

RESEARCH ARTICLE

APOE*4 risk-modifying genes and drug targets in Alzheimer's disease through cell-type-specific genomic analyses

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Abstract

INTRODUCTION: Genetics studies can identify drug targets that counteract the effects of the *apolipoprotein E ε4* allele (APOE*4) on Alzheimer's disease (AD) but have remained limited in power and crucially did not assess genetic findings with regard to APOE*4's cell-type-specific impact on pathobiology.

METHODS: We conducted a novel APOE*4-stratified genome-wide association study (GWAS) of AD ($N = 447,669$) and integrated results with brain cell-type-specific multi-omics data to identify APOE*4 and cell-type-specific AD genes, followed by compound and drug repurposing.

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RESULTS: In *APOE**4 non-carriers (*APOE**4−) and carriers (*APOE**4+), we respectively identified 33 and 11 cell type–gene pairs with strong prioritization support. Oligodendrocytes displayed the largest proportion of *APOE**4+ genes. Several genes were druggable and pinpointed *APOE**4-stratified drugs or compounds.

DISCUSSION: We identified a set of *APOE**4-stratified genes that may be causal for AD through brain cell-type-specific mechanisms. We additionally identified compounds that may shed light on therapeutic avenues for treating AD based on an individual's *APOE**4 status.

KEYWORDS

Alzheimer's disease, apolipoprotein E, cell-type-specific transcriptome-wide association study, chromatin accessibility, differential gene expression, drug target, gene prioritization, genetic colocalization, genome-wide association study, summary-based Mendelian randomization

Highlights

- An *APOE**4-stratified AD GWAS integrated with brain single-cell omics.
- Eleven cell type–gene pairs specific to *APOE**4 carriers, including four prioritized drug targets.
- Oligodendrocytes displayed the largest proportion of *APOE**4 carrier risk genes.
- Drug repurposing shed light on therapeutic avenues for *APOE**4 precision medicine.

1 | BACKGROUND

The *apolipoprotein E* ϵ 4 allele (*APOE**4) is the strongest, most common genetic risk factor for late-onset Alzheimer's disease (AD), with one and two copies respectively increasing risk about four- and 12-fold in European-ancestry populations.¹ While the effect magnitude of *APOE**4 varies across ancestries, it consistently represents the most prominent genetic risk factor for AD.² Despite consensus that countering *APOE**4 represents an important therapeutic objective for AD, few drugs or clinical trials directly target *APOE**4.^{3–6} The challenge in part stems from the highly pleiotropic nature of *APOE**4 and uncertainty about where and how to target it.¹ Importantly, recent work highlights that the impact of *APOE**4 on AD pathobiology differs across brain cell types, suggesting that cell-type-informed approaches may be crucial to identify genes that can counter the effect of *APOE**4.^{7–15}

Genome-wide association studies (GWASs) have been instrumental in identifying AD risk variants and genes,^{16,17} paving the way for novel therapeutic targets.¹⁸ Prior GWASs and targeted genetic analyses that further considered *APOE**4 status helped uncover promising genes such as *Klotho* and *Fibronectin1* that may counter *APOE**4,^{19–24} but novel, larger *APOE**4-stratified AD GWASs are urgently needed. Historically, bulk brain tissue transcriptomics datasets have enabled linking genetic variants to gene expression (expression quantitative trait loci [eQTLs]), which, in turn, have supported mapping genetic signals from AD GWASs to their likely causally related genes.^{16,25,26} Recent advances in single-cell and single-nucleus RNA sequencing

(snRNA-seq) make it possible to study the genetic regulation of gene expression at cell-type resolution (sc-eQTL), revealing many regulatory signals that were missed in bulk eQTL analyses.^{27–29}

