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Meta-analysis of genetic association with diagnosed Alzheimer's disease identifies novel risk loci and implicates Abeta, Tau, immunity and lipid processing

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Introduction

Risk for Late-onset Alzheimer's disease (LOAD), the most prevalent dementia in the elderly[1], is partially driven by genetics[2]. To identify LOAD risk loci, we performed the largest genome-wide association meta-analysis of clinically diagnosed LOAD to date (94,437 individuals), analyzing both common and rare variants. We confirm 20 previous LOAD risk loci and identify five new genome-wide loci (*IQCK*, *ACE*, *ADAM10*, *ADAMTS1* and *WWOX*). 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 the immune system and lipid metabolism, and for the first time tau binding proteins and APP metabolism, showing that genetic variants affecting APP and Aβ processing are not only associated with early-onset autosomal dominant AD but also with LOAD. Analysis of AD risk genes and pathways show enrichment for rare variants ($P=1.32\times10^{-7}$) indicating that additional rare variants remain to be identified. Finally, we also identify important genetic correlations between LOAD and other traits including family history of dementia and education.

Main Text

Our previous work identified 19 genome-wide significant common variant signals in addition to *APOE*[3], that influence risk for LOAD (onset age > 65 years). 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[4]. To search for additional signals, we conducted a genome-wide association (GWAS) meta-analysis of non-Hispanic Whites (NHW) using a larger sample (17 new, 46 total datasets) from our group, the International Genomics of Alzheimer's Project (IGAP) (composed of four AD consortia: ADGC, CHARGE, EADI, and GERAD). This sample increases our previous discovery sample (Stage 1) by 29% for cases and 13% for controls (N=21,982 cases; 41,944 controls) (**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 using a 1000 Genomes reference panel consisting of 36,648,992 single-nucleotide variants, 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 (a 63% increase from our previous common variant analysis in 2013). Genotype dosages were analyzed within each dataset, and then combined with meta-analysis (**Supplementary Figure 1, Supplementary Tables 1-3**).

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[3,5–12]. Genomic inflation factors were slightly inflated (lambda median=1.05; lambda regression=1.09; See **Supplementary Figure 2** for QQ-plot), however, univariate linkage disequilibrium score (LDSC) regression[13,14] 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. = 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.[3] (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 workflow). The final sample was 35,274 clinical and autopsy-documented AD 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 **Figure 1**). Of these, 18 were previously reported as genome-wide significant in Lambert et al.[3]. Three other signals were not initially described in the initial IGAP GWAS: the rare R47H *TREM2* coding variant previously reported by others[8,9,15]; *ECDH3* (rs7920721) which was recently identified as a potential genome-wide significant AD risk locus in several studies[23-25] and *ACE* (rs138190086) (**Supplementary Figures 3-4**). In addition, seven signals showed suggestive association with a $P < 5 \times 10^{-7}$ (respectively rs593742,

rs830500, rs7295246, rs7185636, rs2632516, rs4735340, and rs10467994 for their closest gene *ADAM10, ADAMTS1, ADAMTS20, IQCK*, *miR142/TSPOAP1-AS1*, *NDUFAF6* and *SPPL2A*) (**Supplementary Figures 5-11**). Stage 3A and meta-analysis of all three stages for these 9 variants (excluding the *TREM2* signal; see **Supplementary Table 5** for variant list) identified five genome-wide significant loci. In addition to *ECDH3*, this included four new genome-wide AD risk signals not previously described in other clinical AD GWAS at *IQCK, ADAMTS1, ACE* and *ADAM10* (**Table 2**)*. ACE* and *ADAM10* were previously reported as AD candidate genes[16–20] that were not replicated in some subsequent studies[19,21–24]. Two of the four other signals were close to genome-wide significance: *miR142/TSPOAP1-AS1* ($P = 5.3 \times 10^{-8}$) and *NDUFAF6* ($P = 9.2 \times 10^{-8}$) (**Table 2**). We also extended the analyses of the two loci (*NME8* and *MEF2C*) in Stage 3 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 investigations (*NME8*: $P = 2.7 \times 10^{-7}$; *MEF2C*: $P = 9.1 \times 10^{-8}$; **Supplementary Figures 12-13**). Of note, GCTA-COJO[25] 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 under-estimated.

We also selected 33 variants from Stage 1 (28 common variants 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) 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, 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 Figures 14-15, Supplementary Tables 6 and 7**). In addition, rs62039712 in the *WWOX* locus reached genome-wide significance ($P = 3.7 \times 10^{-8}$) and rs35868327 in the *FST* locus reached

suggestive significance ($P = 2.6 \times 10^{-7}$) (**Table 2 and Supplementary Figures 16-17**). *WWOX* may play a role in AD through its interaction with Tau[26,27], and it's worth noting the sentinel variant (defined as variants with the lowest p-values) is just 2.4 megabases from *PLCG2*, which contains a rare variant we recently associated with AD[15]. Since both rs62039712 and rs35868327 were only analyzed in a restricted number of samples, these loci deserve further attention.

