i>PTK2B</i>	5										
<i>CLU</i>	8	<i>CLU</i>	6										
<i>ECHDC3</i>	8	<i>ECHDC3</i> <i>PSMC3</i> <i>ACP2</i> <i>C1QTNF4</i> <i>CELF1</i> <i>MTC2</i> <i>NDUF53</i> <i>NUP160</i> <i>SPI1</i>	4 6 5 5 5 5 5 5 5										
<i>MS4A2</i>	24	<i>MS4A6A</i> <i>MS4A7</i> <i>MS4A4A</i>	8 6 5										
<i>PICALM</i>	13	<i>EED</i> <i>PICALM</i>	5 5										
<i>SORL1</i>	4	<i>SORL1</i>	5										
<i>FERMT2</i>	9	<i>STYX</i>	5										
<i>SLC24A4</i>	10	<i>RIN3</i>	7										
<i>ABCA7</i>	50	<i>ABCA7</i> <i>HMHA1</i> <i>CNN2</i> <i>WDR18</i>	7 6 5 5										
<i>CASS4</i>	11	<i>CASS4</i>	5										

<sup>a</sup>Genes with rank 6 or above are shown only. An additional 4 genes in *HLA-DRB1* have a priority rank of 5.

**Fig. 2 |. Top prioritized genes of 400 genes located in genome-wide-significant loci.**

The criteria include: (1) deleterious coding, LOF or splicing variant in the gene; (2) significant gene-based tests; (3) expression in a tissue relevant to Alzheimer's disease (astrocytes, neurons, microglia/macrophages, oligodendrocytes); (4) a HuMi microglial-enriched gene; (5) having an eQTL effect on the gene in any tissue, in Alzheimer's disease-relevant tissue, and/ or a co-localized eQTL; (6) being involved in a biological pathway enriched in Alzheimer's disease (from the current study); (7) expression correlated with the BRAAK stage; and (8) differential expression in a 1 + Alzheimer's disease (AD) study.

Novel genome-wide loci from the current study are listed first, followed by known genome-wide loci. Each category is assigned an equal weight of 1, with the priority score equaling the sum of all categories. Colored fields indicate that the gene meets the criteria. Genes with a priority score = 4 are listed for each locus. If no gene reached a score of = 5 in a locus, then the top ranked gene(s) is listed.

**Table 1 |**

Summary of discovery Stage 1, Stage 2 and overall meta-analyses results for identified loci reaching genome-wide significance after Stages 1 and 2