To address these gaps, we conducted a meta-analysis of *APOE**4-stratified AD GWASs across multiple European-ancestry cohorts. We then integrated these results with a large-scale brain sc-eQTL resource to conduct an *APOE**4-stratified, cell-type-specific, transcriptome-wide association study (cTWAS). This approach effectively identifies genetic signals for AD that are present in the *APOE**4-stratified GWAS, display strong *APOE**4 heterogeneity (i.e., mostly observed in *APOE**4 carriers or non-carriers), and appear to regulate expression of a respective gene in specific brain cell types, which together enabled discovery of candidate genes that may be causal to AD in an *APOE**4 and cell-type-dependent manner. Using additional multi-ancestry GWAS samples and various cell-specific multi-omics follow-up analyses, we further prioritized the most promising genes and leveraged them to identify potential *APOE**4-stratified drug targets.

2 | METHODS

Participants or their caregivers provided written informed consent in the original studies. The study protocol was granted an exemption by the Washington University Institutional Review Board because the analyses were carried out on “de-identified, off-the-shelf” data; therefore, additional informed consent was not required.

RESEARCH IN CONTEXT

- 1. Systematic review:** The authors reviewed the literature using PubMed sources. Emerging evidence indicates the existence of genetic variants and genes that can modify the impact of APOE*4 on AD. Other recent work shows that the impact of APOE*4 on AD pathobiology differs across different brain cell types. Therefore, identifying which genes in which cell types causally drive AD is crucial to identifying novel drug targets to counter APOE*4.
- 2. Interpretation:** By integrating a novel, large-scale APOE*4-stratified GWASs of AD with brain cell-type-specific multi-omics data, we prioritized 44 candidate causal cell type–gene pairs, of which 11 were specific to APOE*4 carriers. Oligodendrocytes displayed the largest proportion of APOE*4 carrier risk genes, suggesting this cell type plays a more prominent role in APOE*4 pathobiology. Several implicated genes were druggable and pinpointed compounds or drugs that may shed light on therapeutic avenues for treating AD based on an individual's APOE*4 status.
- 3. Future directions:** Future work should aim to corroborate our prioritized genes and cell-type-specific disease mechanisms, as well as leverage insights from our enriched drugs and compounds to steer novel therapeutic opportunities for APOE*4 carriers and non-carriers, respectively.

2.1 | Genetic data ascertainment and processing

Case-control, family-based, and population AD genetic cohorts from the AD Genetics Consortium (ADGC) and Alzheimer's Disease Sequencing Project (ADSP) were available from public repositories and contributed GWAS data for European (EUR) and African admixed (AFR) ancestry subjects (Figure S1) through whole-genome sequencing (WGS) or imputed single-nucleotide polymorphism (SNP) microarrays (Tables S1 and S2)^{30,31}; subjects were clinically diagnosed with 40% of cases pathology confirmed (Table S3). UK Biobank (UKB) contributed EUR AD GWAS data via imputed SNP microarrays,³² and AD phenotypes were determined from health-registry records or questionnaire-identified proxy cases whose parents were affected by AD or dementia.^{16,33} Japanese AD GWAS data were available through imputed SNP microarrays from the National Center for Geriatrics and Gerontology and Niigata University (Table S4)³⁴; subjects were clinically diagnosed. Details on GWAS processing and variant metrics are given in the Supplementary Methods and Tables S5 and S6.

2.2 | Genetic statistical analyses – APOE*4-stratified GWAS and cTWAS

GWASs were performed separately in APOE*4 non-carriers (APOE*4–) and carriers (APOE*4+), evaluating AD logistic regressions, adjusted

for sex, age, APOE*2, and APOE*4 dosage, technical covariates, and genetic principal components, as applicable per dataset. EUR samples accounted for the majority of the data, with GWASs conducted using mixed models (BOLT-LMM v2.4),³⁵ followed by fixed-effects meta-analyses (GWAMA).³⁶ Variants were intersected with those present in ADGC and a genotyping rate $\geq 90\%$ across cohorts to increase AD specificity.^{37,38} Additional APOE*4-stratified GWASs were conducted in AFR and Japanese cohorts (Plink version 2.0).³⁹ Effective sample sizes were calculated using $N_{\text{Eff}} = 4 \cdot v \cdot (1-v)$,⁴⁰ where $v = N_{\text{Cases}} / (N_{\text{Cases}} + N_{\text{Controls}})$, with contributions from UKB further divided by 4 to account for proxy GWASs.³³