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 BRAAK stage[28] and differential expression in AD versus control brains[29]), 4) evaluation of transcriptomic expression in AD-relevant tissues[30–32], and 5) gene cluster/pathway analyses. For the 24 signals reported here, other evidence indicates that *APOE*[33,34], *ABCA7*[35–38], *BIN1*[39], *TREM2*[8,9], *SORL1*[40,41], *ADAM10*[42], *SPI1*[43], *and CR1*[44] are the true AD risk gene, though there is a possibility that multiple risk genes exist in these regions[45]. 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 ±500kb of the sentinel variant linkage disequilibrium (LD) regions ($r^2 \geq 0.5$) for each locus as a candidate AD 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, loss-of-function (LOF) or splicing variants. In line with findings that most causal variants for complex disease are non-coding[46], only 2% of 1,073 variants across the 24 loci (excluding *APOE*) were exonic variants, with a majority (58%) being intronic (**Supplementary Figure 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[47] (N = 5,740 LOAD cases and 5,096 cognitively normal controls), we also identified 10 genes located in our genome-wide loci as having rare deleterious coding, splicing or LOF burden associations with LOAD (FDR $P < 0.01$), including previously implicated rare-variant signals in *ABCA7*, *TREM2*, and *SORL1*[15,47–53], 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. 71-99% of these variants have regulatory potential when considering all tissues according to RegulomeDB[54] and HaploReg[55], but restricting to AD-relevant tissues (via Ensembl Regulatory Build[56] and GWAS4D[57]) 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 AD relevant tissues (i.e. 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 AD relevant tissue for: *ADAM10* in prefrontal cortex and blood, *FAM63B* in blood, and *SLTM* in putamen in the *ADAM10* locus; *ADAMTS1* in blood in the ADAMTS1 locus; and *ACSM1* and *ANKS4B* in monocytes, *C16orf62* in blood, *GDE1* in cerebellum, and *GPRC5B*, *IQCK*, and *KNOP1* in several brain and blood tissue types in the *IQCK* locus. There were no eQTLs in AD-relevant tissues in the *WWOX* or *ACE* locus, though several eQTLs for *PSMC5* in coronary artery tissue were found for the *ACE* locus. eQTL's for genes in previously identified

loci include *BIN1* in monocytes and cerebellum, *INPP5D* in prefrontal cortex and blood, *CD2AP* in cerebellum and prefrontal cortex, and *SLC24A4* in monocytes. 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 a complete lists). Genes implicated include: *CR1* and *ABCA7* in brain (in the *CR1* and *ABCA7* loci respectively); *BIN1* (in the *BIN1* locus), *SPI1* and *MYBPC3* (both in the *SPI1* locus) in blood; *MS4A2*, *MS4A6A*, and *MS4A4A* (all at the *MS4A2* locus) in blood; and *KNOP1* (in the *IQCK* locus) and *HLA-DRB1* (in the *HLA-DRB1* locus) in both blood and brain. (**Supplementary Table 12**).

To study the differential expression of genes in brains of AD patients versus controls, we used thirteen expression studies[29]. 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 AD related gene expression sets revealed 62 genes were correlated with pathogenic stage (BRAAK) in at least one brain tissue[28] (44 genes in the 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 AD genes ($P = 4.1 \times 10^{-5}$)[32]. 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/macrophage (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 cell of the brain thought to play a key role in the pathologic immune response in LOAD[9,15,58], become the highest expressed cell type (20.3%) 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 highly expressed gene list by cell type).

We conducted pathway analyses (MAGMA[59]) using five gene set resources. Analysis were conducted separately for common (MAF $\geq$ 0.01) and rare variants (MAF < 0.01). For common variants, we detected four function clusters including: 1) APP metabolism/Aβ-formation (regulation of beta-amyloid formation: $P = 4.56 \times 10^{-7}$ and regulation of amyloid precursor protein 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 pathways remains after removal of genes in the *APOE* region. When *APOE*-region genes and genes in the vicinity of genome-wide significant genes are removed, tau shows moderate association ($P = 0.027$) and lipid metabolism and immune related pathways show strong associations ($P < 0.001$) (**Supplementary Table 20**). Genes driving these enrichments (i.e. having a gene-wide $P < 0.05$) include *SCNA*, a Parkinson's risk gene that encodes alpha-synuclein, the main component of Lewy bodies, and may play a role in tauopathies[60,61], 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 have nominal significance in rare-variant-only analyses. Importantly, we also observe a highly significant correlation between common and rare pathway gene results ($P = 1.32 \times 10^{-7}$), suggesting that risk AD genes and pathways are enriched for rare variants. In fact, 50 different genes within tau, lipid, immunity and Aβ pathways show 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[62] 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 Table 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[63]. 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 eQTL, clinical and AD-relevant tissue expression, and gene function/pathway analyses in a priority ranking method similar to Fritsche et al.[64] (**Table 5 and Supplementary Table 24**). For our *ADAM10* signal, of the 11 genes within this locus, *ADAM10* was the top ranked gene. *ADAM10*, the most important α-secretase in the brain, is a component of the non-amyloidogenic pathway of APP metabolism[65], and sheds *TREM2*[66]*,* an innate immunity receptor expressed selectively in microglia. Over-expression of *ADAM10* in mouse models can halt Aβ production and subsequent aggregation[67]. Also two rare *ADAM10* mutations segregating with disease in LOAD families increased Aβ plaque load in “Alzheimer-like” mice, with diminished α-secretase activity from the mutations likely the causal mechanism[17,42]. For the *IQCK* signal, which is also an obesity locus[68,69], *IQCK*, a relatively uncharacterized gene, was top ranked, though 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[70,71] and inflammatory signalling in obesity[72]. Of the 22 genes in the *ACE* locus, *PSMC5*, a key regulator of major histocompatibility complex (MHC)[73,74], has a top score of 4, while *DDX42*, *MAP3K3*, an important regulator of macrophages and innate immunity[75,76], and *CD79B,* a B lymphocyte antigen receptor sub-unit each have a score of 3. Candidate gene studies previously associate *ACE* variants with AD risk[18,20,77], including a strong association in the Wadi Ara, an Israeli Arab community with high risk of AD[19]. However, these studies yielded inconsistent results[21], and our work is the first to report a clear genome-wide association in NHW at this locus. While our analyses did not prioritize *ACE,* it should not be rejected as a candidate gene, as its expression in AD brain tissue is associated with Aβ load and AD severity[78]. Furthermore, CSF levels of the angiotensin-converting enzyme (ACE) are