Variant <i>a</i>	chr.	Position <i>b</i>	Closest gene <i>c</i>	Major/minor alleles	MAF <sup>d</sup>	OR	95% CI <sup>e</sup>	P	Stage 1 discovery ( <i>n</i> = 63,926)			Stage 2 ( <i>n</i> = 18,845)			Overall stage 1 + stage 2 ( <i>n</i> = 82,771)			
									OR	95% CI <sup>f</sup>	P	OR	95% CI <sup>f</sup>	P	OR	95% CI <sup>f</sup>	P	Meta P
<b>Previous genome-wide-significant loci still reaching significance</b>																		
rs4844610	1	207802552	<i>CRJ</i>	C/A	0.187	1.16	1.12–1.20	8.2 × 10 <sup>-16</sup>	1.20	1.13–1.27	3.8 × 10 <sup>-10</sup>	1.17	1.13–1.21	3.6 × 10 <sup>-24</sup>	0.8 × 10 <sup>-1</sup>			
rs6733839	2	127892810	<i>BIN1</i>	C/T	0.407	1.18	1.15–1.22	4.0 × 10 <sup>-28</sup>	1.23	1.18–1.29	2.0 × 10 <sup>-18</sup>	1.20	1.17–1.23	2.1 × 10 <sup>-44</sup>	15, 2 × 10 <sup>-1</sup>			
rs10933431	2	233981912	<i>INPP5D</i>	C/G	0.223	0.90	0.87–0.94	2.6 × 10 <sup>-7</sup>	0.92	0.87–0.97	3.2 × 10 <sup>-3</sup>	0.91	0.88–0.94	3.4 × 10 <sup>-9</sup>	0, 8 × 10 <sup>-1</sup>			
rs9271058	6	32575406	<i>HLA-DRBI</i>	T/A	0.270	1.10	1.06–1.14	5.1 × 10 <sup>-8</sup>	1.11	1.06–1.17	5.7 × 10 <sup>-5</sup>	1.10	1.07–1.13	1.4 × 10 <sup>-11</sup>	10, 3 × 10 <sup>-1</sup>			
rs75932628	6	41129252	<i>TREM2</i>	C/T	0.008	2.01	1.65–2.44	2.9 × 10 <sup>-12</sup>	2.50	1.56–4.00	1.5 × 10 <sup>-4</sup>	2.08	1.73–2.49	2.7 × 10 <sup>-15</sup>	0, 6 × 10 <sup>-1</sup>			
rs9473117	6	47431284	<i>CZDAP</i>	A/C	0.280	1.09	1.05–1.12	2.3 × 10 <sup>-7</sup>	1.11	1.05–1.16	1.0 × 10 <sup>-4</sup>	1.09	1.06–1.12	1.2 × 10 <sup>-10</sup>	0, 6 × 10 <sup>-1</sup>			
rs12539172	7	100091795	<i>NYAP1g</i>	C/T	0.303	0.93	0.91–0.96	2.1 × 10 <sup>-5</sup>	0.89	0.84–0.93	2.1 × 10 <sup>-6</sup>	0.92	0.90–0.95	9.3 × 10 <sup>-10</sup>	0, 8 × 10 <sup>-1</sup>			
rs10808026	7	143099133	<i>EPHA1</i>	C/A	0.199	0.90	0.87–0.94	3.1 × 10 <sup>-8</sup>	0.91	0.86–0.96	1.1 × 10 <sup>-3</sup>	0.90	0.88–0.93	1.3 × 10 <sup>-10</sup>	0, 5 × 10 <sup>-1</sup>			
rs73223431	8	27219987	<i>PTK2B</i>	C/T	0.367	1.10	1.07–1.13	8.3 × 10 <sup>-10</sup>	1.11	1.06–1.16	1.5 × 10 <sup>-5</sup>	1.10	1.07–1.13	6.3 × 10 <sup>-14</sup>	0, 6 × 10 <sup>-1</sup>			
rs9331896	8	27467686	<i>CLU</i>	T/C	0.387	0.88	0.85–0.91	3.6 × 10 <sup>-16</sup>	0.87	0.83–0.91	1.7 × 10 <sup>-9</sup>	0.88	0.85–0.90	4.6 × 10 <sup>-24</sup>	3, 4 × 10 <sup>-1</sup>			
rs3740688	11	47380340	<i>SPIlh</i>	T/G	0.448	0.91	0.89–0.94	9.7 × 10 <sup>-11</sup>	0.93	0.88–0.97	1.2 × 10 <sup>-3</sup>	0.92	0.89–0.94	5.4 × 10 <sup>-13</sup>	4, 4 × 10 <sup>-1</sup>			
rs7933202	11	59936926	<i>M64A2</i>	A/C	0.391	0.89	0.86–0.92	2.2 × 10 <sup>-15</sup>	0.90	0.86–0.95	1.6 × 10 <sup>-5</sup>	0.89	0.87–0.92	1.9 × 10 <sup>-19</sup>	27, 5 × 10 <sup>-2</sup>			
rs3851179	11	85868840	<i>PICALM</i>	C/T	0.356	0.89	0.86–0.91	5.8 × 10 <sup>-16</sup>	0.85	0.81–0.89	6.1 × 10 <sup>-11</sup>	0.88	0.86–0.90	6.0 × 10 <sup>-25</sup>	0, 8 × 10 <sup>-1</sup>			
rs11218343	11	121435587	<i>SCRL1</i>	T/C	0.040	0.81	0.76–0.88	2.7 × 10 <sup>-8</sup>	0.77	0.68–0.87	1.8 × 10 <sup>-5</sup>	0.80	0.75–0.85	2.9 × 10 <sup>-12</sup>	7, 3 × 10 <sup>-1</sup>			
rs1725924	14	53391680	<i>FERMT2</i>	A/G	0.093	1.13	1.08–1.19	6.6 × 10 <sup>-7</sup>	1.15	1.06–1.25	5.0 × 10 <sup>-4</sup>	1.14	1.09–1.18	1.4 × 10 <sup>-9</sup>	8, 3 × 10 <sup>-1</sup>			
rs12881735	14	92932828	<i>SLC24A4</i>	T/C	0.221	0.92	0.88–0.95	4.9 × 10 <sup>-7</sup>	0.92	0.87–0.97	4.3 × 10 <sup>-3</sup>	0.92	0.89–0.94	7.4 × 10 <sup>-9</sup>	0, 6 × 10 <sup>-1</sup>			
rs3752246	19	1056492	<i>ABCA7</i>	C/G	0.182	1.13	1.09–1.18	6.6 × 10 <sup>-10</sup>	1.18	1.11–1.25	4.7 × 10 <sup>-8</sup>	1.15	1.11–1.18	3.1 × 10 <sup>-16</sup>	0, 5 × 10 <sup>-1</sup>			
rs429558	19	454111941	<i>APOE</i>	T/C	0.216	3.32	3.20–3.45	1.2 × 10 <sup>-881</sup>	<i>APOE</i> region not carried forward to replication stage									
rs6024870	20	54997568	<i>CASS4</i>	G/A	0.088	0.88	0.84–0.93	1.1 × 10 <sup>-6</sup>	0.90	0.82–0.97	9.0 × 10 <sup>-3</sup>	0.88	0.85–0.92	3.5 × 10 <sup>-8</sup>	0, 9 × 10 <sup>-1</sup>			
<b>New genome-wide-significant loci reaching significance</b>																		
rs7920721	10	11720308	<i>EHHD3</i>	A/G	0.389	1.08	1.05–1.11	1.9 × 10 <sup>-7</sup>	1.07	1.02–1.12	3.2 × 10 <sup>-3</sup>	1.08	1.05–1.11	2.3 × 10 <sup>-9</sup>	0, 8 × 10 <sup>-1</sup>			
rs138190086	17	61538148	<i>ACE</i>	G/A	0.020	1.29	1.15–1.44	7.5 × 10 <sup>-6</sup>	1.41	1.18–1.69	1.8 × 10 <sup>-4</sup>	1.32	1.20–1.45	7.5 × 10 <sup>-9</sup>	0, 9 × 10 <sup>-1</sup>			
<b>Previous genome-wide-significant loci not reaching significance</b>																		