APOE*4-stratified cTWASs were performed by integrating EUR APOE*4-stratified GWAS findings with snRNA-seq data, paired with WGS data, from the dorsolateral prefrontal cortex of 424 EUR participants in the Religious Orders Study (ROS) and Memory and Aging Project (MAP). Data processing is described in Fujita et al.²⁷ Briefly, seven major cell types were available to link genetic variants to gene expression. For each cell type, sc-eQTL analyses were conducted (Matrix eQTL version 2.3),⁴¹ and transcriptomic weights were generated through FUSION for genes that displayed significant heritability ($p < 0.05$) in their *cis* windows (± 1 Mb around the transcription start site).⁴² The resultant cell-type-specific variant-gene weights were used to conduct APOE*4-stratified cTWASs and identify candidate cell type–gene pairs that may be causal to AD. To ensure findings were specific to a given APOE*4 stratum, genes were filtered to a false discovery rate $p_{\text{FDR}} < 0.05$ in one stratum and either (1) a non-significant association ($p > 0.05$) with the same effect direction in the other stratum or (2) an opposite effect direction in the other stratum. Additionally, for loci with multiple significant genes, if the most significant gene was not biased to a given APOE*4 stratum, as in the previously mentioned criteria, all genes at the locus were excluded. The discovery threshold of $p_{\text{FDR}} < 0.05$ is the conventional threshold in TWASs.^{43,42}

Sensitivity cTWASs were performed to assess the impact of differential power across APOE*4 strata on the number of gene discoveries. First, differences in Z-scores standardized by sample size were evaluated across APOE*4-stratified cTWAS discoveries to determine whether increased power enabled detection of genes with weaker effect sizes, which would be indicative of power biases. Second, an additional APOE*4– GWAS was performed in which APOE*4– UKB subjects were downsampled (maintaining consistent case-control ratios) to the point where the total effective sample size when meta-analyzed with ADGC and ADSP was identical to the APOE*4+ GWAS meta-analysis. The number of APOE*4– cases and control in UKB for this purpose was 22,621 and 158,261, respectively.

2.3 | Gene prioritization

APOE*4 heterogeneous cTWAS candidate genes were further assessed using a series of multi-omics approaches to validate findings within their corresponding cell type and APOE*4 stratum. Increasing levels of support were used to prioritize the most promising genes. Statistical criteria for different gene prioritization analyses are consistent with

prior studies and are independent of one another and the cTWAS gene discoveries.

2.3.1 | Multi-ancestry cTWAS

To assess the cross-ancestry concordance of *APOE**4 heterogeneity, EUR cTWAS genes were evaluated through equivalent FUSION analyses with the corresponding AFR and Japanese *APOE**4-stratified GWAS findings. Meta-analyses were conducted through a sample-size-weighted combination of Z-scores. Cell type–gene pairs were considered consistent if the *p* value in the respective *APOE**4 stratum (e.g., *APOE**4+) improved in cross-ancestry meta-analysis, while the opposite *APOE**4 stratum (e.g., *APOE**4–) maintained *p* > 0.05. Few genes could be assessed in the Japanese cTWAS, likely due to limited variant and linkage disequilibrium (LD) overlap with EUR data, so these results were not used for gene prioritization.