associated with Aβ levels[79] and LOAD risk[80], and studies show ACE can inhibit Aβ toxicity and aggregation[81]. Finally, angiotensin II, a product of ACE function mediates a number of neuropathological processes in AD[82] and is now a target for intervention in phase II clinical trials of AD[83]. Another novel genome-wide locus reported here *ADAMTS1,* is within 665 kb of *APP* on chromosome 21. Of three genes at this locus (*ADAMTS1*, *ADAMTS5*, *CYYR1*), our analyses nominates *ADAMTS1,* as the likely risk gene, though we cannot rule out that this signal is a regulatory element for *APP*. *ADAMTS1* is elevated in Down Syndrome with neurodegeneration and AD[84] and is a potential neuroprotective gene[85,86,87], or a neuroinflammatory gene important to microglial response[88]. Finally, *WWOX* and *MAF*, which surround an intergenic signal in an obesity associated locus[89], were both prioritized, with *MAF,* another important regulator of macrophages[90,91], being highly expressed in microglia in the Brain-RNA-seq database, and *WWOX*, an HDL-cholesterol and triglyceride associated gene[92,93], being expressed in several brain cell types, most highly in astrocytes and neurons. *WWOX* has been implicated in several neurological phenotypes[94], binds Tau and may play a critical role in regulating Tau hyper-phosphorylation, neurofibrillary formation, and amyloid β aggregation[26,27]. Intriguingly, treatment of mice with its binding partner restores memory deficits[95], hinting at its potential in neurotherapy.

For previously reported loci, named for the closest gene, applying the same approach for prioritization highlights several genes as described in **Table 5**, some of which are involved in APP metabolism (*FERMT2, PICALM*) or Tau toxicity (*BIN1*, *CD2AP*, *FERMT2*, *CASS4*, *PTK2B*)[96–99]. Pathway, tissue and disease traits enrichment analysis supports the utility of our prioritization method, as the 53 prioritized genes with a score ≥ 5 are: 1) enriched in substantially more AD relevant pathways, processes, and dementia-related traits, 2) enriched in candidate AD cell types such as monocytes (adjusted-P = 9.0 x 10^{-6}) and macrophages (adjusted-P = 5.6 x 10^{-3}), and 3) increased in strength of associations for dementia-related traits and AD relevant pathways (**Supplementary Table 25 and 26;** see **Supplementary Figure 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 using GTEx[100] tissues, and identified significant differential expression in several potentially relevant AD 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, hippocampus, basal ganglia, and amygdala). Furthermore, the 53 genes are overexpressed in 'adolescence' and 'young adult' brain tissues in BrainSpan[101], a transcriptomics atlas of the developing human brain, which is consistent with accumulating evidence suggesting AD may start decades before the onset of disease[102,103] (**Supplementary Figure 20;** see **Supplementary Figure 21** for a tissue expression heat map for the 53 genes).

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 Figure 22** for Stage 1 results plot of region). Previous analyses in the ADGC (5,728 AD cases and 5,653 controls) has linked both HLA class I and class II haplotypes with AD risk[104]. 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 (*HLA-A*, *HLA-B*, *HLA-C*) and class II (*HLA-DRB1*, *HLA-DQA1*, *HLA-DQB1*, *HLA-DPA1*, *HLA-DPB1*) genes in 14,776 cases and 23,047 controls from our datasets (**Supplementary Table 27**) (see Methods). We found risk effects of *HLA-DQA1*01:02* (false discovery rate (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 variant in this region from the meta-analysis (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 AD in our sample (FDR *P* = 0.013) (**Supplementary Table 29**). When considering only 2-loci haplotypes, *HLA-DQB1*06:02~HLA-DRB1*15:01* (FDR *P* = 0.013), *HLA-DQA1*01:02~HLA-DRB1*15:01* (FDR *P* = 0.013), *HLA-DQA1*01:02~HLA-DQB1*06:02* (FDR *P* = 0.013) also show association with AD. Taken together, these results suggest a central role of the HLA-*DQA1*01:02~HLA-DQB1*06:02~HLA-DRB1*15:01* haplotype in AD risk. This haplotype was associated with risk of AD originally in a small study in the Tunisian population[105], and more recently in a large ADGC analysis[104]. Intriguingly, this haplotype and its component alleles also associate with protection against diabetes[106], a high risk for multiple sclerosis[107,108], and risk or protective effects with many other immune-mediated diseases (**Supplementary Table 30**). Moreover, the associated diseases at these loci include a large number of traits queried from an HLA-specific Phewas[109], including neurological diseases (i.e. Parkinson's disease[110,111]) and diseases with risk factors for AD (i.e. hyperthyroidism[112]), pointing to potential shared and/or interacting mechanisms and co-morbidities, a common paradigm in the MHC locus[113]. Two additional alleles, *HLA-DQA1*03:01* and *HLA-DQB1*03:02*, belonging to another haplotype, show protective effect on AD, 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 AD (FDR *P* = 0.651).

As described above, several of our genome-wide loci have potentially interesting co-morbid or pleiotropic associations with traits that may be relevant to pathology of AD. 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[13,114] (**Supplementary Table 31**). The common variant genetic architecture of LOAD was positively correlated with maternal family history of Alzheimer's disease/dementia (rg = 0.81; FDR $P = 2.79 \times 10^{-7}$), similar to a recent GWAS using family history of AD as a proxy[115] which found maternal genetic correlation with AD to be higher than paternal AD (rg = 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 rg estimates with maternal history of dementia. While use of proxy AD cases introduces less sensitivity and specificity for true AD signals overall in comparison to clinically-diagnosed AD association analyses, the investigation did identify 17 of our 25 genome-wide loci including the *ACE* and *ADAM10* loci, suggesting that familial proxy AD studies can identify AD relevant loci. We also find significant negative correlation between AD and multiple measures of educational attainment (i.e. college completion, rg = -0.24; years of schooling, rg range = -0.19 to -0.24; cognitive scores, rg's = -0.24 and -0.25) (FDR $P < 0.05$), supporting the theory that a greater cognitive reserve could help protect against development of LOAD[116]. The extent to which socioeconomic (ses), environmental or cultural factors contribute to the correlation between educational attainment and risk for AD is unknown, but research has shown dementia risk to be associated with lower ses status, independent of education status[117,118]. Furthermore, we also found negative correlations at $P < 0.05$ with multiple measures of cardiovascular health (i.e. family history of high blood pressure, family history of heart disease, vascular/heart problems diagnosis) and diabetes (i.e. fasting proinsulin, basal metabolic rate, fasting insulin main effect), supporting previous research that suggested use of blood pressure and diabetic medications may reduce risk of AD[119]. In fact, use of blood pressure medication does show negative genetic correlation with AD in our study (rg = -0.12; $P = 0.035$), though this result does not survive FDR correction. These and other top results from this analysis (i.e. body mass index, height; see **Supplementary Table 31** for a full list of other nominally significant correlations) have been linked to AD previously[114,119–126], either through suggestive or significant genetic or epidemiological associations (see Kuzma et al. 2018[127] 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.