Variant <sup>a</sup>	chr.	Position <sup>b</sup>	Closest gene <sup>c</sup>	Major/minor alleles	Stage 1 discovery ( <i>n</i> = 63,926)			Stage 2 ( <i>n</i> = 18,845)			Overall stage 1 + stage 2 ( <i>n</i> = 82,771)			
					MAF <sup>d</sup>	OR	95% CI <sup>e</sup>	P	OR	95% CI <sup>e</sup>	P	OR	95% CI <sup>e</sup>	
rs190982	5	88223420	<i>MEF2C</i>	A/G	0.390	0.95	0.92–0.97	$2.8 \times 10^{-4}$	0.93	0.89–0.98	$2.7 \times 10^{-3}$	0.94	0.92–0.97	$2.8 \times 10^{-6}$
rs4723711	7	37844263	<i>NME8</i>	A/T	0.356	0.95	0.92–0.98	$2.7 \times 10^{-4}$	0.91	0.87–0.95	$1.0 \times 10^{-4}$	0.94	0.91–0.96	$2.8 \times 10^{-7}$

<sup>a</sup>Variants showing the best level of association after meta-analysis of Stages 1 and 2.<sup>b</sup>Build 37, assembly hg19.<sup>c</sup>Based on position of top SNP in reference to the RefSeq assembly.<sup>d</sup>Average in the discovery sample.<sup>e</sup>Calculated with respect to the minor allele.<sup>f</sup>Cochran's Q test<sup>g</sup>Previously the *ZCWPW1* locus.<sup>h</sup>Previously the *CELF1* locus. Chr., chromosome; CI, confidence interval; OR, odds ratio;  $\hat{\rho}^2$ , heterogeneity estimate.

