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New insights on the genetic etiology of Alzheimer's and related dementia

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New insights on the genetic etiology of Alzheimer's and related dementia

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ABSTRACT

Alzheimer's disease (AD) is a severe and incurable neurodegenerative disease, and the failure to find effective treatments suggests that the underlying pathology remains poorly understood. Due to its strong heritability, deciphering the genetic landscape of AD and related dementia (ADD) is a unique opportunity to advance our knowledge. We completed a meta-analysis of genome-wide association studies (39,106 clinically AD-diagnosed cases, 46,828 proxy-ADD cases and 401,577 controls) with the most promising signals followed-up in 25,392 independent AD cases and 276,086 controls. We report 75 risk loci for ADD, including 42 novel ones. Pathway-enrichment analyses confirm the involvement of amyloid/Tau pathways, highlight the role of microglia and its potential interaction with APP metabolism. Numerous genes exhibited differential expression or splicing in AD-related conditions and gene prioritization implies EGFR signaling and TNF-α pathway through LUBAC complex. We also generated a novel polygenic risk score strongly associated with the risk of future dementia or progression from mild cognitive impairment to dementia. In conclusion, by more than doubling the number of loci associated with ADD risk, our study offers new insights into the pathophysiological processes underlying AD and offers additional therapeutic entry-points and tools for translational genomics.

Main

Alzheimer's disease (AD) is the most common form of dementia. It exhibits a high heritability estimated between 60 and 80%[1]. This strong genetic component presents an opportunity to decipher the pathophysiological processes in AD and related dementia (ADD) and to identify novel biology, new prognosis/diagnosis markers and novel treatment targets (translational genomics). Characterizing the genetic risk factors of ADD is therefore a major objective and following the advent of the high-throughput genomic approaches, many loci/genes have been associated with the risk of ADD[2]. However, much of the underlying heritability remains unexplained and increasing the sample size of genome-wide association studies (GWAS) is an obvious route, already successfully applied in other common, complex diseases like diabetes, to facilitate the characterization of new genetic risk factors.

GWAS analysis.

The European Alzheimer's Disease BioBank (EADB) consortium brings together the various European GWAS consortia already working on AD and a new dataset of 20,464 AD cases and 22,244 controls collated from 15 European countries. The EADB GWAS results were meta-analysed with a proxy-ADD GWAS performed in the UK Biobank (UKBB; the UKBB proxy-ADD designation is based on questionnaire data asking if parents had AD which is less specific than clinically or pathological diagnosed AD). The EADB Stage I (GWAS meta-analysis) was based on 39,106 clinically diagnosed AD cases, 46,828 proxy-ADD cases (as defined in the Supplementary Information) and 401,577 controls (Supplementary Tables 1 and 2) and on 21,101,114 variants that passed quality control measures (Fig.1 and see Supplementary Fig. 1 for QQ plot and genomic inflation factors). We selected all variants with *P* value less than 1×10^{-5} in Stage I. We defined non-overlapping regions around those variants, excluded the region corresponding to *APOE*, and examined the remaining variants in a large follow-up sample that included clinically diagnosed AD cases and controls from the ADGC, FinnGen and CHARGE consortia (Stage II; 25,392 AD cases and 276,086 controls). A signal was considered as genome-wide significant if nominally associated ($P\leq0.05$) in Stage II, with same direction of association in the Stage I and Stage II analyses and if associated with ADD risk with $P\leq5\times10^{-8}$ in the Stage I + Stage II meta-analysis. In addition, we applied a PLINK clumping procedure[3] to define potential independent hits from the Stage I results (see Methods). After validation by conditional analyses (see Supplementary Information and Supplementary Tables 3 and 4), this approach led us to define 39 signals in 33 loci already known to be associated with the risk of developing ADD[4–10] and to propose 42 new loci (Table 1, Supplementary Table 5 and Supplementary Fig. 2-29). Of the 42 new loci, 17 had $P\leq5\times10^{-8}$ in Stage I and 25 were associated with $P\leq5\times10^{-8}$ after follow-up (Stage I +

Stage II meta-analysis including ADGC, CHARGE and FinnGen data). We also identified 6 loci with $P \leq 5 \times 10^{-8}$ in the Stage I + Stage II analysis, but failing replication in Stage II (Supplementary Table 6). Of note, the magnitude of associations in Stage I did not change substantially if we restricted the Stage I analyses to clinically-diagnosed AD cases (Supplementary Table 7 and Supplementary Fig. 30). Similarly, none of the signals observed seems to be especially driven by the UKBB data (Supplementary Table 7 and Forest plots in Supplementary Fig. 2-29). We finally provide a detailed analysis of the HLA locus (Supplementary Fig. 31-32 and Supplementary Tables 8-9).

We tested the association of the lead variants within our novel loci with the risk of developing other neurodegenerative diseases or AD-related disorders (Supplementary Fig. 33 and Supplementary Tables 10-12) and performed colocalization analyses for three loci known to be associated with Parkinson's disease (PD) (*IDUA*) or frontotemporal lobar degeneration with TAR DNA binding protein (TDP-43) inclusions (FTLD-TDP) (*TMEM106B* and *GRN*). The *IDUA* signal in PD is independent of the signal in AD (coloc PP3=99.9%) while the *TMEM106B* and *GRN* signals in FTLD-TDP probably share the same causal variants with AD (coloc PP4=99.8% and PP4=80.1% respectively, Supplementary Tables 13-14).

Pathway analyses

To better understand the novel biological insights emerging from this newly expanded AD genetic landscape, we first performed pathway enrichment analyses in Stage I association results. 150 gene sets remained significant after multiple testing correction ($q \leq 0.05$, see Methods, Supplementary Table 15). The most significant gene sets relate to amyloid and tau; other significant gene sets relate to lipids and immunity, including macrophage and microglial cell activation.

We then performed a single-cell expression enrichment analysis using two complementary measures in different human brain cell types: average gene expression per nucleus (Av. exp) and percentage of nuclei in a cell type expressing each gene (% Cell exp). Only microglial expression of these genes reached significance across the two measurements after correcting for multiple testing (Supplementary Table 16), with increased expression corresponding to more significant association with ADD. A similar result was also observed using the mouse single cell dataset (Supplementary Table 17). We finally tested whether the relationship between microglial expression and association with ADD risk was specific to particular areas of biology (Supplementary Table 18). The most significant interaction was detected between GO:1902991 (regulation of amyloid precursor protein catabolic process) and gene expression level in microglia ($q = 1.2 \times 10^{-12}$ and 8.3×10^{-8} for % Cell Exp. and Av. Exp. respectively). Thus, genes in the amyloid-beta pathways with highest microglial expression show the strongest association with ADD, suggesting a functional relationship between microglia and APP/Aβ pathways (Supplementary Table 19).

Gene prioritization

We next attempted to identify those genes most likely to be responsible for the ADD association signal at each locus. All the prioritized genes are summarized in Fig. 2 with a full description of the genes analyzed in the Supplementary Information (see also Supplementary Tables 20-30 and Supplementary Fig. 34-42).

For ten of the novel loci, brain molecular quantitative trait loci (QTL) analyses and transcriptome-wide association studies (TWAS) in AD-relevant brain regions, blood genetics-driven methylation (MetaMeth) analyses and/or APP metabolism results supported the genes closest to the lead variant: *TNIP1* (L11), *ICA1* (L15), *TMEM106B* (L16), *JAZF1* (L17), *CTSB* (L19), *ABCA1* (L21), *CTSH* (L29), *MAF* (L31), *SIGLEC11* (L38) and *RBCK1* (L40). Five other genes in the new loci can be prioritized as likely to be causal since the lead variants correspond to protein-altering variants within the gene itself: *SORT1* (L1), *MME* (L6), *SHARPIN* (L20), *DOC2A* (L30) and *WDR81* (L34). For *SHARPIN, DOC2A,* and *WDR81*, we found additional evidences that ADD risk is associated with expression and/or splicing

events. Of note, while *DOC2A* and *WDR81* are the most likely candidates, these loci also include other plausible genes (Fig. 2).

For seven loci: *NCK2* (L4), *COX7C* (L10), *RASGEF1C* (L12), *HS3HT5* (L13), *UMAD1* (L14), *FOXF1* (L32) and *APP* (L42), none of the genes presented any AD-related modulations (see Methods), therefore we considered that their proximity to the lead variant was in favor of their prioritization but at this stage at a lower level of confidence, except for *APP* (an obvious candidate for ADD) and *NCK2* (where the lead variant is rare).