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 (i.e. *TREM2*). The enrichment of rare-variants in pathways associated with AD indicates that additional rare-variants remain to be identified, and larger samples and better imputation panels will facilitate identifying these rare variants. While these rare-variants may not contribute substantially to the predictive value of genetic findings, it will add to 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 not only associated with early-onset but also late-onset AD, 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 tau is involved in late-onset AD supports recent evidence that tau may play an early pathological role in AD[128–130], and confirms that therapies targeting tangle formation/degradation could potentially affect late-onset AD. Finally, our fine-mapping analyses of HLA and genetic correlation results point to LOAD's shared genetic architecture with many immune-mediated and cognitive traits, and suggests that research and interventions that elucidate the mechanisms behind these relationships could also yield fruitful therapeutic strategies for LOAD.

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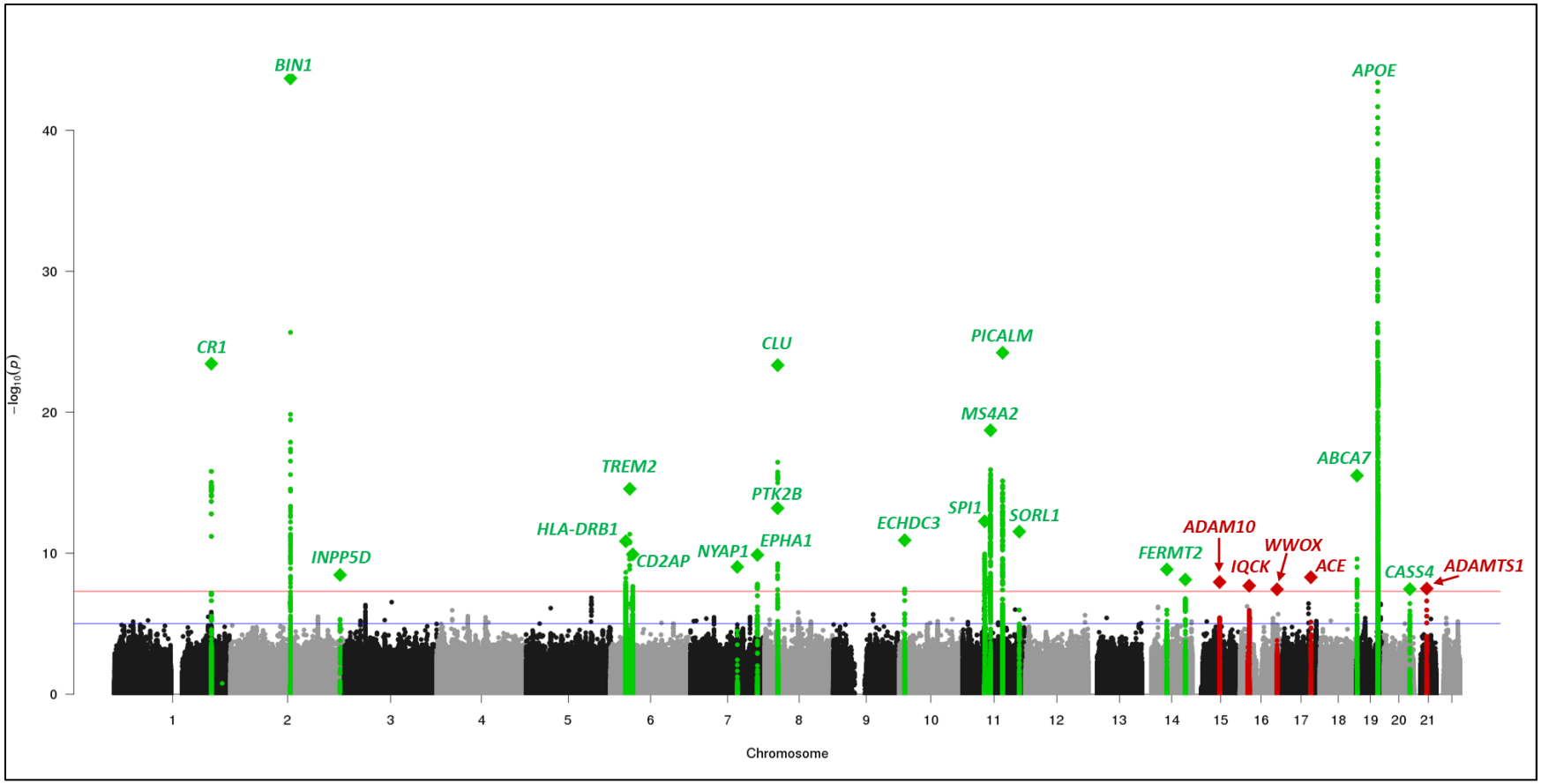

Figure 1. Manhattan plot of meta-analysis of Stage 1, 2 and 3 results for genome-wide association with Alzheimer's disease. The threshold for genome-wide significance ($P < 5 \times 10^{-8}$) is indicated by the red line, while the blue line represents the suggestive threshold ($P < 1$ x 10-5). Loci previously identified by the Lambert et al. 2013 IGAP GWAS are shown in green, and newly associated loci are shown in red. Loci are named for the closet gene to the sentinel variant for each locus. Diamonds represent variants with the smallest *P* values for each genome-wide locus.

