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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 antidementia 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 Posiphen, 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), Neurotrope 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 Aβ, tau, immunity and lipid processing

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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 Merch, 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 antidementia 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, Axon Neuroscience, 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 antidementia 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

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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 canbe 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 Aβ 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)[1]. These signals, combined with 'subthreshold' common variant associations, account for ~31% of the genetic variance of LOAD[2], leaving the majority of genetic risk uncharacterized[3]. 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 ($P \leq 5 \times 10^{-8}$) (Table 1), all of which are previously described[1,4–11]. Genomic inflation factors (λ) were slightly inflated (λ median = 1.05; λ regression = 1.09; see Supplementary Figure 2 for a quantile–quantile (QQ) plot); however, univariate linkage disequilibrium score (LDSC) regression[12,13] 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.[1] (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 ($P \leq 5 \times 10^{-8}$) (Table 1 and Fig. 1), 18 of which were previously reported as genome-wide significant in Lambert et al.[1]. Three other signals were not initially described in the initial IGAP GWAS: the rare R47H *TREM2* coding variant previously reported by others[7,8,14]; *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[15–17], 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/ TSPOAP1-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[18–22] but were not replicated in some subsequent studies[23–25]. A recent GWAS using family history of Alzheimer's disease or dementia as a proxy[26] 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/TSPOAP1-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[27] conditional analysis of the genome-wide loci indicates that *TREM2* and three other loci (*BIN1*, *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[28,29], 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[14]. 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[30] and differential expression in Alzheimer's disease versus control brains[31]); (4) evaluation of transcriptomic expression in Alzheimer's disease–relevant tissues[32–34]; and (5) gene cluster/pathway analyses. For the 24 signals reported here, other evidence indicates that *APOE*[35,36], *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[47]. 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 ±500 kilobases (kb) of the sentinel variant linkage disequilibrium (LD) regions ($r^2 \geq 0.5$) 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[48], 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[49] ($n = 5{,}740$ 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[56] and HaploReg[57], but restricting to Alzheimer's disease–relevant tissues (via Ensembl Regulatory Build[58] and GWAS4D[59]) 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 *SLTM* (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[31]. 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[30] (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 ($P = 4.1 \times 10^{-5}$)[34]. 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[8,14,60,] 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[61]) separately for common (MAF > 0.01) and rare variants (MAF < 0.01). For common variants, we detected four function clusters including (1) APP metabolism/Aβ formation (regulation of Aβ 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

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, whch may play a role in tauopathies[62,63], 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 Aβ 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 Aβ pathways showed nominal rare-variant driven associations ($P < 0.05$) with LOAD.

To further explore the APP/Aβ pathway enrichment, we analyzed a comprehensive set of 335 APP metabolism genes[64] 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 Aβ', and 'aggregation of Aβ', along with its subcategory 'microglia', the latter supporting microglial cells suspected role in response to Aβ in LOAD[65]. Nominal enrichment for risk from rare variants was found for the pathway 'aggregation of Aβ: 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 Fritsche et al.[66] (Fig. 2 and Supplementary Table 24). *ADAM10* was the top ranked gene of the 11 genes within the *ADAM10* locus. ADAM10, the most important α-secretase in the brain, is a component of the non-amyloidogenic pathway of APP metabolism[67] and sheds TREM2 (ref. [68]), an innate immunity receptor expressed selectively in microglia. Overexpression of ADAM10 in mouse models can halt Aβ production and subsequent aggregation[69]. In addition, two rare *ADAM10* alterations segregating with disease in LOAD families increased Aβ plaque load in 'Alzheimer-like' mice, with diminished α-secretase activity from the alterations probably the causal mechanism[19,44]. For the *IQCK* signal, which is also an obesity locus[70,71], *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[72,73] and inflammatory signaling in obesity[74]. Of the 22 genes in the *ACE* locus, *PSMC5*, a key regulator of major histocompatibility complex (MHC)[75,76], has a top score of 4, while *DDX42*, *MAP3K3*, an important regulator of macrophages and innate immunity[77,78], 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[20,22,79,] including a strong association in the Wadi Ara, an Israeli Arab community with high risk of Alzheimer's disease[21]. However, these studies yielded inconsistent results[23], 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 Aβ load and Alzheimer's disease severity[80]. Furthermore, cerebrospinal fluid (CSF) levels of the angiotensin-converting