The remaining twenty novel loci present a more complicated pattern since several genes exhibit AD-related modulations at the same locus, and/or the prioritized gene is not the nearest protein-coding gene. We could efficiently prioritize candidate risk genes in twelve additional loci: *ADAM17* (L2), *ICA1L* (L5), *RHOH* (L8), *OTULIN* (L9), *EGFR* (L18), *CCDC6* (L22), *TSPAN14* (L23), *BLNK* (L24), *PLEKHA1* (L25), *RITA1* (L26), *MYO15A* (L35) and *GRN* (L36). Some of these loci also include other genes of potential interest. In locus 18, *EGFR* is a likely candidate gene: its eQTL signals colocalize with the ADD risk association signal, and its fine-mapped eTWAS hits (with FOCUS posterior inclusion probability values of ~1) associate a predicted increased *EGFR* expression with increased ADD risk (Fig. 3, Supplementary Fig. 39). In the complex locus 23, *TSPAN14* was identified as exhibiting numerous AD-related expression and splicing modulations, including novel cryptic complex splicing events that we identified and experimentally confirmed (Fig. 3, Supplementary Fig. 40). In the remaining eight loci, we did not clearly identify a single candidate but current evidence points towards the following genes: *DGKQ*, *SLC26A1* and *IDUA* in locus 7, *FAM96A* and *SNX1* in locus 28, *ATP8B3*, *REXO1* and *KLF16* in locus 37, *RTEL1* and *LIME1* in locus 41. For the locus 39, we consider *LILRB2* as the plausible risk gene based on literature review[13,14]. Finally, we were not able to prioritize a gene in the complex IGH cluster (L27), nor in the *PRKD3* (L3) and *PRDM7* (L33) loci.

We performed protein-protein interaction (PPI) analyses based on previously known GWAS genes, our prioritized novel genes (dark green in Figure 2 and Supplementary Table 20) and a combination of both lists (see Supplementary Information section 11 for a description of the method). The largest network was 14, 8 and 31 proteins respectively (Supplementary Fig. 43). These networks were larger than expected by chance ($P<2x10^{-5}$, $P<3.9x10^{-3}$, $P<2x10^{-5}$ respectively). Notably, the number of interactions between our prioritized genes and previously known genes is also significantly larger than expected ($P=1x10^{-4}$), indicating the biological relevance of the newly prioritized genes to AD pathology. No such enrichment (p=0.77) was observed for the remaining genes in the new loci, highlighting again the value of our prioritization approach.

Polygenic risk score

We explored whether the genetic ADD burden as measured by a polygenic risk score (PRS) generated from our genome-wide significant variants (n=83, see Methods and Supplementary Table 31) might influence rate of progression to dementia starting from either normal cognition or mild cognitive impairment (MCI) using several longitudinal population-based and memory clinic cohorts (Supplementary Table 32).

In a meta-analysis of population-based studies, the PRS was significantly associated with risk of progression to all-causes of dementia (HR=1.05 per average risk variant, 95%CI [1.03-1.06], $P=1.2x10^{-13}$) and to AD (HR=1.06 per average risk variant, 95%CI [1.04-1.07], $P=1.1x10^{-12}$) (Figure 4). Results were confirmed in the Rotterdam population-based study: a PRS based on 77 variants (due to missing variant information) was also significantly associated with risk of progression to all-causes of dementia (HR=1.09 per average risk variant, 95%CI [1.08-1.11], $P=7.6x10^{-32}$) or with the risk of progression to AD (HR=1.10 per average risk variant, 95%CI [1.08-1.12], $P=1.0x10^{-27}$).

Similarly, in MCI patients from memory clinics, we observed a significant association of this PRS with the risk of progressing to all-causes of dementia (HR=1.04 per average risk variant,

95%CI [1.03-1.06], P=2.6x10^{-10}) or AD (HR=1.06 per average risk variant, 95%CI [1.04-1.07], P=2.8x10^{-12}) (Figure 4). All analyses were adjusted for age, sex, principal components and the number of APOE-ε4 and APOE-ε2 alleles (Figure 4, Supplementary Table 33).

Association of the PRS with the risk of dementia progression was not modified by APOE-ε4 (interaction P=0.95 and 0.44 in population-based or MCI studies respectively; see also APOE-ε4 strata analyses in Supplementary Fig. 44-45). As previously reported, APOE-ε4 influenced progression to all-causes of dementia (Supplementary Table 33).

DISCUSSION

This meta-analysis combining a new large case-control study and previous GWAS identified 75 independent genetic risk factors for ADD, 33 previously reported and 42 corresponding to novel signals, greatly expanding our knowledge of the complex genetic landscape of AD. A short description of the prioritized genes and their potential significance in AD pathophysiology is presented in the Supplementary Information.

Our meta-analysis and the characterization of these new loci refine and expand our current understanding of AD etiology. The pathway enrichment analyses remove ambiguities concerning the involvement of Tau binding proteins and APP/Aβ metabolism in late-onset AD processes. In addition, we implicated for the first time *ADAM17,* a gene whose protein product is known to carry α-secretase activity as ADAM10[15]. This observation affirms that a deregulation of the non-amyloidogenic pathway of APP metabolism is also important in the AD process. In addition, we identified four highly plausible candidate genes likely to modulate APP metabolism based on biological evidence (*ICA1L*, *ICA1*, *DOC2A* and *WDR81).*

These pathway enrichment analyses also confirmed the involvement of innate immunity and microglial activation in ADD (Supplementary Table 15). In addition, single-cell expression enrichment analysis also highlighted genes expressed in microglia (Supplementary Tables 16 and 17). Finally, ten of our prioritized genes appeared to be primarily expressed in microglia (Fig. 2 and Supplementary Table 34). Several publications have already demonstrated involvement of the corresponding proteins in microglia function/activation (see Supplementary Information) and importantly three, i.e. *GRN*, *SIGLEC11* and *LILRB2* have also been linked to Aβ peptides/amyloid plaques[13,16,17]. However, it is also important to keep in mind that six of our prioritized genes are expressed at only a very low level in microglia (Supplementary Table 34), emphasizing that ADD results from a complex crosstalk between different cell-types in the brain[18,19]. Of note, we report here the implication of the EGFR but also TNF-alpha signaling through the LUBAC complex (three out of its four complements are coded by ADD genetic risk factors, i.e. *OTULIN*, *SHARPIN*, and *RBCK1*) reinforcing the role of neuroinflammation in ADD[20].

Of note, several novel loci were also associated with the risk of developing FTLD, i.e. *MAPT*, *GRN*, and *TMEM106B*. This may be related to the misclassification in the diagnosis of clinical AD and the proxy-ADD diagnoses in the UKBB. However, both *GRN* and *TMEM106B* are associated with AD neuropathological features and *MAPT* encodes tau, the protein in AD neurofibrillary tangles. Our results may thus also emphasize a continuum between AD and FTD[20–22].

Increasing our understanding of the pathophysiological processes operating in AD will lead to better and more specific therapies. Doubling the number of genetic loci associated with ADD risk also gave us the opportunity to create a novel PRS. There are differing opinions regarding the best strategy to define PRS and the model used to evaluate prediction[24–28]. In our approach, we found an association of the PRS with the risk of incident dementia in a healthy population, as well as with progression from MCI to dementia. These results suggest that ADD susceptibility variants, in general, have a similar effect on progression at different clinical stages (independent of age and *APOE*). We also observed that inclusion of confirmed low frequency and rare variants could improve the power of our PRS (we compare HR between PRSs including different MAF thresholds in Supplementary Table 33).

In conclusion, our work doubles the number of ADD associated loci, expanding current knowledge of AD pathophysiological processes, presenting novel opportunities for the development of gene-specific treatments and PRS, further clarifying a path to translational genomics and personalized medicine.

METHODS Online

Samples. All discovery meta-analysis samples are from the following consortia/datasets: EADB, GR@ACE, EADI, GERAD/PERADES, DemGene, Bonn, the Rotterdam study, the CCHS study, NxC and the UK Biobank. Of note, in the UK Biobank, individual who did not report dementia or any family history of dementia were used as controls: analysis included 2,447 diagnosed cases, 46,828 proxy cases of dementia and 338,440 controls. Summary demographics of these case-control studies are described in Supplementary Table 1 and more detailed descriptions are available in the Supplementary Information. Replication samples are from the ADGC, CHARGE and FinnGen consortia (Supplementary Table 1 and Supplementary Information) and fully described elsewhere[5,6,9,10,29–31]. 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.

Quality control and imputation. Standard quality control was performed on variants and samples on all datasets individually. The samples were then imputed with the Trans-Omics for Precision Medicine (TOPMed) reference panel[32,33]. The Haplotype Reference Consortium (HRC) panel[34] was also used for some datasets (Supplementary Table 2). For the UK Biobank, we used the provided imputed data, generated from a combination of the 1000 Genomes (1000G), HRC and UK10K reference panels. See Supplementary Information for details.