**Table 2 |**

Summary of discovery Stage 1, Stage 2, Stage 3 (A and B), and overall meta-analysis results of potential novel loci

Stage 3A							Stage 1 + 2 ( <i>n</i> = 82,771)							Stage 3A ( <i>n</i> = 11,666)							Overall ( <i>n</i> = 94,437)	
SNP <sup>a</sup>	Chr.	Position <sup>b</sup>	Closest gene <sup>c</sup>	Major/ minor allele	MAF <sup>e</sup>	OR	95% CI <sup>f</sup>	P	OR	95% CI <sup>f</sup>	P	OR	95% CI <sup>f</sup>	P	OR	95% CI <sup>f</sup>	P	OR	95% CI <sup>f</sup>	P	Meta P	
rs4735340	8	95976251	<i>NDUFAF6</i>	T/A	0.476	0.94	0.92–0.96	3.4 × 10 <sup>-7</sup>	0.92	0.83–1.02	9.7 × 10 <sup>-2</sup>	0.94	0.92–0.96	9.2 × 10 <sup>-8</sup>								
rs7920721g	10	11720308	<i>EHDC3</i>	A/G	0.390	1.08	1.05–1.11	2.3 × 10 <sup>-9</sup>	1.11	1.04–1.18	1.5 × 10 <sup>-3</sup>	1.08	1.06–1.11	1.8 × 10 <sup>-11</sup>								
rs7295246	12	43967677	<i>ADAMTS20</i>	T/G	0.413	1.07	1.04–1.09	2.7 × 10 <sup>-7</sup>	1.02	0.96–1.09	4.5 × 10 <sup>-1</sup>	1.06	1.04–1.08	3.9 × 10 <sup>-7</sup>								
rs10467994	15	51008687	<i>SPPL2A</i>	T/C	0.333	0.94	0.91–0.96	3.9 × 10 <sup>-7</sup>	0.97	0.87–1.08	6.2 × 10 <sup>-1</sup>	0.94	0.92–0.96	4.3 × 10 <sup>-7</sup>								
rs593742	15	59045774	<i>ADAM10</i>	A/G	0.295	0.93	0.91–0.96	1.3 × 10 <sup>-7</sup>	0.91	0.85–0.98	1.5 × 10 <sup>-2</sup>	0.93	0.91–0.95	6.8 × 10 <sup>-9</sup>								
rs7185636	16	19808163	<i>IQCK</i>	T/C	0.180	0.92	0.89–0.95	8.4 × 10 <sup>-8</sup>	0.94	0.86–1.01	1.1 × 10 <sup>-1</sup>	0.92	0.89–0.95	2.4 × 10 <sup>-8</sup>								
rs2632516	17	56409089	<i>MIR142/TSPoAP1-AS1/d</i>	G/C	0.440	0.94	0.92–0.96	2.3 × 10 <sup>-7</sup>	0.91	0.82–1.01	7.5 × 10 <sup>-2</sup>	0.94	0.91–0.96	5.3 × 10 <sup>-8</sup>								
rs138190086	17	61558148	<i>ACE</i>	G/A	0.020	1.32	1.20–1.45	7.5 × 10 <sup>-9</sup>	1.17	0.92–1.48	2.1 × 10 <sup>-1</sup>	1.30	1.19–1.42	5.3 × 10 <sup>-9</sup>								
rs2830500	21	28156856	<i>ADAMTS1</i>	C/A	0.308	0.93	0.91–0.96	7.4 × 10 <sup>-8</sup>	0.95	0.89–1.02	1.3 × 10 <sup>-1</sup>	0.93	0.91–0.96	2.6 × 10 <sup>-8</sup>								
<b>Stage 3B</b>							<b>Stage 1 (<i>n</i> = 63,926)</b>							<b>Stage 3B (<i>n</i> = 30,511)<sup>h</sup></b>							<b>Overall (<i>n</i> = 94,437)<sup>h</sup></b>	
SNP <sup>a</sup>	Chr.	Position <sup>b</sup>	Closest gene <sup>c</sup>	Major/ minor allele	MAF <sup>e</sup>	OR	95% CI <sup>f</sup>	P	OR	95% CI <sup>f</sup>	P	OR	95% CI <sup>f</sup>	P	OR	95% CI <sup>f</sup>	P	OR	95% CI <sup>f</sup>	P	Meta P	
rs71618613	5	29005985	<i>SUCLG2P4</i>	A/C	0.010	0.68	0.57–0.80	9.8 × 10 <sup>-6</sup>	0.76	0.63–0.93	6.8 × 10 <sup>-3</sup>	0.71	0.63–0.81	3.3 × 10 <sup>-7</sup>								
rs35868327	5	52665230	<i>FSTTAA</i>	A/C	0.013	0.69	0.59–0.80	7.8 × 10 <sup>-7</sup>	0.58	0.29–1.17	1.2 × 10 <sup>-1</sup>	0.68	0.59–0.79	2.6 × 10 <sup>-7</sup>								
rs114812713	6	41034000	<i>ORDI</i>	G/C	0.030	1.35	1.24–1.47	4.5 × 10 <sup>-12</sup>	1.23	1.06–1.42	7.2 × 10 <sup>-3</sup>	1.32	1.22–1.42	2.1 × 10 <sup>-13</sup>								
rs62039712	16	79355857	<i>WWOX</i>	G/A	0.116	1.17	1.10–1.23	1.2 × 10 <sup>-7</sup>	1.14	0.96–1.36	1.3 × 10 <sup>-1</sup>	1.16	1.10–1.23	3.7 × 10 <sup>-8</sup>								