Meta-analysis of genetic association with diagnosed Alzheimer's disease identifies novel risk loci and implicates Abeta, Tau, immunity and lipid processing - Tables

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	*NYAP1*[g]	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	*SPI1*[h]	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)	7.4×10^{-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	*ECDH3*	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												
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}	$0, 6 \times 10^{-1}$
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}	$0, 5 \times 10^{-1}$

[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.

Table 2. Summary of discovery Stage 1, Stage 2, Stage 3 (A and B), and overall meta-analyses results of potential novel loci. Novel loci were defined as loci not reported in Lambert et al. 2013 with 1) a Stage 1+2 Meta $P < 5 \times 10^{-7}$ (9 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).

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}
rs7920721[g]	10	11720308	*ECHDC3*	A/G	0.390	1.08 (1.05-1.11)	2.30×10^{-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	0.97 (0.87-1.08)	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-AS1*[d]	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)	7.45×10^{-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)	7.3×10^{-8}	0.95 (0.88-1.02)	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	0.013	0.69 (0.59-0.80)	7.8×10^{-7}	0.58 (0.29-1.17)	0.126	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)	0.129	1.16 (1.10-1.23)	3.7×10^{-8}

[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 *LOC257396,FST*, and 69,898 for *WWOX*)

Table 3. Significant pathways (q-value≤0.05) from MAGMA pathway analysis for common SNV and rare SNV subsets.

Pathway	N genes in pathway in dataset	Common SNVs *P**	Common SNVs q-value	Rare SNVs *P**	Rare SNVs q-value	Pathway description
GO:65005	20	1.45E-07*	9.53E-04	6.76E-02	8.42E-01	protein-lipid complex assembly
GO:1902003	10	4.56E-07*	1.49E-03	4.94E-02	8.42E-01	regulation of beta-amyloid formation
GO:32994	39	1.16E-06*	2.54E-03	1.78E-02	8.17E-01	protein-lipid complex
GO:1902991	12	3.54E-06*	5.80E-03	5.66E-02	8.42E-01	regulation of amyloid precursor protein catabolic process
GO:43691	17	5.55E-06*	6.75E-03	3.08E-02	8.17E-01	reverse cholesterol transport
GO:71825	35	6.18E-06*	6.75E-03	1.27E-01	8.42E-01	protein-lipid complex subunit organization
GO:34377	18	1.64E-05*	1.53E-02	1.82E-01	8.42E-01	plasma lipoprotein particle assembly
GO:48156	10	3.19E-05*	2.61E-02	7.77E-01	8.54E-01	tau protein binding
GO:2253	382	6.32E-05*	4.60E-02	2.09E-01	8.42E-01	activation of immune response

*Significant after FDR-correction (q-value≤0.05)

Table 4. Top results of pathway analysis of Aβ-beta centered biological network from Campion et al (see Supplementary Table 12 for full results).

Category	Subcategory	N Genes	Common SNVs *P* 0kb	Common SNVs *P* 35kb-10kb	Rare SNVs *P* 0kb	Rare SNVs *P* 35kb-10kb
Aβ -centered biological network (all genes)	--	331	2.27E-04*	1.54E-04*	8.26E-01	5.19E-01
Clearance and degradation of Aβ	--	74	2.18E-04*	3.27E-03	3.13E-01	5.11E-01
Clearance and degradation of Aβ	Microglia	47	2.24E-04*	1.83E-02	2.49E-01	6.87E-01
Aggregation of Aβ	--	35	7.09E-04*	9.93E-03	9.02E-02	1.68E-01
Aggregation of Aβ	Miscellaneous	21	1.08E-03*	3.38E-02	9.53E-02	1.90E-01
APP processing and trafficking	Clathrin/caveolin-dependent endocytosis	10	1.19E-03	1.15E-02	3.64E-01	1.84E-01
Mediator of Aβ toxicity	--	51	3.82E-02	4.69E-02	5.89E-01	5.70E-01
Mediator of Aβ toxicity	Calcium homeostasis	6	6.90E-02	1.21E-01	3.96E-01	2.54E-01
Mediator of Aβ toxicity	Miscellaneous	3	7.61E-02	2.35E-02	9.79E-01	7.61E-01
Clearance and degradation of Aβ	Enzymatic degradation of Aβ	15	7.77E-02	2.63E-02	6.10E-01	2.95E-01
Mediator of Aβ toxicity	Tau toxicity	20	9.03E-02	3.48E-01	7.17E-01	6.85E-01
Aggregation of Aβ	Chaperone	9	1.52E-01	3.09E-01	1.98E-01	1.13E-02

*Significant after Bonferroni correction for 33 pathway sets tested

Table 5. Top prioritized genes of 400 genes located in genome-wide significant loci. The criteria include: 1) deleterious coding, loss-of-function or splicing variant in gene, 2) significant gene-based test, 3) expression in a tissue relevant to AD (astrocytes, neurons, microglia/macrophages, oligodendrocytes), 4) HuMi microglial-enriched gene, 5) having an eQTL effect on the gene in any tissue, in AD relevant tissue, and/or a co-localized eQTL, 6) being involved in a biological pathway enriched in AD (from the current study), 7) expression correlated with BRAAK stage, and 8) differential expression in 1+ Alzheimer disease (AD) study. Novel genome-wide loci from the current study are listed first, followed by known genome-wide loci. Each category is assigned equal weight of 1, with the priority score equaling the sum of all categories. Colored fields indicate 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.