Stage I analyses. Association tests between ADD clinical or proxy status and autosomal genetic variant were conducted separately in each dataset using logistic regression assuming an additive genetic model as implemented in SNPTEST[35] or in PLINK[3], except in the UK Biobank where a logistic mixed model as implemented in SAIGE[36] was considered. Analyses were performed on the genotype probabilities in SNPTEST (newml method) and on dosages in PLINK and SAIGE. Analyses were adjusted for principal components and genotyping centers when necessary (Supplementary Table 2). For the UK Biobank dataset, effect sizes and standard errors were corrected by a factor of two to take into account that proxy cases were analysed[7]. We filtered out duplicated variants and variants with (i) missing effect size, standard error or P value, (ii) absolute value of effect size above 5, (iii) imputation quality less than 0.3, (iv) the product of the minor allele count (MAC) and the imputation quality (mac-info score) less than 20. In the UK Biobank dataset, only variants with minor allele frequency (MAF) above 0.01% and MAC above 3 were analyzed. For datasets not imputed with the TOPMed reference panel, we also excluded (i) variants for which conversion of position or alleles from the GRCh37 assembly to the GRCh38 assembly was not possible or problematic, or (ii) variants with very large difference of frequency between the TOPMed reference panel and the reference panels used to perform imputation.
Results were then combined across studies with a fixed-effect meta-analysis using the inverse variance weighted approach as implemented in the METAL software[37]. We filtered (i) variants with heterogeneity P value below 5×10^{-8}, (ii) variants analyzed in less than 20% of the total number of cases and (iii) variants with frequency amplitude above 0.4 (defined as the difference between the maximum and minimum frequency across studies). We further excluded variants analyzed in the UK Biobank only or variants not analyzed in the EADB-TOPMed dataset.
Genomic inflation factor lambda was computed with the R package GenABEL[38] using the median approach after exclusion of the *APOE* region (44 Mb to 46 Mb on chromosome 19 in GRCh38). The linkage disequilibrium (LD) score (LDSC) regression intercept was computed with the LDSC software using the “baselineLD” LD scores built from 1000 Genomes Phase 3 [39]. The analysis was restricted to HapMap 3 variants and excluded multi-allelic variants, variants without an rsID and variants in the *APOE* region.

Definition of associated loci. A region of +/- 500kb was defined around each variant with a Stage I P value below $1x10^{-5}$. Those regions were then merged with the bedtools software to define non-overlapping regions. The region corresponding to the APOE locus was excluded. We then applied the PLINK clumping procedure to define independent hits in each of those regions. The clumping procedure was applied on all variants with a Stage I P value below $1x10^{-5}$. It is an iterative process beginning with the variant with the lowest P value, named index variant. Variants with a Stage I P value below $1x10^{-5}$, located within 500 kb of this index variant, and in LD with the index variant (r^2 above 0.001) are assigned to the clump of this index variant. The clumping procedure is then applied on all the remaining variants, until no variant is left. LD was computed in the EADB-TOPMed dataset using high quality (probability ≥ 0.8) imputed genotypes.

Stage II analyses. Variants with a Stage I P value below $1x10^{-5}$ were followed up (see Supplementary Information). A fixed-effect meta-analysis was performed with METAL (inverse variance weighted approach) to combine the results across Stages I and II. In each clump, we then reported the replicated variant (same direction of effects between Stage I and Stage II, with a Stage II P value below 0.05) with the lowest P value in the meta-analysis. Those variants were considered associated at the genome-wide significance level if they had a P value below $5x10^{-8}$ in the Stages I + II meta-analysis. Among them, we excluded the variant chr6:32657066:G:A because its frequency amplitude was large.

Pathway analysis. The assignment of Gene Ontology (GO) terms to human genes was obtained from the "gene2go" file, downloaded from NCBI on March 11th 2020. "Parent" GO terms were assigned to genes using the ontology file also downloaded on the same date. GO terms were assigned to genes based on experimental or curated evidence of a specific type, so evidence codes IEA (electronic annotation), NAS (non-traceable author statement), RCA (inferred from reviewed computational analysis) were excluded. Pathways were downloaded from the Reactome website on April 26th 2020. Biocarta, KEGG and Pathway Interaction Database (PID) pathways were downloaded from v7.1 (March 2020) of the Molecular Signatures Database. Analysis was restricted to GO terms containing between 10 and 2000 genes. No size restrictions were placed on the other gene sets, since there were fewer of them. This resulted in a total of 10,271 gene sets for analysis. Gene set enrichment analyses were performed in MAGMA[40], correcting for the number of variants in each gene, linkage disequilibrium (LD) between variants and LD between genes. LD was computed in the EADB-TOPMed dataset using high quality (probability ≥ 0.9) imputed genotypes. The measure of pathway enrichment is the MAGMA "competitive" test (where the association statistic for genes in the pathway is compared to those of all other protein-coding genes), as recommended by De Leeuw et al.[41]. We used the "mean" test statistic, which uses the sum of -log(variant P value) across all genes. The primary analysis assigned variants to genes if they lie within the gene boundaries, but a secondary analysis used a window of 35kb upstream and 10kb downstream to assign variants to genes, as in Kunkle et al[5]. The primary analysis used all variants with imputation quality above 0.8. We used q-values[42] to account for multiple testing. Enrichment analyses were performed on single cell expression data from human (Allen Brain Atlas) or mouse (Skene et al[43]) by using average gene expression per nucleus or percentage of nuclei in a cell type expressing each gene as quantitative covariates in a MAGMA gene property analysis.

QTLs/TWAS/MetaMeth. In order to prioritize candidate genes in the new loci, we employed several approaches: (i) expression quantitative trait loci (eQTLs) and colocalization (eQTL coloc) analyses combined with expression transcriptome-wide association studies (eTWAS) in AD-relevant brain regions; (ii) splicing quantitative trait loci (sQTL) and colocalization (sQTL coloc) analyses combined with splicing transcriptome-wide association studies (sTWAS) in AD-relevant brain regions; (iii) genetic-driven methylation as a biological mediator of genetic signals in blood (MetaMeth). In our regions of interest, we systematically searched if a gene has a significant e/sQTL, colocalization e/sTWAS and/or MetaMeth

signal(s) within a region of 1 Mb around the lead variant. In addition to the "nearest" genes from the lead variant, we kept for further analyses those exhibiting such AD-related modulations. We then added several additional approaches: (i) data from a genome-wide, high-content siRNA screening approach to assess the functional impact of gene under-expression on APP metabolism[44], (ii) methylation QTL (mQTL) and histone acetylation QTL (haQTL) effects of the lead variants in DLPFC[45], (iii) eQTL effects of the lead variants in monocytes and macrophages[46–51], (iv) e/sQTL effects of lead variants in LCL along with e/sQTL coloc and e/sTWAS analyses in LCL, and (v) e/sQTL effects of lead variants in microglia along with e/sQTL coloc analyses[52]. A full description of how the genes were prioritized is reported in the Supplementary Information (see also Supplementary Tables 20-30 and Supplementary Fig. 34-42).

Cell type expression. Assignment of newly identified ADD risk genes to specific cell classes of the adult brain was performed as previously described[53]. Briefly, middle temporal gyrus (MTG) single-nucleus transcriptomes (15,928 total nuclei derived from 8 human tissue donors ranging in age from 24-66 year), were used to annotate and select 6 main cell classes using S*eurat 3.1.1*[54]: Glutamatergic Neurons, GABAergic Neurons, Astrocytes, Oligodendrocytes, Microglia and Endothelial cells.

PRS analysis. Eight longitudinal MCI cohorts and six population-based studies were included in the analysis and are fully described in the Supplementary Information and Supplementary Table 32.
PRS were calculated as previously described[24]. Briefly, we considered variants with genome-wide significant evidence of association with ADD in our study and used three different MAF thresholds (Fig. 1, Table 1 and Supplementary Table 33). Variants were directly genotyped or imputed ($R^2 \geq 0.3$). We did not include any *APOE* variants in the PRS. The PRS (based on dosage) was calculated as the weighted average of the number of risk increasing alleles for each variant using dosages. Weights were based on the respective log(OR) obtained in the Stage II. The PRS was then multiplied by the number of included variants. Thus, an increase in HR corresponds to carry one additional average risk allele.
All principal components (PCs) used were generated per cohort, using the same variants that were used on the case/control study PCA. The number of *APOE*-e4 alleles was obtained based on direct genotyping or, if missing, based on genotypes (with probability > 0.8) derived from the TOPMed imputations.
The association of the PRS with risk of progression to dementia in cognitively normal persons or in patients with MCI was assessed using Cox proportional hazards models, initially for all-cause dementia and next, using analysis focused on conversion to AD. Herein, converter to non-AD dementias were coded as censored.
Each Cox-regression analysis was first performed unadjusted for covariates and then repeated, adjusted for age, sex and the first four PCs to correct for potential population stratification. In the 3C study, analysis was adjusted on age, sex, the two first PCs and center. Analyses were additionally controlled for the number of *APOE*-e4 and *APOE*-e2 alleles (assuming an additive effect) to assess the independence of the PRS from *APOE*. The interaction between the PRS and the number of *APOE*-e4 alleles was tested. Analyses were repeated stratified by the presence or absence of at least one *APOE*-e4 allele. Results from individual cohorts were meta-analyzed using fixed effects meta-analysis.
Imputations in Rotterdam were performed using the HRC imputation panel and 6 variants were missing. This study was therefore not included in the meta-analysis.