enzyme (ACE) are associated with Aβ levels[81] and LOAD risk[82], and studies show ACE can inhibit Aβ toxicity and aggregation[83]. Finally, angiotensin II, a product of ACE function, mediates a number of neuropathological processes in Alzheimer's disease[84] and is now a target for intervention in phase II clinical trials of Alzheimer's disease[85]. 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[86], and it is a potential neuroprotective gene[87–89] or a neuroinflammatory gene important to microglial response[90]. Finally, *WWOX* and *MAF*, which surround an intergenic signal in an obesity associated locus[91], were both prioritized for the *WWOX* locus, with *MAF*, another important regulator of macrophages[92,93], being highly expressed in microglia in the Brain RNA-seq database, and *WWOX*, a high-density-lipoprotein cholesterol and triglyceride–associated gene[94,95], being expressed most highly in astrocytes and neurons. WWOX has been implicated in several neurological phenotypes[96]; in addition, it binds tau and may play a critical role in regulating tau hyper-phosphorylation, neurofibrillary formation and Aβ aggregation[28,29]. Intriguingly, treatment of mice with its binding partner restores memory deficits[97], 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*)[98–101]. 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[102] 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[103], 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[104,105] (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[106]. 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[107] and more recently in a large ADGC analysis[106]. Intriguingly, the *DR15* haplotype and its component alleles also associate with protection against diabetes[108], a high risk for multiple sclerosis[109,110,] 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[111], including neurological diseases (for example, Parkinson's disease[112,113]) and diseases with risk factors for Alzheimer's disease (for example, hyperthyroidism[114]), pointing to potential shared and/or interacting mechanisms and co-morbidities, a common paradigm in the MHC locus[115]. 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[12,116] (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[26], 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[117]. 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[118,119]. 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[120]. 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[116,120–127], either through suggestive or significant genetic or epidemiological associations (see Kuzma et al.[128] 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[129–131] 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)[132] using SHAPEIT/IMPUTE2[133,134] or MaCH/Minimac[135,136] software (Supplementary Table 3). All reference population haplotypes were used for the imputation, as this method improves accuracy of imputation for low-frequency variants[137]. 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[138]. 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[139]. Family datasets were tested using GWAF[140], 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[141] 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 (λ) in the GenABEL package[142]. In addition, we performed LDSC regression via LD Hub v.1.9.0 (refs. [12,13]) 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)[116] between LOAD and a wide range of other disorders, diseases and human traits, including 518 UK BioBank traits[143]. 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[144], 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[27] 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; 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 MAF < 0.05 and $P < 1 \times 10^{-5}$ or variants with MAF ≥ 0.05 and $P < 5 \times 10^{-6}$ in novel loci not covered in the 2013 iSelect genotyping[1] (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[145], 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 1×10^{-6} or a *P* value for missingness between cases and controls lower than 1×10^{-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[141] 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[146]. 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 ($r^2 \geq 0.5$) with the top associated variant from the Stage 2 meta-analysis for each region ±500 kb of the ends of the LD blocks (as eQTL controlled genes are typically less than 500 kb from their controlling variant[147]) were input into the UCSC genome browser's 'Table Browser' for RefSeq[148] and GENCODEv24lift37[149] 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[150] 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[151] for annotation of the set of sentinel variants and their proxies. We used BLOSUM62 (ref. [152]), SIFT[153], Polyphen-2 (ref. [154]), CADD[155], Condel[156], MPC[157] and Eigen[158] 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[159] 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.[49] 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 ($r^2 \geq 0.5$) using INFERNO[160] LD expansion (n = 1,339) and variants with suggestive significance ($P < 10^{-5}$) and LD ($r^2 \geq 0.5$) 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[56], HaploReg v.4.1 (refs. [57,161]), GWAS4D[59], and the Ensembl Regulatory Build[58]. We used the ChromHMM (core 15-state model) as 'source epigenomes' for the HaploReg analyses. We used immune (Monocytes-CD14$^+$, GM12878 lymphoblastoid, HSMM myoblast) and brain (NH-A astroctyes) 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[14,45,162,163]. 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[164]; 51–70% for monocytes and lymphoblastoid cell lines[165]) 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[166] via INFERNO and (2) Summary Mendelian Randomization (SMR)-Heidi analysis[167]. 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[168] 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[31], brain tissue expression from the Brain RNA-seq Database[32,33] (see URLs), and the HuMi_Aged gene set[34], 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.[30] study of 1,647 post-mortem brain tissues from LOAD patients and non-demented subjects.