Novel loci were defined as loci not reported in Lambert et al.<sup>1</sup> with (1) a Stage 1 + 2 meta *P* < 5 × 10<sup>-7</sup> (nine variants after excluding TREM2) (Stage 3A) or (2) a MAF < 0.05 and Stage 1 *P* < 1 × 10<sup>-5</sup> or MAF < 0.05 and Stage 1 *P* < 5 × 10<sup>-6</sup> for genome regions not covered on the Stage 2 custom array (Stage 3B).

<sup>2</sup>SNPs showing the best level of association after meta-analysis of Stages 1, 2 and 3.

<sup>b</sup>Build 37, assembly hg19.

<sup>c</sup>Based on position of top SNP in reference to the RefSeq assembly.

<sup>d</sup>Variant is annotated to both gene features.

<sup>e</sup>Average in the discovery sample.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

*f*Calculated with respect to the minor allele.

*g*Recently identified as a LOD locus in two separate 2017 studies.

*h*Sample sizes<sup>a</sup> for these loci are smaller (overall  $n = 89,769$  for *SUCLG2P4*,  $n = 65,230$  for *FST*, and  $n = 69,888$  for *WWY*).

**Table 3 |**

Significant pathways ( $q$  value  $< 0.05$ ) from MAGMA pathway analysis for common and rare variant subsets

Pathway	No. of genes in the pathway in the dataset	Common variant $P^a$	Common variant $q$ value	Rare variant $P^a$	Rare variant $q$ value	Pathway description
GO:65005	20	$1.4 \times 10^{-7a}$	$9.5 \times 10^{-4}$	$6.7 \times 10^{-2}$	$8.4 \times 10^{-1}$	Protein–lipid complex assembly
GO:1902003	10	$4.5 \times 10^{-7a}$	$1.4 \times 10^{-3}$	$4.9 \times 10^{-2}$	$8.4 \times 10^{-1}$	Regulation of A $\beta$ formation
GO:32994	39	$1.1 \times 10^{-6a}$	$2.5 \times 10^{-3}$	$1.7 \times 10^{-2}$	$8.1 \times 10^{-1}$	Protein–lipid complex
GO:1902991	12	$3.5 \times 10^{-6a}$	$5.8 \times 10^{-3}$	$5.6 \times 10^{-2}$	$8.4 \times 10^{-1}$	Regulation of amyloid precursor protein catabolic process
GO:43691	17	$5.5 \times 10^{-6a}$	$6.7 \times 10^{-3}$	$3.0 \times 10^{-2}$	$8.1 \times 10^{-1}$	Reverse cholesterol transport
GO:71825	35	$6.1 \times 10^{-6a}$	$6.7 \times 10^{-3}$	$1.2 \times 10^{-1}$	$8.4 \times 10^{-1}$	Protein–lipid complex subunit organization
GO:34377	18	$1.6 \times 10^{-5a}$	$1.5 \times 10^{-2}$	$1.8 \times 10^{-1}$	$8.4 \times 10^{-1}$	Plasma lipoprotein particle assembly
GO:48156	10	$3.1 \times 10^{-5a}$	$2.6 \times 10^{-2}$	$7.7 \times 10^{-1}$	$8.5 \times 10^{-1}$	Tau protein binding
GO:2253	382	$6.3 \times 10^{-5a}$	$4.6 \times 10^{-2}$	$2.0 \times 10^{-1}$	$8.4 \times 10^{-1}$	Activation of immune response

<sup>a</sup>Significant after FDR correction ( $q$  value  $< 0.05$ ).