URLs:
Bedtools: https://bedtools.readthedocs.io/en/latest/
BCFtools: http://samtools.github.io/bcftools/bcftools.html
Samtools: http:/www.htslib.org/doc/samtools.html
gene2go: ftp://ftp.ncbi.nlm.nih.gov/gene/DATA/
Gene Ontology: http://geneontology.org/docs/download-ontology/

Reactome: https://reactome.org/download-data
KEGG and Pathway Interaction Database (PID) pathways: https://www.gsea-msigdb.org/gsea/msigdb/index.jsp
AMP-AD rnaSeqReprocessing Study: https://www.synapse.org/#!Synapse:syn9702085
MayoRNAseq WGS VCFs: https://www.synapse.org/#!Synapse:syn11724002
ROSMAP WGS VCFs: https://www.synapse.org/#!Synapse:syn11724057
MSBB WGS VCFs: https://www.synapse.org/#!Synapse:syn11723899
GTEx pipeline: https://github.com/broadinstitute/gtex-pipeline
Leafcutter: https://github.com/davidaknowles/leafcutter
RegTools: https://github.com/griffithlab/regtools
Enhanced version of FastQTL: https://github.com/francois-a/fastqtl
Picard: https://broadinstitute.github.io/picard/
eQTLGen: https://www.eqtlgen.org/
eQTL Catalogue database: https://www.ebi.ac.uk/eqtl/
Brain xQTL serve: http://mostafavilab.stat.ubc.ca/xqtl/
GTEx v8 eQTL and sQTL catalogues: https://www.gtexportal.org/
coloc: https://github.com/chr1swallace/coloc
FUSION: https://github.com/gusevlab/fusion_twas
GTEx v8 expression and splicing prediction models: http://predictdb.org/
MetaXcan: https://github.com/hakyimlab/MetaXcan
FOCUS: https://github.com/bogdanlab/focus
qcat: https://github.com/nanoporetech/qcat
minimap2: https://github.com/lh3/minimap2
NanoStat: https://github.com/wdecoster/nanostat
mosdepth: https://github.com/brentp/mosdepth
ggplot2: https://ggplot2.tidyverse.org/
LocusZoom: https://github.com/statgen/locuszoom-standalone
pyGenomeTracks: https://github.com/deeptools/pyGenomeTracks
BECon website: https://redgar598.shinyapps.io/BECon/
VCFs of phased biallelic SNV and INDEL variants of 1KG samples (de novo called on GRCh38):
ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/data_collections/1000_genomes_project/release/20190312_biallelic_SNV_and_INDEL/
MiGA eQTLs: https://doi.org/10.5281/zenodo.4118605
MiGA sQTLs: https://doi.org/10.5281/zenodo.4118403
MiGA Meta-analysis: https://doi.org/10.5281/zenodo.4118676

References:

1. Gatz, M. *et al.* Role of genes and environments for explaining Alzheimer disease. *Arch. Gen. Psychiatry* **63**, 168–74 (2006).

2. Bellenguez, C., Grenier-Boley, B. & Lambert, J. C. Genetics of Alzheimer's disease: where we are, and where we are going. *Current Opinion in Neurobiology* vol. 61 40–48 (2020).

3. Chang, C. C. *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).

4. Jansen, I. E. *et al.* Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat. Genet.* **51**, 404–413 (2019).

5. Kunkle, B. W. *et al.* Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat. Genet.* **51**, 414–430 (2019).

6. Lambert, J. C. *et al.* Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat. Genet.* **45**, 1452–8 (2013).

7. Liu, J. Z., Erlich, Y. & Pickrell, J. K. Case-control association mapping by proxy using family history of disease. *Nat. Genet.* **49**, 325–331 (2017).

8. Marioni, R. E. *et al.* GWAS on family history of Alzheimer's disease. *Transl. Psychiatry* **8**, (2018).

9. Sims, R. *et al.* Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. *Nat. Genet.* (2017) doi:10.1038/ng.3916.

10. Jun, G. *et al.* A novel Alzheimer disease locus located near the gene encoding tau protein. *Mol. Psychiatry* **21**, 108–17 (2016).

11. Schwartzentruber, J. *et al.* Genome-wide meta-analysis, fine-mapping, and integrative prioritization identify new Alzheimer's disease risk genes. *medRxiv* 2020.01.22.20018424 (2020) doi:10.1101/2020.01.22.20018424.

12. de Rojas, I. *et al.* Common variants in Alzheimer's disease: Novel association of six genetic variants with AD and risk stratification by polygenic risk scores. *medRxiv* 19012021 (2019) doi:10.1101/19012021.

13. Kim, T. *et al.* Human LilrB2 is a β-amyloid receptor and its murine homolog PirB regulates synaptic plasticity in an Alzheimer's model. *Science (80-.).* **341**, 1399–1404 (2013).

14. Cao, Q. *et al.* Inhibiting amyloid-ß cytotoxicity through its interaction with the cell surface receptor LilrB2 by structure-based design. *Nat. Chem.* **10**, (2018).

15. Deuss, M., Reiss, K. & Hartmann, D. Part-Time α-Secretases: The Functional Biology of ADAM 9, 10 and 17. *Curr. Alzheimer Res.* **5**, 187–201 (2008).

16. Salminen, A. & Kaarniranta, K. Siglec receptors and hiding plaques in Alzheimer's disease. *Journal of Molecular Medicine* vol. 87 697–701 (2009).

17. Takahashi, H. *et al.* Opposing effects of progranulin deficiency on amyloid and tau pathologies via microglial TYROBP network. *Acta Neuropathol.* **133**, 785–807 (2017).

18. De Strooper, B. & Karran, E. The Cellular Phase of Alzheimer's Disease. *Cell* vol. 164 603–615 (2016).

19. Dourlen, P., Kilinc, D., Malmanche, N., Chapuis, J. & Lambert, J. C. The new genetic landscape of Alzheimer's disease: from amyloid cascade to genetically driven synaptic failure hypothesis? *Acta Neuropathologica* vol. 138 221–236 (2019).

20. Spit, M., Rieser, E. & Walczak, H. Linear ubiquitination at a glance. *J. Cell Sci.* **132**, (2019).

21. Mendsaikhan, A., Tooyama, I. & Walker, D. G. Microglial Progranulin: Involvement in Alzheimer's Disease and Neurodegenerative Diseases. *Cells* **8**, 230 (2019).

22. Li, Z. *et al.* The TMEM106B FTLD-protective variant, rs1990621, is also associated with increased neuronal proportion. *Acta Neuropathol.* **139**, 45–61 (2020).

23. Yang, H. S. *et al.* Genetics of Gene Expression in the Aging Human Brain Reveal TDP-43 Proteinopathy Pathophysiology. *Neuron* **107**, 496-508.e6 (2020).

24. Chouraki, V. *et al.* Evaluation of a Genetic Risk Score to Improve Risk Prediction for Alzheimer's Disease. *J. Alzheimers. Dis.* **53**, 921–32 (2016).

25. Leonenko, G. *et al.* Polygenic risk and hazard scores for Alzheimer's disease prediction. *Ann. Clin. Transl. Neurol.* **6**, 456–465 (2019).

26. Desikan, R. S. *et al.* Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. *PLOS Med.* **14**, e1002258 (2017).

27. Lacour, A. *et al.* Genome-wide significant risk factors for Alzheimer's disease: Role in progression to dementia due to Alzheimer's disease among subjects with mild cognitive impairment. *Mol. Psychiatry* **22**, 153–160 (2017).

28. Leonenko, G. *et al.* Genetic risk for alzheimer disease is distinct from genetic risk for amyloid deposition. *Ann. Neurol.* **86**, 427–435 (2019).

29. Psaty, B. M. *et al.* Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium design of prospective meta-analyses of genome-wide association studies from 5 Cohorts. *Circulation: Cardiovascular Genetics* vol. 2 73–80 (2009).

30. Naj, A. C. *et al.* Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat. Genet.* **43**, 436–41 (2011).

31. Jun, G. *et al.* Meta-analysis confirms CR1, CLU, and PICALM as alzheimer disease risk loci and reveals interactions with APOE genotypes. *Arch. Neurol.* **67**, 1473–84 (2010).

32. Taliun, D. *et al.* Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. *bioRxiv* **2**, 563866 (2019).

33. Das, S. *et al.* Next-generation genotype imputation service and methods. *Nat. Genet.* **48**, 1284–1287 (2016).

34. McCarthy, S. *et al.* A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–83 (2016).

35. Marchini, J., Howie, B., Myers, S., McVean, G. & Donnelly, P. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat. Genet.* **39**, 906–13 (2007).