Pathway analysis.

Pathway analyses were performed with MAGMA[61], 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[169,170,] KEGG[171,172,] REACTOME[173,174], BIOCARTA, and MGI[175] 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[176]. 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.[64] 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[177], and Jensen Diseases[178], Jensen Tissues[179], dbGAP gene sets, and the ARCHS4[180] resource via the EnrichR[181] tool. We evaluated both the 400 genes set list and a list of 53 genes with priority score ≥ 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[182]. These analyses were performed in order to assess whether our 53 prioritized genes were significantly differentially expressed in certain GTEx v.7 (ref. [102]; 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)[103]. FUMA defines DEG sets by calculating a two-sided *t*-test per tissue versus all remaining tissue types or developmental periods. Genes with a Bonferonni-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 Bonferonni-corrected $P \leq 0.05$.

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. [183]) 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[184]. 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[185] 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[141]. 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.

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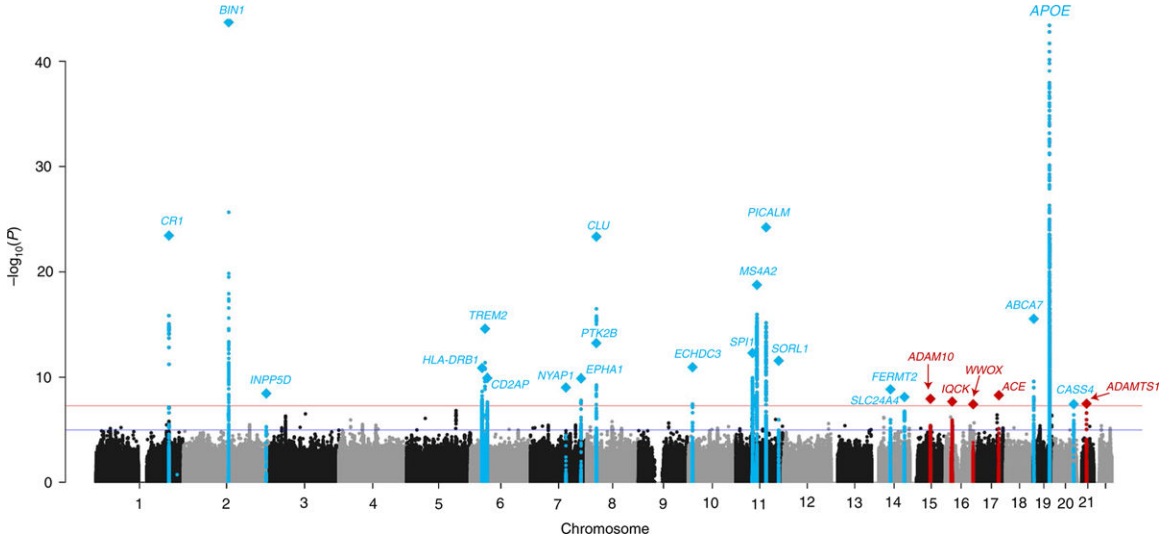
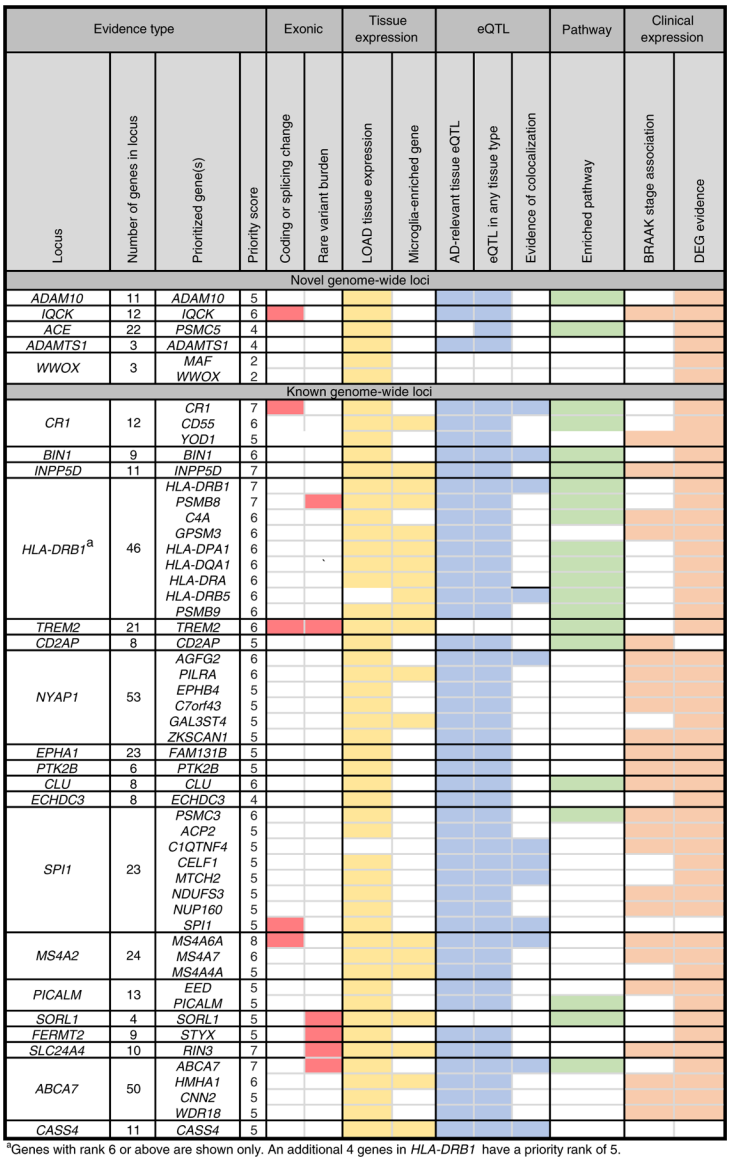