2.3.2 | Colocalization analysis

Consistent with TWAS and cTWAS follow-up approaches in prior studies,^{44,45,27,46} genetic colocalization (COLOC) analyses were conducted for cell type–gene pairs of interest across the AD GWAS and ROSMAP sc-eQTL data. The goal of these analyses is to evaluate support for a causally shared variant (posterior probability PP4), which helps corroborate a potential causal link for the respective gene to AD. COLOC was performed using (1) standard approximate Bayes factor (ABF) analyses,⁴⁷ (2) ABF analyses with priors adjusted to reflect increased probabilities of variants being associated with both AD and gene expression (i.e., the conditions for cTWAS discoveries), and (3) SuSiE-based COLOC,⁴⁸ which accounts for scenarios where multiple causal variants are present at the locus. Across analyses, the best PP4 value was used with values ≥ 0.4 and ≥ 0.7 respectively marking suggestive and strong COLOC support.

2.3.3 | Summary-data-based Mendelian randomization (SMR)

Consistent with TWAS and cTWAS follow-up approaches in prior studies,^{44,45,27,46} SMR analyses were conducted for cell type–gene pairs of interest across the AD GWAS and ROSMAP sc-eQTL data. The goal of SMR is to assess the potential causal effects of gene expression on AD using the top *cis* sc-eQTL variant as an instrumental variable, while the HEIDI test assesses whether the association is driven by LD.⁴⁹ Cell type–gene pairs with $p_{\text{FDR}} < 0.05$ and $p_{\text{HEIDI}} > 0.05$ were considered to have SMR support.

2.3.4 | scATAC-seq validation

For all cell type–gene pairs supported by COLOC, the top colocalizing variants and those in close LD ($R^2 > 0.8$) were assessed for overlap with regulatory peaks from single-cell ATAC-seq data in matching cell types

from human brain tissues.⁵⁰ These analyses aim to corroborate that the cTWAS-identified cell-type-specific genetic signals may manifest via cell-type-specific epigenetic mechanisms.

2.3.5 | Single-cell differential expression of genes (scDEG)

Pseudobulk expression matrices for seven brain cell types from ROSMAP snRNA-seq data were count-normalized using the trimmed mean of M values (TMM) in edgeR.^{27,51} scDEG analyses were performed with limma,⁵² adjusting for sex, *post mortem* interval, age at death, *APOE**2 and *APOE**4 dosage, and batch. Outcome phenotypes comprised both binary and global quantitative metrics of clinical and pathological AD (cf. [Supplementary Methods](#)). Analyses were conducted in both non-stratified and *APOE**4-stratified settings. In non-stratified scDEG, support was defined as FDR *p* < 0.05 in the respective cell type–gene pair. In *APOE**4-stratified scDEG, support required (i) FDR *p* < 0.05 in the respective *APOE**4 stratum and cell type–gene pair and (ii) an opposite effect direction or absolute log fold change ≥ 1.5 larger compared to the opposite stratum. FDR correction corresponds to the evaluated cell type–gene pairs.^{43,42} These analyses aim to corroborate a direct gene association with AD dementia or pathology within the respective cell types and *APOE**4 strata. The non-stratified scDEG was included to leverage extra power in the full sample and considers that gene–AD associations, even independent of *APOE**4 status, still represent meaningful support for cell-type specificity. If a gene was validated by both *APOE**4-stratified and non-stratified scDEG analyses, this was treated as only one evidence count in order to not inflate gene prioritization through scDEG.

2.4 | Drug target analyses

*APOE**4-stratified cTWAS genes prioritized through more than half of the follow-up analyses were intersected with a list of 4479 druggable genes from Finan et al. to identify Tier-1 druggable cTWAS genes.⁵³ Remaining prioritized cTWAS genes were expanded into networks of AD-related genes through EpiGraphDB,⁵⁴ with expanded genes restricted to those with evidence of druggability.⁵³ *APOE**4-stratified compound and drug enrichment analyses were performed on the expanded gene lists using the DSigDB drug signature database (clusterProfiler package).^{55,56} Compounds and drugs were considered significantly enriched at $p_{\text{FDR}} < 0.05$ and further filtered to those targeting at least two prioritized genes to increase robustness. These enrichment analyses reflect a preliminary approach to linking genes to potential drugs and compounds to enable hypothesis generation of potential therapeutic avenues.