36. Zhou, W. *et al.* Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. *Nat. Genet.* **50**, 1335–1341 (2018).

37. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190–1 (2010).

38. Aulchenko, Y. S., Ripke, S., Isaacs, A. & van Duijn, C. M. GenABEL: an R library for genome-wide association analysis. *Bioinformatics* **23**, 1294–1296 (2007).

39. Bulik-Sullivan, B. *et al.* LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).

40. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: Generalized Gene-Set Analysis of GWAS Data. *PLoS Comput. Biol.* **11**, (2015).

41. De Leeuw, C. A., Neale, B. M., Heskes, T. & Posthuma, D. The statistical properties of gene-

set analysis. *Nat. Rev. Genet.* **17**, 353–364 (2016).

42. Storey, J. D. & Tibshirani, R. Statistical significance for genomewide studies. *Proc. Natl. Acad. Sci. U. S. A.* **100**, 9440–9445 (2003).

43. Skene, N. G. *et al.* Genetic identification of brain cell types underlying schizophrenia. *Nat. Genet.* **50**, 825–833 (2018).

44. Chapuis, J. *et al.* Genome-wide, high-content siRNA screening identifies the Alzheimer's genetic risk factor FERMT2 as a major modulator of APP metabolism. *Acta Neuropathol.* **133**, 955–966 (2017).

45. Ng, B. *et al.* An xQTL map integrates the genetic architecture of the human brain's transcriptome and epigenome. *Nat. Neurosci.* **20**, 1418–1426 (2017).

46. Alasoo, K. *et al.* Shared genetic effects on chromatin and gene expression indicate a role for enhancer priming in immune response. *Nat. Genet.* **50**, 424–431 (2018).

47. Nédélec, Y. *et al.* Genetic Ancestry and Natural Selection Drive Population Differences in Immune Responses to Pathogens. *Cell* **167**, 657-669.e21 (2016).

48. Chen, L. *et al.* Genetic Drivers of Epigenetic and Transcriptional Variation in Human Immune Cells. *Cell* **167**, 1398-1414.e24 (2016).

49. Momozawa, Y. *et al.* IBD risk loci are enriched in multigenic regulatory modules encompassing putative causative genes. *Nat. Commun.* **9**, (2018).

50. Fairfax, B. P. *et al.* Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression. *Science (80-.).* **343**, (2014).

51. Quach, H. *et al.* Genetic Adaptation and Neandertal Admixture Shaped the Immune System of Human Populations. *Cell* **167**, 643-656.e17 (2016).

52. De, K. *et al.* Atlas of genetic effects in human microglia transcriptome across brain regions, aging and disease pathologies. *bioRxiv* 2020.10.27.356113 (2020) doi:10.1101/2020.10.27.356113.

53. Coelho, D. M., Carvalho, L. I. da C., Melo-de-Farias, A. R., Lambert, J.-C. & Costa, M. R. Differential transcript usage unravels gene expression alterations in Alzheimer's disease human brains. *medRxiv* 2020.03.19.20038703 (2020) doi:10.1101/2020.03.19.20038703.

54. Butler, A., Hoffman, P., Smibert, P., Papalexi, E. & Satija, R. Integrating single-cell transcriptomic data across different conditions, technologies, and species. *Nat. Biotechnol.* **36**, 411–420 (2018).

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Author contributions
EADB Coordination: A.B., K.M., F.J., M.T., R.F-S., J.C., J-F.D., O.A.A., M.I., M.H., K.S., C.VD., R.S., W.M.VDF., A.Ruiz., A.Ramirez., J-C.L; **Data Analyses** : C.B., F.K., I.J. V.A. S.M-G., N.A., B.G-B., P.A.H., R.C-M., L.K., V.D., S.J.VDL., T.K., I.R., J.C., M.C., P.G-G.; **ADGC analysis and coordination**: A.C.N, W.S.B, L.A.F., J.L.H., K.L.H-N., P.P.K., B.W.K., C-Y.L., E.R.M., R.M., M.A.P-V., J.S., L-S.W., Y.Z., G.D.S.; **Charge analysis and coordination**: Q.Y., J.C.B., A.DS., C.S., B.P., R.W., O.L., S.S.; **FinnGen analysis**: T.K., M.H.; **Rotterdam Analysis**: A.Y., I.P-N, M.G., A.I.; **Core writing group**: C.B., F.K., V.A., B.G-B., P.A.H., R.C-M., L.K., S.J.VDL., K.S., A.Ruiz., A.Ramirez., J-C.L. All other authors contributed data and all authors critically reviewed the paper.

Data Availability Statement
Summary statistics will be made available upon publication.
All the data used in the gene prioritization are publically available:
AMP-AD rnaSeqReprocessing Study: https://www.synapse.org/#!Synapse:syn9702085
MayoRNAseq WGS VCFs: https://www.synapse.org/#!Synapse:syn11724002
ROSMAP WGS VCFs: https://www.synapse.org/#!Synapse:syn11724057
MSBB WGS VCFs: https://www.synapse.org/#!Synapse:syn11723899
GTEx pipeline: https://github.com/broadinstitute/gtex-pipeline
eQTLGen: https://www.eqtlgen.org/
eQTL Catalogue database: https://www.ebi.ac.uk/eqtl/
Brain xQTL serve: http://mostafavilab.stat.ubc.ca/xqtl/
GTEx v8 eQTL and sQTL catalogues: https://www.gtexportal.org/
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Table 1: Summary of association results in Stage I + II for (a) known loci and (b) new loci with a genome-wide significant signal.
[a]Reference SNP (rs) number according to dbSNP build 153; [b]Chromosome; [c]GRCh38 assembly; [d]Nearest protein coding gene according to Gencode release 33; [e]Weighted average of minor allele frequency across discovery studies; [f]Approximate odds-ratio calculated with respect to the minor allele; [g]95% confidence interval; [h]P value.

Figure 1: Manhattan plot of the Stage I results. Variants with P value below $1x10^{-36}$ are not shown. Loci with a genome-wide significant signal are annotated (known loci in black and new loci in red). Variants in new loci are highlighted in red. The red dotted line represents the genome-wide significance level (P=$5x10^{-8}$), while the black dotted line represents the suggestive significance level (P=$1x10^{-5}$).

Figure 2: (A) Top candidate genes in the 42 new genome-wide-significant loci and (B) their level of expression in different brain cell types. In order to prioritize candidate genes in the new loci, we considered the nearest protein-coding gene from the lead variant and the genes exhibiting AD-related modulations within a region of 1 Mb around the lead variant. The average expression of each gene expressed by at least 10% of cells (pct.exp > 0.1) was rescaled from 0 to 2, allowing the identification of genes expressed by unique or multiple cell classes. On the left panel, the brown squares represent significant hits for the respective columns. The prioritized genes in each locus are marked with dark green colour, meanwhile light green colour is used when several candidate genes were retained in the same locus and/or the overall evidence is weaker than the evidence for the prioritized genes with the dark green squares. CADD (v1.6) PHRED scores of protein-altering lead variants are shown in the respective column. The columns demonstrating lead variant m/haQTL effects in DLPFC and lead variant eQTL effects in naive state monocyte, macrophages and microglia are annotated for the type of association (mQTL: methylation QTL, haQTL: histone acetylation QTL, mon: monocyte eQTL, mac: macrophage eQTL).

Figure 3: QTL mapping, QTL colocalization, and TWAS results on SEC61G and TSPAN14 loci. (a) An intergenic, distant, and low-frequency cis-eQTL for *EGFR* locus colocalizes (PP4: 0.98) with EADB GWAS signal where genetic downregulation of *EGFR* is significantly associated with lower ADD risk. (b) Elucidation of *TSPAN14* locus: through e/sQTLs, the protective signal is associated with decreased *TSPAN14* expression and increased cryptic splicing (within ADAM10-interacting domain) that are confirmed by long-read single-molecule sequencing on cDNA derived from hippocampus (Hipp.), frontal cortex (FC), lymphoblastoid cell lines (LCL). GWAS and e/sQTL association signals are shown as $-\log_{10}(P)$ and cumulative coverage tracks are in $\log_{10}$ scale. The purple dots show the lead variants in the investigated loci, and LD r^2 values were calculated with respect to these lead variants using the 1000 Genomes non-Finnish European LD reference panel prepared for the TWAS analyses.