Fig. 1 |. Manhattan plot of meta-analysis of stage 1, 2, and 3 results for genome-wide association with Alzheimer's disease.

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.[1] 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.



[a]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

						Stage 1 discovery (*n* = 63,926)			Stage 2 (*n* = 18,845)			Overall stage 1 + stage 2 (*n* = 82,771)			
Variant [a]	**chr.**	**Position** [b]	**Closest gene** [c]	**Major/ minor alleles**	**MAF** [d]	**OR**	**95% CI** [e]	***P***	**OR**	**95% CI** [e]	***P***	**OR**	**95% CI** [e]	**Meta *P***	I^2 **(%),** P^f
Previous genome-wide-significant loci still reaching significance															
rs4844610	1	207802552	*CR1*	C/A	0.187	1.16	1.12–1.20	8.2×10^{-16}	1.20	1.13–1.27	3.8×10^{-10}	1.17	1.13–1.21	3.6×10^{-24}	$0, 8 \times 10^{-1}$
rs6733839	2	127892810	*BIN1*	C/T	0.407	1.18	1.15–1.22	4.0×10^{-28}	1.23	1.18–1.29	2.0×10^{-18}	1.20	1.17–1.23	2.1×10^{-44}	$15, 2 \times 10^{-1}$
rs10933431	2	233981912	*INPP5D*	C/G	0.223	0.90	0.87–0.94	2.6×10^{-7}	0.92	0.87–0.97	3.2×10^{-3}	0.91	0.88–0.94	3.4×10^{-9}	$0, 8 \times 10^{-1}$
rs9271058	6	32575406	*HLA-DRB1*	T/A	0.270	1.10	1.06–1.14	5.1×10^{-8}	1.11	1.06–1.17	5.7×10^{-5}	1.10	1.07–1.13	1.4×10^{-11}	$10, 3 \times 10^{-1}$
rs75932628	6	41129252	*TREM2*	C/T	0.008	2.01	1.65–2.44	2.9×10^{-12}	2.50	1.56–4.00	1.5×10^{-4}	2.08	1.73–2.49	2.7×10^{-15}	$0, 6 \times 10^{-1}$
rs9473117	6	47431284	*CD2AP*	A/C	0.280	1.09	1.05–1.12	2.3×10^{-7}	1.11	1.05–1.16	1.0×10^{-4}	1.09	1.06–1.12	1.2×10^{-10}	$0, 6 \times 10^{-1}$
rs12539172	7	100091795	*NYAP1g*	C/T	0.303	0.93	0.91–0.96	2.1×10^{-5}	0.89	0.84–0.93	2.1×10^{-6}	0.92	0.90–0.95	9.3×10^{-10}	$0, 8 \times 10^{-1}$
rs10808026	7	143099133	*EPHA1*	C/A	0.199	0.90	0.87–0.94	3.1×10^{-8}	0.91	0.86–0.96	1.1×10^{-3}	0.90	0.88–0.93	1.3×10^{-10}	$0, 5 \times 10^{-1}$
rs73223431	8	27219987	*PTK2B*	C/T	0.367	1.10	1.07–1.13	8.3×10^{-10}	1.11	1.06–1.16	1.5×10^{-5}	1.10	1.07–1.13	6.3×10^{-14}	$0, 6 \times 10^{-1}$