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													
ADAM10	11	*ADAM10*	5										
IQCK	12	*IQCK*	6										
ACE	22	*PSMC5*	4										
ADAMTS1	3	*ADAMTS1*	4										
WWOX	3	*MAF*	2										
		WWOX	2										
Known genome-wide loci													
CR1	12	*CR1*	7										
		CD55	6										
		YOD1	5										
BIN1	9	*BIN1*	6										
INPP5D	11	*INPP5D*	7										
HLA-DRB1 [†]	46	*HLA-DRB1*	7										
		PSMB8	7										
		C4A	6										
		GPSM3	6										
		HLA-DPA1	6										
		HLA-DQA1	6										
		HLA-DRA	6										
		HLA-DRB5	6										
		PSMB9	6										
TREM2	21	*TREM2*	6										
CD2AP	8	*CD2AP*	5										
NYAP1	53	*AGFG2*	6										
		PILRA	6										
		EPHB4	5										
		C7orf43	5										
		GAL3ST4	5										
		ZKSCAN1	5										
EPHA1	23	*FAM131B*	5										
PTK2B	6	*PTK2B*	5										
CLU	8	*CLU*	6										
ECHDC3	8	*ECHDC3*	4										
SPI1	23	*PSMC3*	6										
		ACP2	5										
		C1QTNF4	5										
		CELF1	5										
		MTCH2	5										
		NDUFS3	5										
		NUP160	5										
		SPI1	5										
MS4A2	24	*MS4A6A*	8										
		MS4A7	6										
		MS4A4A	5										
PICALM	13	*EED*	5										
		PICALM	5										
SORL1	4	*SORL1*	5										
FERMT2	9	*STYX*	5										
SLC24A4	10	*RIN3*	7										
ABCA7	50	*ABCA7*	7										
		HMHA1	6										
		CNN2	5										
		WDR18	5										
CASS4	11	*CASS4*	5										

[†]Genes with rank 6 or above are shown only. An additional 4 genes in *HLA-DRB1* have a priority rank of 5.

Meta-analysis of genetic association with diagnosed Alzheimer's disease identifies novel risk loci and implicates Abeta, Tau, immunity and lipid processing - Methods

Samples. All stage I meta-analysis samples are from four Consortia: the Alzheimer's Disease Genetics Consortium (ADGC), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, the European Alzheimer's Disease Initiative (EADI), and the Genetic and Environmental Risk in Alzheimer's Disease (GERAD) Consortium. 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 (QC) 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 (PCs) analysis of ancestry informative markers were excluded from the further analysis.

Imputation and pre-analysis quality control. Following genotype chip QC, each dataset was phased and imputed with data to the 1000 Genomes Project (phase 1 integrated release 3, March 2012)[1] using SHAPEIT/IMPUTE2[2,3] or MaCH/Minimac[4,5] software (**Supplementary Table 3**). All reference population haplotypes were used for the imputation as this method improves accuracy of imputation for low-frequency variants[6]. 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 variants 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 AD cases and 30% of controls across all datasets.

Stage 1 Association Analysis and Meta-analysis. The Stage 1 discovery meta-analysis was followed by Stage 2, and Stage 3 (A and B) replication analyses. Stage 2 was data from a custom array with 11,632 assays selected as variants with $P < 10^{-3}$ from our 2013 work[7]. Genotypes were determined for 8,362 cases and 10,483 controls (**Supplementary Table 4**). 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**). Stage 3B, which combined samples from Stage 2 and 3A, analysis was conducted for variants with MAF < 0.05 and $P < 1 \times 10^{-5}$ or variants with MAF ≥ 0.05 and $P < 5 \times 10^{-6}$ from genome regions not covered on the Stage 2 custom array (13,292 cases and 17,219 controls) (**Supplementary Table 7**). For Stages 1, 2, and 3, samples did not overlap.

Stage 1 single variant-based association analysis was conducted on genotype dosages modeling for an additive genotype model and adjusting for age (defined as age-at-onset for cases and age-at-last exam for controls), sex and population substructure using PCs[8]. The score test was implemented on all case-control datasets. This test was shown to be optimal for meta-analysis of rare variants due to its balance between power and control of type 1 error[9]. Family datasets were tested using the R package GWAF[10], 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 internal data showing behavior of 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[11] using an inverse-variance based model with genomic control. The meta-analysis was split into two separate analyses based on 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. We also conducted a second meta-analysis in METAL using a sample-size weighted meta-analysis model. Results of this model were compared to the inverse-variance weighted meta-analysis, and results that differed by more than 3 logs on both *P*-values were removed from further analysis. Regression coefficients for rare variants can at times be unstable[12], and this step attempted to control for these problematic variants by using a second method of meta-analysis that may be less sensitive to certain properties of rare variant analysis. In total, 11 variants were removed through this comparison, and most results showed very little difference in *P*-values between the two methods. An additional 106 variants with high heterogeneity between studies (defined as $I^2 > 75$) were removed. Figures for association signals were generated with LocusZoom software[13]. Genome-wide summary statistics are available from The National Institute on Aging Genetics of Alzheimer's Disease (NIAGADS) website

(https://www.niagads.org/). These analyses were conducted by two independent consortia (ADGC and EADI) and then cross-validated.

Stage 1 summary statistics quality control and analysis. Genomic inflation was calculated for lambda in the GenABEL package[14]. In addition, we performed linkage-disequilibrium score (LDSC) regression via LD Hub v1.9.0[15,16] 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. = 0.011) to 0.0637 (s.e. = 0.009).

LDSC was also employed via the LD-Hub web server to obtain genetic correlation estimates (rg)[17] between LOAD and a wide range of other disorders, diseases, and human traits, including 518 UK BioBank traits[18]. UK BioBank is a large long-term study begun in 2006 in the United Kingdom (UK) which is investigating the contributions of genetic predisposition and environmental exposure (i.e. nutrition, lifestyle, medications) to the development of disease. Approximately 500,000 volunteers aged 40 to 69 have been enrolled in the study, with the stated goal of following their health indicators and exposures for 30 years or more after enrollment. While volunteers in the study are generally healthier than the overall UK population[19], it's 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. Prior to 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 (Chr19:45,116,911-46,318,60) 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 a 5% Benjamini-Hochberg false discovery rate (FDR)-corrected *P*-values.