Figure 4: Association of PRS with the risk of progression to dementia starting from either (A) normal cognition or (B) mild cognitive impairment (MCI). Polygenic risk score (PRS) was based on the genetic data of 83 variants (see Methods and Supplementary Table 31).
HR: Hazard Ratio; MCI: Mild cognitive impairment; FE: fixed-effect; *P* het: heterogeneity *P* value

Table 1

a)

Variant[a]	Chr.[b]	Position[c]	Gene[d]	Known locus	Minor/Major allele	MAF[e]	App. OR[f]	95% CI[g]	P[h]
rs679515	1	207577223	CR1	CR1	T/C	0.188	1.13	1.11-1.15	$7.2x10^{-46}$
rs6733839	2	127135234	BIN1	BIN1	T/C	0.389	1.17	1.16-1.19	$6.1x10^{-110}$
rs10933431	2	233117202	INPP5D	INPP5D	G/C	0.234	0.93	0.92-0.95	$3.6x10^{-15}$
rs6846529	4	11023507	CLNK	CLNK/HS3ST1	C/T	0.283	1.07	1.05-1.08	$2.2x10^{-17}$
rs6605556	6	32615322	HLA-DQA1	HLA	G/A	0.161	0.91	0.90-0.93	$7.1x10^{-20}$
rs10947943	6	41036354	UNC5CL	TREM2	A/G	0.142	0.94	0.93-0.96	$1.1x10^{-9}$
rs143332484	6	41161469	TREM2	TREM2	T/C	0.013	1.41	1.32-1.50	$2.8x10^{-25}$
rs75932628	6	41161514	TREM2	TREM2	T/C	0.003	2.39	2.09-2.73	$2.5x10^{-37}$
rs60755019	6	41181270	TREML2	TREM2	G/A	0.004	1.55	1.33-1.80	$2.1x10^{-8}$
rs7767350	6	47517390	CD2AP	CD2AP	T/C	0.271	1.08	1.06-1.09	$7.9x10^{-22}$
rs6966331	7	37844191	EPDR1	NME8	T/C	0.349	0.96	0.94-0.97	$4.6x10^{-10}$
rs7384878	7	100334426	SPDYE3	ZCWPW1/NYAP1	C/T	0.31	0.92	0.91-0.94	$1.1x10^{-26}$
rs11771145	7	143413669	EPHA1	EPHA1	A/G	0.348	0.95	0.93-0.96	$3.3x10^{-14}$
rs73223431	8	27362470	PTK2B	PTK2B	T/C	0.369	1.07	1.06-1.08	$4.0x10^{-22}$
rs11787077	8	27607795	CLU	CLU	T/C	0.392	0.91	0.90-0.92	$1.7x10^{-44}$
rs7912495	10	11676714	USP6NL	ECHDC3	G/A	0.462	1.06	1.05-1.08	$9.7x10^{-19}$
rs10437655	11	47370397	SPI1	CELF1/SPI1	A/G	0.399	1.06	1.04-1.07	$5.3x10^{-14}$
rs1582763	11	60254475	MS4A4A	MS4A	A/G	0.371	0.91	0.90-0.92	$3.7x10^{-42}$
rs3851179	11	86157598	EED	PICALM	T/C	0.358	0.9	0.89-0.92	$3.0x10^{-45}$
rs74685827	11	121482368	SORL1	SORL1	G/T	0.019	1.19	1.13-1.25	$2.8x10^{-11}$
rs11218343	11	121564878	SORL1	SORL1	C/T	0.039	0.84	0.81-0.87	$1.4x10^{-21}$
rs17125924	14	52924962	FERMT2	FERMT2	G/A	0.089	1.1	1.07-1.12	$8.3x10^{-10}$
rs7401792	14	92464917	SLC24A4	SLC24A4/RIN3	G/A	0.371	1.04	1.02-1.05	$4.8x10^{-6}$
rs12590654	14	92472511	SLC24A4	SLC24A4/RIN3	A/G	0.328	0.93	0.92-0.95	$4.2x10^{-21}$
rs8025980	15	50701814	SPPL2A	SPPL2A	G/A	0.345	0.96	0.94-0.97	$1.3x10^{-6}$
rs602602	15	58764824	MINDY2	ADAM10	A/T	0.28	0.94	0.93-0.96	$2.1x10^{-15}$
rs117618017	15	63277703	APH1B	APH1B	T/C	0.144	1.11	1.09-1.13	$2.2x10^{-25}$
rs889555	16	31111250	BCKDK	KAT8	T/C	0.281	0.95	0.94-0.97	$2.0x10^{-11}$
rs4985556	16	70660097	IL34	IL34	A/C	0.115	1.07	1.05-1.09	$6.0x10^{-10}$
rs12446759	16	81739398	PLCG2	PLCG2	G/A	0.403	0.95	0.94-0.96	$1.2x10^{-13}$
rs72824905	16	81908423	PLCG2	PLCG2	G/C	0.008	0.74	0.68-0.81	$8.5x10^{-12}$
rs7225151	17	5233752	SCIMP	SCIMP/RABEP1	A/G	0.124	1.08	1.05-1.10	$4.1x10^{-13}$
rs199515	17	46779275	WNT3	MAPT	G/C	0.219	0.94	0.93-0.96	$9.3x10^{-13}$
rs616338	17	49219935	ABI3	ABI3	T/C	0.012	1.32	1.23-1.42	$2.8x10^{-14}$
rs2526377	17	58332680	TSPOAP1	TSPOAP1	G/A	0.445	0.95	0.94-0.97	$1.6x10^{-12}$
rs4277405	17	63471557	ACE	ACE	C/T	0.384	0.94	0.93-0.95	$8.8x10^{-20}$
rs12151021	19	1050875	ABCA7	ABCA7	A/G	0.336	1.1	1.09-1.12	$1.6x10^{-37}$
rs6014724	20	56423488	CASS4	CASS4	G/A	0.09	0.89	0.87-0.91	$4.1x10^{-21}$
rs2830489	21	26775872	ADAMTS1	ADAMTS1	T/C	0.281	0.95	0.94-0.97	$1.7x10^{-10}$

b)

Locus number	Variant[a]	Chr.[b]	Position[c]	Gene[d]	Minor/Major allele	MAF[e]	App. OR[f]	95% CI[g]	P[h]
1	rs141749679	1	109345810	SORT1	C/T	0.004	1.38	1.24-1.54	$7.5x10^{-9}$
2	rs72777026	2	9558882	ADAM17	G/A	0.144	1.06	1.04-1.08	$2.7x10^{-8}$
3	rs17020490	2	37304796	PRKD3	C/T	0.145	1.06	1.04-1.08	$3.3x10^{-9}$
4	rs143080277	2	105749599	NCK2	C/T	0.005	1.47	1.33-1.63	$2.1x10^{-13}$
5	rs139643391	2	202878716	WDR12	T/TC	0.131	0.94	0.92-0.96	$1.1x10^{-8}$
6	rs16824536	3	155069722	MME	A/G	0.054	0.92	0.89-0.95	$3.6x10^{-8}$
6	rs61762319	3	155084189	MME	G/A	0.026	1.16	1.11-1.21	$2.2x10^{-11}$
7	rs3822030	4	993555	IDUA	G/T	0.429	0.95	0.94-0.96	$8.3x10^{-12}$
8	rs2245466	4	40197226	RHOH	G/C	0.343	1.05	1.03-1.06	$1.2x10^{-9}$
9	rs112403360	5	14724304	ANKH	A/T	0.073	1.09	1.06-1.12	$2.3x10^{-9}$
10	rs62374257	5	86927378	COX7C	C/T	0.23	1.07	1.05-1.09	$1.4x10^{-15}$
11	rs871269	5	151052827	TNIP1	T/C	0.326	0.96	0.95-0.97	$8.7x10^{-9}$
12	rs113706587	5	180201150	RASGEF1C	A/G	0.11	1.09	1.07-1.12	$2.2x10^{-16}$
13	rs785129	6	114291731	HS3ST5	T/C	0.35	1.04	1.03-1.06	$2.4x10^{-9}$
14	rs6943429	7	7817263	UMAD1	T/C	0.42	1.05	1.03-1.06	$1.0x10^{-10}$
15	rs10952097	7	8204382	ICA1	T/C	0.114	1.07	1.05-1.10	$6.8x10^{-9}$
16	rs13237518	7	12229967	TMEM106B	A/C	0.411	0.96	0.94-0.97	$4.9x10^{-11}$
17	rs1160871	7	28129126	JAZF1	G/GTCTT	0.222	0.95	0.93-0.97	$9.8x10^{-9}$
18	rs76928645	7	54873635	SEC61G	T/C	0.103	0.93	0.91-0.95	$1.6x10^{-10}$
19	rs1065712	8	11844613	CTSB	C/G	0.053	1.09	1.06-1.12	$1.9x10^{-9}$
20	rs34173062	8	144103704	SHARPIN	A/G	0.081	1.13	1.09-1.16	$1.7x10^{-16}$
21	rs1800978	9	104903697	ABCA1	G/C	0.13	1.06	1.04-1.08	$1.6x10^{-9}$
22	rs7068231	10	60025170	ANK3	T/G	0.403	0.95	0.94-0.96	$3.3x10^{-13}$
23	rs6586028	10	80494228	TSPAN14	C/T	0.196	0.93	0.91-0.94	$2.0x10^{-19}$
24	rs6584063	10	96266650	BLNK	G/A	0.043	0.89	0.86-0.92	$6.7x10^{-11}$
25	rs7908662	10	122413396	PLEKHA1	G/A	0.467	0.96	0.95-0.97	$2.6x10^{-9}$
26	rs6489896	12	113281983	TPCN1	C/T	0.076	1.08	1.05-1.10	$1.8x10^{-9}$
27	rs7157106	14	105761758	IGH gene cluster	A/G	0.36	1.05	1.03-1.07	$2.0x10^{-8}$
27	rs10131280	14	106665591	IGH gene cluster	A/G	0.133	0.94	0.92-0.96	$4.3x10^{-10}$
28	rs3848143	15	64131307	SNX1	G/A	0.22	1.05	1.04-1.07	$8.4x10^{-11}$
29	rs12592898	15	78936857	CTSH	A/G	0.133	0.94	0.92-0.96	$4.2x10^{-9}$
30	rs1140239	16	30010081	DOC2A	T/C	0.379	0.94	0.93-0.96	$2.6x10^{-13}$
31	rs450674	16	79574511	MAF	C/T	0.373	0.96	0.95-0.98	$3.2x10^{-5}$
32	rs16941239	16	86420604	FOXF1	A/T	0.029	1.13	1.08-1.17	$1.3x10^{-8}$
33	rs56407236	16	90103687	PRDM7	A/G	0.069	1.11	1.08-1.14	$6.5x10^{-15}$
34	rs35048651	17	1728046	WDR81	T/TGAG	0.214	1.06	1.04-1.08	$7.7x10^{-11}$
35	rs2242595	17	18156140	MYO15A	A/G	0.112	0.94	0.92-0.96	$1.1x10^{-9}$
36	rs5848	17	44352876	GRN	T/C	0.289	1.07	1.06-1.09	$2.4x10^{-20}$
37	rs149080927	19	1854254	KLF16	G/GC	0.48	1.05	1.04-1.07	$5.1x10^{-10}$
38	rs9304690	19	49950060	SIGLEC11	T/C	0.24	1.05	1.03-1.07	$4.7x10^{-9}$
39	rs587709	19	54267597	LILRB2	C/T	0.325	1.05	1.04-1.07	$3.6x10^{-11}$
40	rs1358782	20	413334	RBCK1	A/G	0.246	0.95	0.94-0.97	$1.6x10^{-5}$
41	rs6742	20	63743088	SLC2A4RG	T/C	0.221	0.95	0.93-0.97	$2.6x10^{-9}$
42	rs2154481	21	26101558	APP	C/T	0.476	0.95	0.94-0.97	$1.0x10^{-12}$