rs9331896	8	27467686	*CLU*	T/C	0.387	0.88	0.85–0.91	3.6×10^{-16}	0.87	0.83–0.91	1.7×10^{-9}	0.88	0.85–0.90	4.6×10^{-24}	$3, 4 \times 10^{-1}$
rs3740688	11	47380340	*SPI1h*	T/G	0.448	0.91	0.89–0.94	9.7×10^{-11}	0.93	0.88–0.97	1.2×10^{-3}	0.92	0.89–0.94	5.4×10^{-13}	$4, 4 \times 10^{-1}$
rs7933202	11	59936926	*MS4A2*	A/C	0.391	0.89	0.86–0.92	2.2×10^{-15}	0.90	0.86–0.95	1.6×10^{-5}	0.89	0.87–0.92	1.9×10^{-19}	$27, 5 \times 10^{-2}$
rs3851179	11	85868640	*PICALM*	C/T	0.356	0.89	0.86–0.91	5.8×10^{-16}	0.85	0.81–0.89	6.1×10^{-11}	0.88	0.86–0.90	6.0×10^{-25}	$0, 8 \times 10^{-1}$
rs11218343	11	121435587	*SORL1*	T/C	0.040	0.81	0.76–0.88	2.7×10^{-8}	0.77	0.68–0.87	1.8×10^{-5}	0.80	0.75–0.85	2.9×10^{-12}	$7, 3 \times 10^{-1}$
rs17125924	14	53391680	*FERMT2*	A/G	0.093	1.13	1.08–1.19	6.6×10^{-7}	1.15	1.06–1.25	5.0×10^{-4}	1.14	1.09–1.18	1.4×10^{-9}	$8, 3 \times 10^{-1}$
rs12881735	14	92932828	*SLC24A4*	T/C	0.221	0.92	0.88–0.95	4.9×10^{-7}	0.92	0.87–0.97	4.3×10^{-3}	0.92	0.89–0.94	$7.4\times 10_{-9}$	$0, 6 \times 10^{-1}$
rs3752246	19	1056492	*ABCA7*	C/G	0.182	1.13	1.09–1.18	6.6×10^{-10}	1.18	1.11–1.25	4.7×10^{-8}	1.15	1.11–1.18	3.1×10^{-16}	$0, 5 \times 10^{-1}$
rs429358	19	45411941	*APOE*	T/C	0.216	3.32	3.20–3.45	1.2×10^{-881}	*APOE* region not carried forward to replication stage						
rs6024870	20	54997568	*CASS4*	G/A	0.088	0.88	0.84–0.93	1.1×10^{-6}	0.90	0.82–0.97	9.0×10^{-3}	0.88	0.85–0.92	3.5×10^{-8}	$0, 9 \times 10^{-1}$
New genome-wide-significant loci reaching significance															
rs7920721	10	11720308	*ECHDC3*	A/G	0.389	1.08	1.05–1.11	1.9×10^{-7}	1.07	1.02–1.12	3.2×10^{-3}	1.08	1.05–1.11	2.3×10^{-9}	$0,8 \times 10^{-1}$
rs138190086	17	61538148	*ACE*	G/A	0.020	1.29	1.15–1.44	7.5×10^{-6}	1.41	1.18–1.69	1.8×10^{-4}	1.32	1.20–1.45	7.5×10^{-9}	$0, 9 \times 10^{-1}$
Previous genome-wide-significant loci not reaching significance															