3 | RESULTS

The study design is summarized in Figure 1. *APOE**4-stratified GWASs included 432,508 EUR, 7270 AFR, and 7891 Japanese individuals

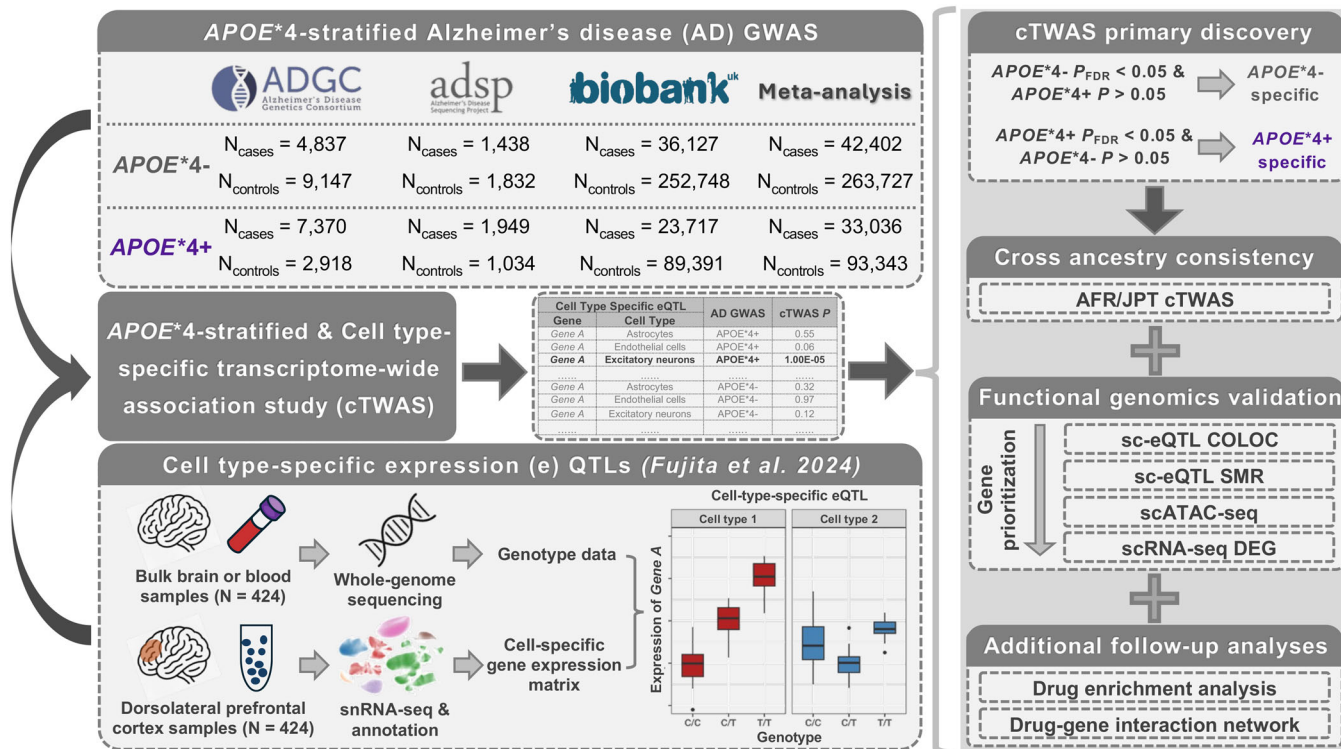


FIGURE 1 Schematic overview of study design. Left: APOE*4-stratified GWAS of AD in European-ancestry subjects were integrated with snRNA-seq and paired whole-genome sequencing data from ROSMAP brain tissue to perform an APOE*4-stratified cTWAS. This approach implicates cell type-gene pairs that are candidate causal for AD in an APOE*4-dependent manner. Top right: cTWAS findings were filtered for APOE*4 specificity by retaining only significant ($p_{FDR} < 0.05$) genes in a given APOE*4 stratum that were not significant ($p > 0.05$) or showed discordant effect directions in the opposite stratum. Middle right: Following cTWAS gene discoveries, multiple types of gene prioritization analyses were conducted, including cross-ancestry cTWASs, leveraging smaller AD genetic datasets in AFR and Japanese cohorts to assess consistent APOE*4 heterogeneity effects, and a series of cell-type-specific multi-omics analyses. Bottom right: Top prioritized genes were used to perform drug repurposing analyses. ADGC, Alzheimer's Disease Genetics Consortium; ADSP, Alzheimer's Disease Sequencing Project; UKB, UK Biobank; ROSMAP, Religious Orders Study and Memory and Aging Project; GWAS, genome-wide association study; cTWAS, cell-type-specific transcriptome-wide association study; AFR, African; JPT, Japanese in Tokyo; sc-eQTL, single-cell expression quantitative trait locus; COLOC, genetic colocalization analysis; SMR, summary-based Mendelian randomization; scATAC-seq, single-cell assay for transposase-accessible chromatin using sequencing; scDEG, cell-type-specific differential expression of genes.