Figure 1

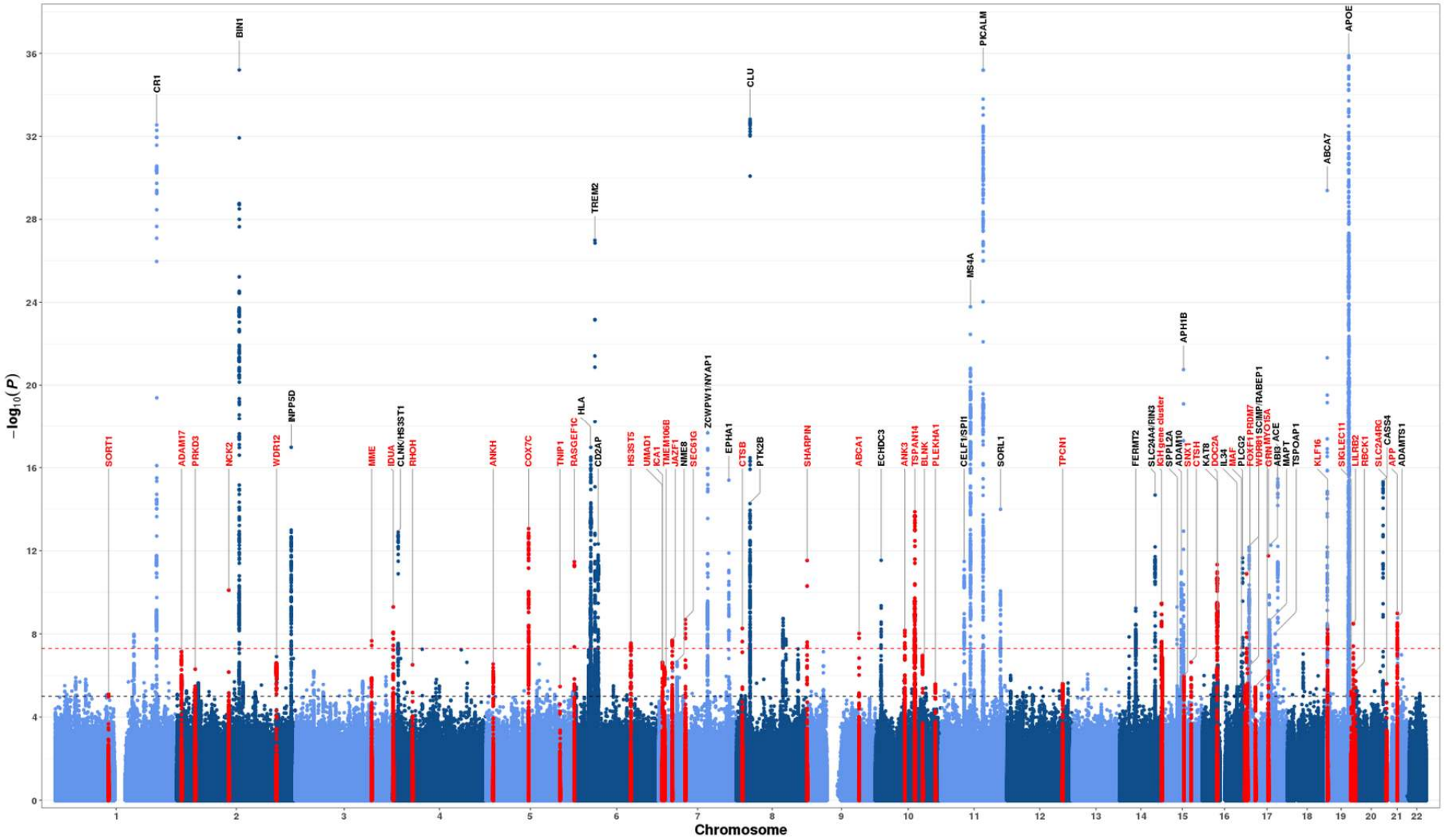


Figure 2

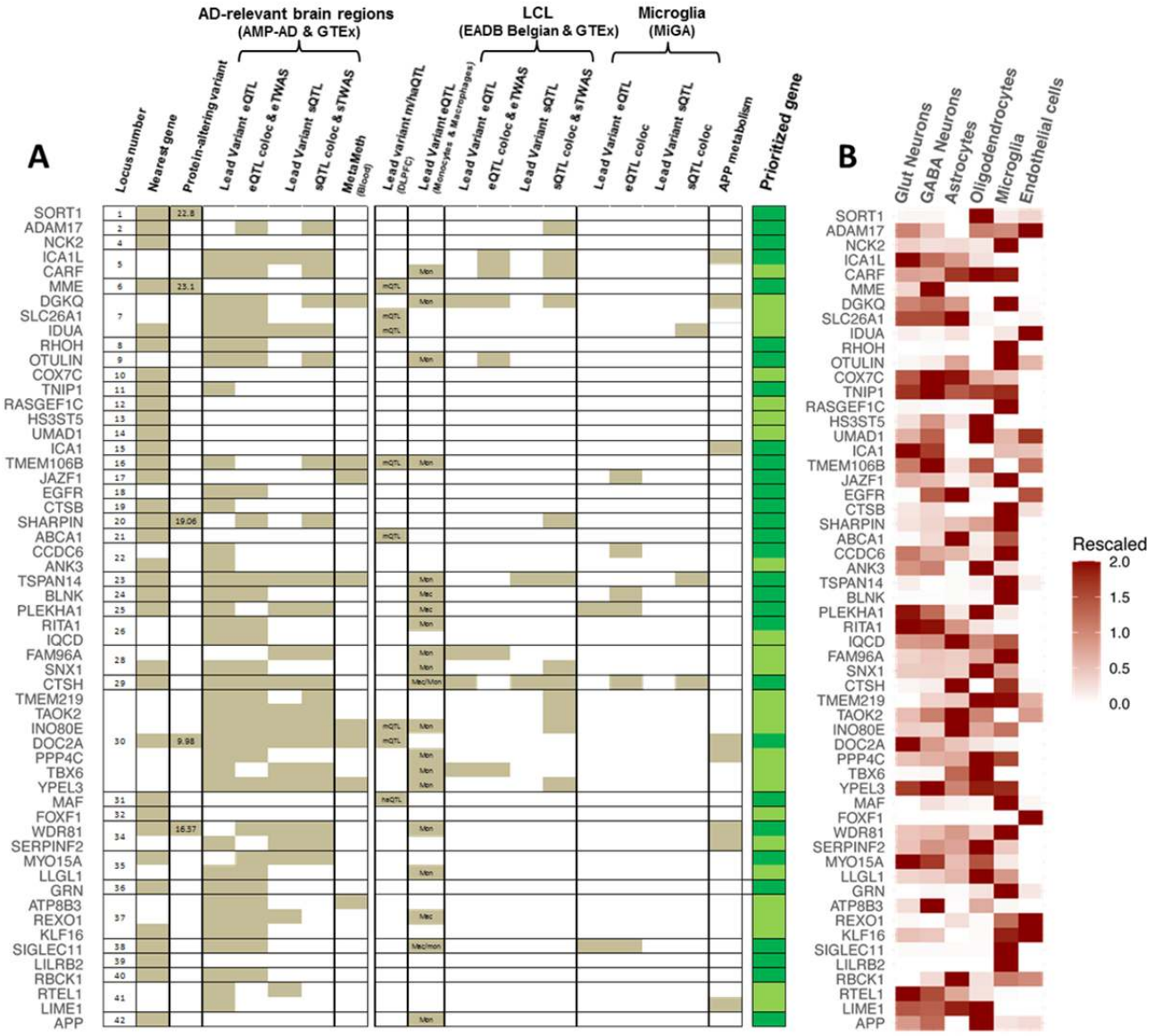