						Stage 1 discovery (*n* = 63,926)			Stage 2 (*n* = 18,845)			Overall stage 1 + stage 2 (*n* = 82,771)			
Variant [a]	**chr.**	**Position**[b]	**Closest gene**[c]	**Major/ minor alleles**	**MAF**[d]	**OR**	**95% CI**[e]	***P***	**OR**	**95% CI**[e]	***P***	**OR**	**95% CI**[e]	**Meta *P***	***I*²** **(%), *P***[f]
rs190982	5	88223420	*MEF2C*	A/G	0.390	0.95	0.92–0.97	2.8×10^{-4}	0.93	0.89–0.98	2.7×10^{-3}	0.94	0.92–0.97	2.8×10^{-6}	0, 6×10^{-1}
rs4723711	7	37844263	*NME8*	A/T	0.356	0.95	0.92–0.98	2.7×10^{-4}	0.91	0.87–0.95	1.0×10^{-4}	0.94	0.91–0.96	2.8×10^{-7}	0, 5×10^{-1}

[a] Variants showing the best level of association after meta-analysis of Stages 1 and 2.

[b] Build 37, assembly hg19.

[c] Based on position of top SNP in reference to the RefSeq assembly.

[d] Average in the discovery sample.

[e] Calculated with respect to the minor allele.

[f] Cochran's *Q* test

[g] Previously the *ZCWPW1* locus.

[h] Previously the *CELF1* locus. Chr., chromosome; CI, confidence interval; OR, odds ratio; I^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 (*n* = 82,771)**			**Stage 3A (*n* = 11,666)**			**Overall (*n* = 94,437)**		
SNP[a]	**Chr.**	**Position**[b]	**Closest gene**[c]	**Major/ minor allele**	**MAF**[e]	**OR**	**95% CI**[f]	***P***	**OR**	**95% CI**[f]	***P***	**OR**	**95% CI**[f]	**Meta *P***
rs4735340	8	95976251	*NDUFAF6*	T/A	0.476	0.94	0.92–0.96	3.4×10^{-7}	0.92	0.83–1.02	9.7×10^{-2}	0.94	0.92–0.96	9.2×10^{-8}
rs7920721g	10	11720308	*ECHDC3*	A/G	0.390	1.08	1.05–1.11	2.3×10^{-9}	1.11	1.04–1.18	1.5×10^{-3}	1.08	1.06–1.11	1.8×10^{-11}
rs7295246	12	43967677	*ADAMTS20*	T/G	0.413	1.07	1.04–1.09	2.7×10^{-7}	1.02	0.96–1.09	4.5×10^{-1}	1.06	1.04–1.08	3.9×10^{-7}
rs10467994	15	51008687	*SPPL2A*	T/C	0.333	0.94	0.91–0.96	3.9×10^{-7}	0.97	0.87–1.08	6.2×10^{-1}	0.94	0.92–0.96	4.3×10^{-7}
rs593742	15	59045774	*ADAM10*	A/G	0.295	0.93	0.91–0.96	1.3×10^{-7}	0.91	0.85–0.98	1.5×10^{-2}	0.93	0.91–0.95	6.8×10^{-9}
rs7185636	16	19808163	*IQCK*	T/C	0.180	0.92	0.89–0.95	8.4×10^{-8}	0.94	0.86–1.01	1.1×10^{-1}	0.92	0.89–0.95	2.4×10^{-8}
rs2632516	17	56409089	*MIR142/TSPOAP1-AS1d*	G/C	0.440	0.94	0.92–0.96	2.3×10^{-7}	0.91	0.82–1.01	7.5×10^{-2}	0.94	0.91–0.96	5.3×10^{-8}
rs138190086	17	61538148	*ACE*	G/A	0.020	1.32	1.20–1.45	7.5×10^{-9}	1.17	0.92–1.48	2.1×10^{-1}	1.30	1.19–1.42	5.3×10^{-9}
rs2830500	21	28156856	*ADAMTS1*	C/A	0.308	0.93	0.91–0.96	7.4×10^{-8}	0.95	0.89–1.02	1.3×10^{-1}	0.93	0.91–0.96	2.6×10^{-8}
Stage 3B						**Stage 1 (*n* = 63,926)**			**Stage 3B (*n* = 30,511)**[h]			**Overall (*n* = 94,437)**[h]		
SNP[a]	**Chr.**	**Position**[b]	**Closest gene**[c]	**Major/ minor allele**	**MAF**[e]	**OR**	**95% CI**[f]	***P***	**OR**	**95% CI**[f]	***P***	**OR**	**95% CI**[f]	**Meta *P***
rs71618613	5	29005985	*SUCLG2P4*	A/C	0.010	0.68	0.57–0.80	9.8×10^{-6}	0.76	0.63–0.93	6.8×10^{-3}	0.71	0.63–0.81	3.3×10^{-7}
rs35868327	5	52665230	*FST* T/A	A/C	0.013	0.69	0.59–0.80	7.8×10^{-7}	0.58	0.29–1.17	1.2×10^{-1}	0.68	0.59–0.79	2.6×10^{-7}
rs114812713	6	41034000	*OARD1*	G/C	0.030	1.35	1.24–1.47	4.5×10^{-12}	1.23	1.06–1.42	7.2×10^{-3}	1.32	1.22–1.42	2.1×10^{-13}
rs62039712	16	79355857	*WWOX*	G/A	0.116	1.17	1.10–1.23	1.2×10^{-7}	1.14	0.96–1.36	1.3×10^{-1}	1.16	1.10–1.23	3.7×10^{-8}