GCTA[20] COJO was used to conduct conditional analysis of the Stage 1 summary statistics and using 28,730 unrelated individuals from the ADGC as a reference panel for calculation of linkage disequilibrium (LD). Methods for how the ADGC reference dataset was created are described elsewhere[21,22]. LDLink[23] was used to assess LD, using all 5 CEU populations as the reference for calculations.

Stage 2 and 3 genotyping, quality control, and analysis. Datasets for Stage 2 analysis were obtained from previous genotyping from Lambert et al. 2013[7] using Illumina iSelect technology. The I-select chip has a total of 11,632 single nucleotide variants passing quality control available

for analysis. 1,633 variants 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 the *HLA-DQB1* locus (763 variants), *M24A2* locus (202 variants), and *PICALM* locus (156 variants); the least covered loci were the *MAF* locus (0 variant), *ADAMTS1* locus (4 variants), and the *INPP5D* locus (5 variants). Eleven variants from Stage 3A were genotyped using Taqman technology. Stage 3B included 23 variants included as part of Sequenom MassArray iPLEX panels and 10 additional variants genotyped using Taqman technology.

Per sample quality checks for genetic sex and relatedness were performed in PLINK. Individuals not matching their reported sex or showing a high degree of relatedness (IBD value of 0.98 or greater) were removed from the analysis. A panel of ancestry-informative markers (AIMs), was used to perform PCA analysis with SMARTPCA from EIGENSOFT 4.2 software[24], 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}. Please see Lambert et al. for a more detailed description of the QC procedures followed in Stage 2 analysis. After quality control, 18,845 individuals (8,362 cases and 10,483 controls) were available for the stage 2 analysis. The same quality control measures were applied to data for the Stage 3B variants attained from follow-up genotyping.

Selection of variants for Stage 3B follow-up genotyping. In order to prioritize variants for genotyping in Stage 3B, we first selected all MAF < 0.05 variants with $P < 1 \times 10^{-5}$ or MAF ≥ 0.05 variants with $P < 5 \times 10^{-6}$ in novel loci not covered in the iSelect genotyping from Stage 2 of Lambert et al.[7] A total of 180 variants were considered for follow up due to meeting the *P*-value criteria and not being in an IGAP 2013 locus. 88 of these variants were in a region covered in the replication genotyping chip from 2013 and thus were removed from further consideration. 33 loci remained after their removal, with 19 loci having only one prioritized variant, which we selected for genotyping. Remaining variants in 14 regions with multiple prioritized variants were then annotated with GWAVA[25] and CADD[26] scores (using ANNOVAR[27]), Ensembl Variant Effect Predictor (VEP) Consequences (using Ensembl VEP[28]), GWAS4D[29], RegulomeDB[30], and FANTOM5[31] (using NIAGADS GenomicsDB) in order to rank their functional potential. A CADD score > 10, GWAVA score > 0.5, FATHHM > 0.5, RegulomeDB score < 5 and GWAS4D top p-value score were considered 'functional' in the ranking. The top ranked variant for functional

potential for each locus with multiple variants was selected for further genotyping and analysis. Removal of 59 variants in regions with multiple variants left 33 total variants for follow-up genotyping.

Stage 2 and 3 analyses. Per study analysis for Stage 2 and Stage 3 followed the same analysis procedures described for Stage 1, except 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 PCs. Within-study results for were meta-analyzed in METAL[11] using an inverse-variance based model.

Characterization of gene(s) and non-coding features in associated loci. We determined the basepair (bp) 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[23]. LDLink uses 1000 genomes genotypes to calculate LD for a selected population; in our case all five European population were selected (CEU, TSI, FIN, GBR, and IBS). The boundaries for all variants in LD (r2 ≥ 0.5) with the top associated variant from the stage 2 meta-analysis for each region ±500kb of the ends of the LD blocks (as expression quantitative trait loci (eQTL) controlled genes are typically less than 500kb from their controlling variant[32]) were input into the UCSC genome browser's 'Table Browser' for RefSeq[33] and GENCODEv24[34] genes at each associated locus. The average size of the LD blocks was 123kb.

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[35] 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 variant with the lowest *P* in each genome-wide locus. We then used Ensembl VEP[36] for annotation of the set of sentinel variants and their proxies. We used BLOSUM62[37], SIFT[38], Polyphen-2[39], CADD[26], Condel[40], MPC[41], and Eigen[42] 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[43] 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 be contribute to the association signal through rare deleterious coding, splicing or loss-of-function (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 445 protein coding genes within our LD defined genome-wide loci were annotated with the gene-based results from this study. Complete details of the analysis can be found in Bis et al. 2018[44]. Briefly, SKAT-O gene-based testing was implemented with seqMeta[45] using multiple models of adjustment (model 0: PC and sequencing center adjusted; model 1: age, sex, PC and sequencing center adjusted; model 2: age, sex, PC, *APOE* and sequencing center adjusted). Only rare (MAF < 0.05), predicted functional and LOF variants were included in the analyses which employed Ensembl VEP consequence categories (high and moderate) and CADD annotation for filtering of variants for inclusion in the SKAT-O analyses. Four annotation models were considered: 1) only rare variants with "HIGH" (splicing or LOF variants) or "MODERATE" (inframe insertions/deletions, missense variants, and predicted protein altering variants) VEP consequences, 2) only rare variants with "HIGH" VEP consequences, 3) only rare variants with CADD Phred scores > 15 (the median value for all possible canonical splice site changes and non-synonymous variants), and 4) only rare variants with CADD Phred scores > 20. The CADD "Phred-scaled" score is obtained from a ranking of all ~8.6 billion variants from the GRCh37/hg19 reference in terms of magnitude and then transforming these ranks to Phred scores, allowing for example a cutoff of the top 0.1% predicted deleterious variants, which is equivalent to our CADD Phred > 20 cutoff. We corrected the results of these models for the 455 genome-wide loci gene list results using a 1% FDR P as a cutoff for significance.