Figure 3

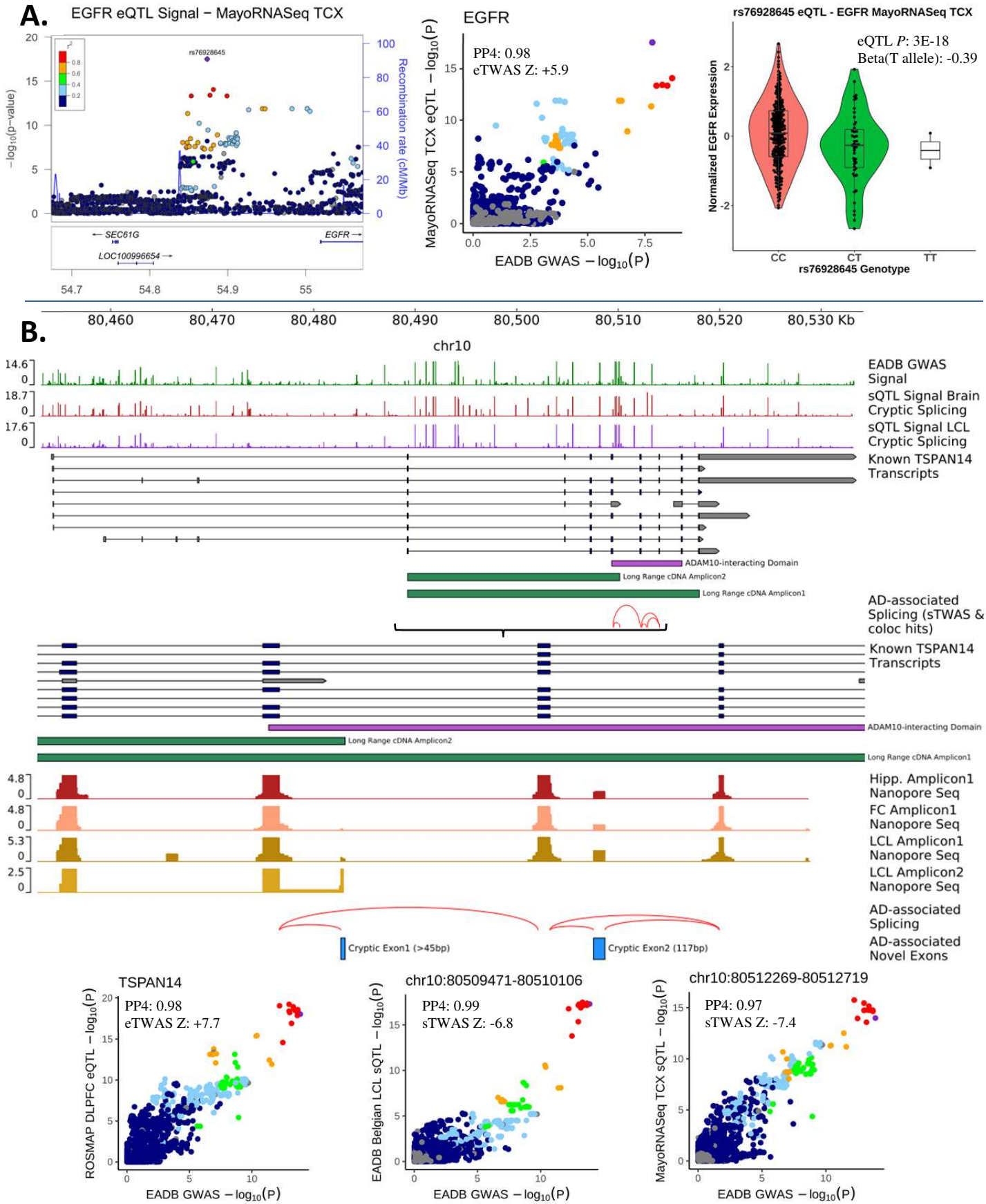
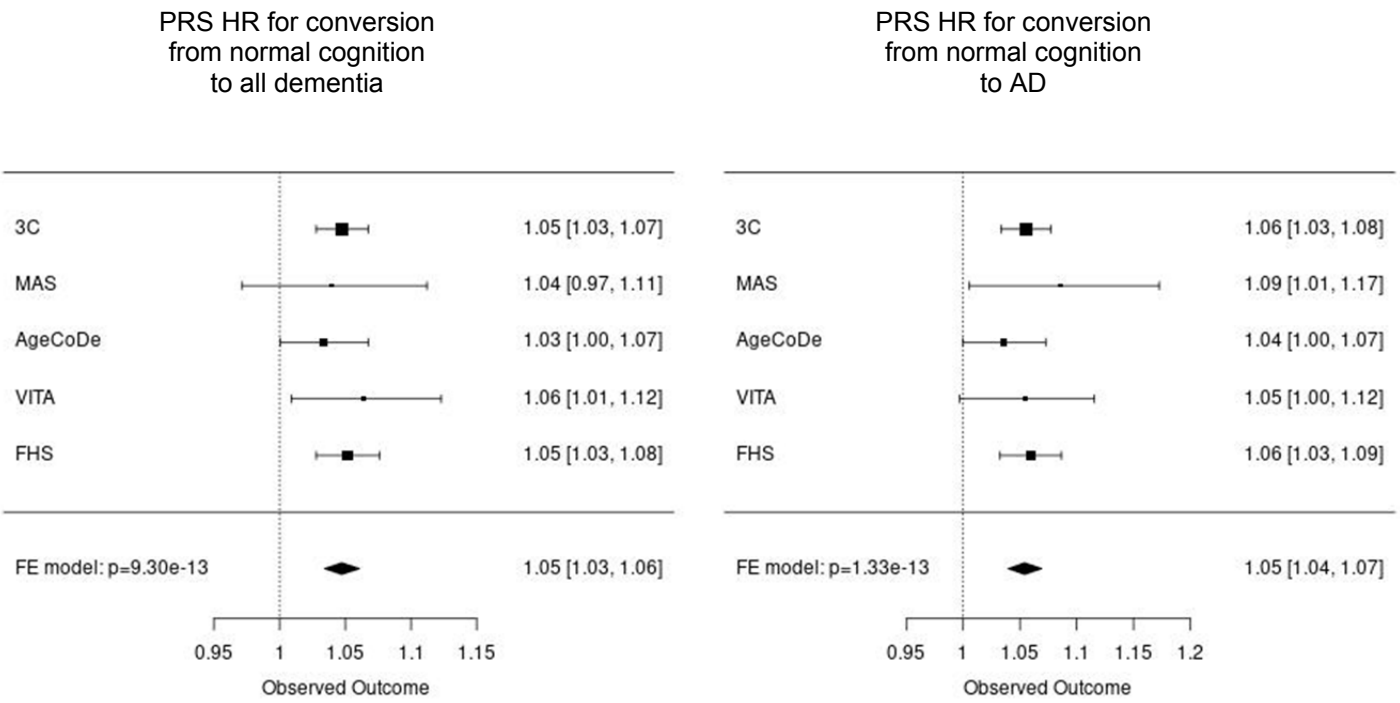


Figure 4

A



B