Novel loci were defined as loci not reported in Lambert et al.[1] with (1) a Stage 1 + 2 meta $P < 5 \times 10^{-7}$ (nine variants after excluding TREM2) (Stage 3A) or (2) a MAF < 0.05 and Stage 1 $P < 1 \times 10^{-5}$ or MAF ≥ 0.05 and Stage 1 $P < 5 \times 10^{-6}$ for genome regions not covered on the Stage 2 custom array (Stage 3B).

[a] SNPs showing the best level of association after meta-analysis of Stages 1, 2 and 3.

[b] Build 37, assembly hg19.

[c] Based on position of top SNP in reference to the RefSeq assembly.

[d] Variant is annotated to both gene features.

[e] Average in the discovery sample.

[f] Calculated with respect to the minor allele.

[g] Recently identified as a LOAD locus in two separate 2017 studies.

[h] Sample sizes for these loci are smaller (overall $n = 89{,}769$ for *SUCLG2P4*, 65,230 for *FST*, and $n = 69{,}898$ for *WWOX*).

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	1.4×10^{-7}[a]	9.5×10^{-4}	6.7×10^{-2}	8.4×10^{-1}	Protein−lipid complex assembly
GO:1902003	10	4.5×10^{-7}[a]	1.4×10^{-3}	4.9×10^{-2}	8.4×10^{-1}	Regulation of Aβ formation
GO:32994	39	1.1×10^{-6}[a]	2.5×10^{-3}	1.7×10^{-2}	8.1×10^{-1}	Protein−lipid complex
GO:1902991	12	3.5×10^{-6}[a]	5.8×10^{-3}	5.6×10^{-2}	8.4×10^{-1}	Regulation of amyloid precursor protein catabolic process
GO:43691	17	5.5×10^{-6}[a]	6.7×10^{-3}	3.0×10^{-2}	8.1×10^{-1}	Reverse cholesterol transport
GO:71825	35	6.1×10^{-6}[a]	6.7×10^{-3}	1.2×10^{-1}	8.4×10^{-1}	Protein−lipid complex subunit organization
GO:34377	18	1.6×10^{-5}[a]	1.5×10^{-2}	1.8×10^{-1}	8.4×10^{-1}	Plasma lipoprotein particle assembly
GO:48156	10	3.1×10^{-5}[a]	2.6×10^{-2}	7.7×10^{-1}	8.5×10^{-1}	Tau protein binding
GO:2253	382	6.3×10^{-5}[a]	4.6×10^{-2}	2.0×10^{-1}	8.4×10^{-1}	Activation of immune response

[a]Significant after FDR correction (q value ≤ 0.05).

Table 4 |

Top results of pathway analysis of the Aβ-centered biological network from Campion et al.[64] (see Supplementary Table 12 for full results)

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

[a]Significant after Bonferroni correction for 33 pathway sets tested.