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 variant in LD with the sentinel variants (r2 ≥ 0.5) using INFERNO[46] 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[30], HaploReg v4.1[47,48], GWAS4D[29], and the Ensembl Regulatory Build[49]. 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 tissue types and blood tissue types, including all immune-related cell types, most specifically myeloid cells (macrophages and monocytes) and B-lymphoid cells, cell types implicated in LOAD and neurodegeneration by a number of recent studies[50–53]. While their specificity may be lower for identifying AD risk eQTLs, we included whole blood cell studies in our AD relevant tissue class due to their high correlation of eQTLs with AD relevant tissues (70% with brain[54]; 51-70% for monocytes and lymphoblastoid cell lines (LCL) respectively[55]) and their large sample sizes which allow for increased discovery power. The eQTL databases and studies searched included: BRAINEAC[56] (12 brain regions), GTEx v7 (48 tissues)[57], BIOSQTL[58], CommonMind Consortium (dorsolateral prefrontal cortex)[59], and xQTLServer[60] (all via FUMA[61]); the NESDA NTR Conditional eQTL Catalog (whole blood)[62]; and Fairfax et al. 2012 (monocytes and B Cells)[63], Gibbs et al. 2010 (frontal cortex, pons)[64], Lappalainen et al. 2013 (LCL)[65], Montgomery et al. 2010 (LCL)[66], MuTHer (Adipose, LCL, skin)[67], and Zeller et al. 2010 (monocytes)[68] (all via exSNP[69]). An additional eQTL overlap search was conducted with INFERNO[46], where 44 GTEx v6 tissues were searched, with prioritization on the INFERNO tissue classes of brain and blood (see **Supplementary Table 13 for sample sizes of each database/study**).

Formal co-localization testing of our summary Stage 1 results was also conducted using 1) COLOC[70] via INFERNO, and 2) Summary Mendelian Randomization (SMR)-Heidi analysis[71]. 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 1Mb of the GWAS sentinel variants that pass a 5% Benjamini-Hochberg FDR-corrected p-SMR significance threshold and a p-HEIDI > 0.05 threshold were considered significant. The Westra eQTL[72] summary data and Consortium for the Architecture of Gene Expression (CAGE) eQTL summary data was used for analysis. These datasets, conducted in whole blood, are the largest eQTL studies conducted to date (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. Recent studies have shown significant overlap (50-70%) between brain and blood eQTL's[54]. 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, defined as all genes within ±500kb of the sentinel variant LD regions ($r^2 \geq 0.5$) (see **Supplementary Table 8** for a complete list of genes searched), using differential AD gene expression results from AlzBase[73], brain tissue expression from the Brain-RNAseq Database (http://www.brainrnaseq.org/[74,75]), and the HuMi_Aged gene set[76], a set of genes preferentially expressed in aged human brain by microglia. This set of genes was established through RNAseq expression analysis of aged human microglial cells from 10 post-mortem brains, and is enriched for AD genes ($P = 4.1 \times 10^{-5}$)[76]. AlzBase includes transcription data from brain and blood from aging, non-dementia, mild cognitive impairment, early stage AD and late stage AD. Please see ALZBase (http://alz.big.ac.cn/alzBase/Document) for a complete list of studies included in the search. Correlation values for the BRAAK stage expression were taken from the Zhang et al. 2013[77] study of 1,647 post-mortem brain tissues from LOAD patients and nondemented subjects.

Pathway Analysis. Pathway analyses were performed with MAGMA[78], 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 (i.e. LOAD), compared to other genes across the genome. Adaptive permutation was used to produce an empirical p-value and a FDR-corrected q-value. Gene-sets used in the analyses were from GO[79,80], KEGG[81,82], REACTOME[83,84], BIOCARTA, and MGI[85] 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 (Chr19:45,116,911-46,318,605). 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 potential regulatory variants for each gene, while secondary analyses was run using a 0-kb window[86]. 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 Aβ processing related genes from Campion et al.[87] Thirty-two Aβ–related gene sets and all 335 genes combined (see Campion et al.[87] for details) were run in MAGMA pathway analysis on both common (MAF ≥ 0.01) and rare (MAF < 0.01) variant summary results. The combined dataset of 28,730 unrelated individuals from the ADGC referenced in the GCTA COJO analysis were 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[88], and Jensen Diseases[89], Jensen Tissues[90], dbGAP gene sets and the ARCHS4[91] resource via the EnrichR[92] 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 use 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[61]. These analyses were performed in order to assess whether our 53 prioritized genes are significantly differentially expressed in certain GTEx v7[57] (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)[93]. 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-value < 0.05 and absolute log fold change ≥ 0.58) are considered DEGs. Input genes were tested against each of the DEG sets using the hypergeometric test. Significant enrichment is defined by Bonferonni corrected P-value ≤ 0.05.

HLA region analysis. Non-familial datasets from ADGC, EADI and GERAD consortiums were used for HLA analysis. After quality control on the imputation quality, 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 UMCWRMSSM datasets were not imputed as Affymetrix genotyping arrays are not supported by the imputation software.

Imputation of HLA alleles. Two-fields resolution HLA alleles were imputed using the R package HIBAG v1.4[94] and the non-Hispanic White (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 the developers of the imputation package. *HLA-A*, *HLA-B*, *HLA-C* class I genes and *HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, *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[95]. Associations of HLA alleles with disease were tested using logistic regressions, adjusting for age, sex and PCs as specified above for the SNP association analysis. Only HLA alleles with a frequency higher than 1% were analyzed. Haplotype estimations and association analyses with disease were performed using 'haplo.glm' function from the haplo.stats R package[96] with age, sex and PCs as covariates. Analysis was performed on 2-loci and 3-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 a 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[11]. 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. FDR threshold was set to 10%.

Data Availability

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 a NIAGADS- and NIA/NIH-sanctioned qualified-access data repository. 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. Genome-wide summary statistics for the Stage 1 discovery are available from The National Institute on Aging Genetics of Alzheimer's Disease (NIAGADS) website (https://www.niagads.org/). Stage 2 and stage 3 primary data are available upon request.

URLs:

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/

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