**Table 4 |**

Top results of pathway analysis of the A $\beta$ -centered biological network from Campion et al.<sup>64</sup> (see Supplementary Table 12 for full results)

Category	Subcategory	No. of genes	Common variant <i>P</i> 0 kb	Common variant <i>P</i> 35–10 kb	Rare variant <i>P</i> 0 kb	Rare variant <i>P</i> 35–10 kb
A $\beta$ -centered biological network (all genes)	—	331	2.2 × 10 <sup>-4</sup> <sup>a</sup>	1.5 × 10 <sup>-4</sup> <sup>a</sup>	8.2 × 10 <sup>-1</sup>	5.1 × 10 <sup>-1</sup>
Clearance and degradation of A $\beta$	—	74	2.1 × 10 <sup>-4</sup> <sup>a</sup>	3.2 × 10 <sup>-3</sup>	3.1 × 10 <sup>-1</sup>	5.1 × 10 <sup>-1</sup>
Clearance and degradation of A $\beta$	Microglia	47	2.2 × 10 <sup>-4</sup> <sup>a</sup>	1.8 × 10 <sup>-2</sup>	2.4 × 10 <sup>-1</sup>	6.8 × 10 <sup>-1</sup>
Aggregation of A $\beta$	—	35	7.0 × 10 <sup>-4</sup> <sup>a</sup>	9.9 × 10 <sup>-3</sup>	9.0 × 10 <sup>-2</sup>	1.6 × 10 <sup>-1</sup>
Aggregation of A $\beta$	Miscellaneous	21	1.0 × 10 <sup>-3</sup> <sup>a</sup>	3.3 × 10 <sup>-2</sup>	9.5 × 10 <sup>-2</sup>	1.9 × 10 <sup>-1</sup>
APP processing and trafficking	Clathrin/caveolin-dependent endocytosis	10	1.1 × 10 <sup>-3</sup>	1.1 × 10 <sup>-2</sup>	3.6 × 10 <sup>-1</sup>	1.8 × 10 <sup>-1</sup>
Mediator of A $\beta$ toxicity	—	51	3.8 × 10 <sup>-2</sup>	4.6 × 10 <sup>-2</sup>	5.8 × 10 <sup>-1</sup>	5.7 × 10 <sup>-1</sup>
Mediator of A $\beta$ toxicity	Calcium homeostasis	6	6.9 × 10 <sup>-2</sup>	1.2 × 10 <sup>-1</sup>	3.9 × 10 <sup>-1</sup>	2.5 × 10 <sup>-1</sup>
Mediator of A $\beta$ toxicity	Miscellaneous	3	7.6 × 10 <sup>-2</sup>	2.3 × 10 <sup>-2</sup>	9.7 × 10 <sup>-1</sup>	7.6 × 10 <sup>-1</sup>
Clearance and degradation of A $\beta$	Enzymatic degradation of A $\beta$	15	7.7 × 10 <sup>-2</sup>	2.6 × 10 <sup>-2</sup>	6.1 × 10 <sup>-1</sup>	2.9 × 10 <sup>-1</sup>
Mediator of A $\beta$ toxicity	Tau toxicity	20	9.0 × 10 <sup>-2</sup>	3.4 × 10 <sup>-1</sup>	7.1 × 10 <sup>-1</sup>	6.8 × 10 <sup>-1</sup>
Aggregation of A $\beta$	Chaperone	9	1.5 × 10 <sup>-1</sup>	3.0 × 10 <sup>-1</sup>	1.9 × 10 <sup>-1</sup>	1.1 × 10 <sup>-2</sup>

<sup>a</sup>Significant after Bonferroni correction for 33 pathway sets tested.