(Table S3 and S4) and revealed a novel APOE*4+ (*RBM6*) and APOE*4- locus (*TECPR2*) in EUR individuals (Figure S2; all loci Table S7). There were no signs of genomic inflation (Figure S3). By integrating our GWAS with genetically tethered brain snRNA-seq data to perform APOE*4-stratified cTWAS, we identified 84 cell type-gene pairs that additionally met APOE*4 heterogeneity criteria (Figure 2, Figure 3A; full results Table S8-S10). These involved 59 unique genes – 45 APOE*4- and 14 APOE*4+ genes – across 42 genomic loci of which 29 were novel compared to prior AD GWASs. The *MAPT* locus, known for its broad and complex LD structure,⁵⁷ contained the highest number of APOE*4- candidate genes across multiple cell types. Most genes ($n = 45$) were, however, identified in only one cell type (Figure 3B). Oligodendrocytes exhibited the highest proportion of APOE*4+ genes (Figure 3C; Figure S4) of which three genes were related to vesicular transport, mitochondrial metabolism, autophagy, and iron homeostasis pathways (Table S11; cf. Supplementary Methods). Locus zoom plots for cell type-gene pairs showcase the APOE*4 heterogeneity of regional AD genetic signals (Figure S5).

Considering recent reports that proxy-AD GWASs can confer biases to genetic association signals,^{38,58,59} the APOE*4 proxy-AD GWAS in UKB was performed according to recommendations from Wu et al. to reduce bias (cf. Supplementary Methods).³⁸ Still, to further assess signal robustness, we inspected the effect sizes of AD genetic signals underlying the cTWAS findings and observed they were strongly correlated across ADGC/ADSP and UKB analyses ($\rho = 0.90$, $R^2 = 0.81$), confirming gene discoveries were not driven by the use of proxy-AD GWAS (Figure S6). In additional sensitivity analyses, we also showed that these underlying genetic signals displayed a strong correlation of APOE*4 effect heterogeneity (i.e., the delta of variant beta coefficients in APOE*4+ vs APOE*4- subjects) across ADGC/ADSP and UKB (Figure S7), with the exception of four loci that appeared more driven by inclusion of UKB (*SLC23A2*, *ZDHHC16*, *CTU2*, *RASGEF1C*) and three loci more driven by ADGC+ADSP (*CARMIL3*, *SLC24A4/RIN3*, and *TNIP1*), suggesting their APOE*4-biased associations may be less robust and warrant replication. Further, with regard to the larger number of APOE*4- cTWAS loci we observed (33 compared to 11

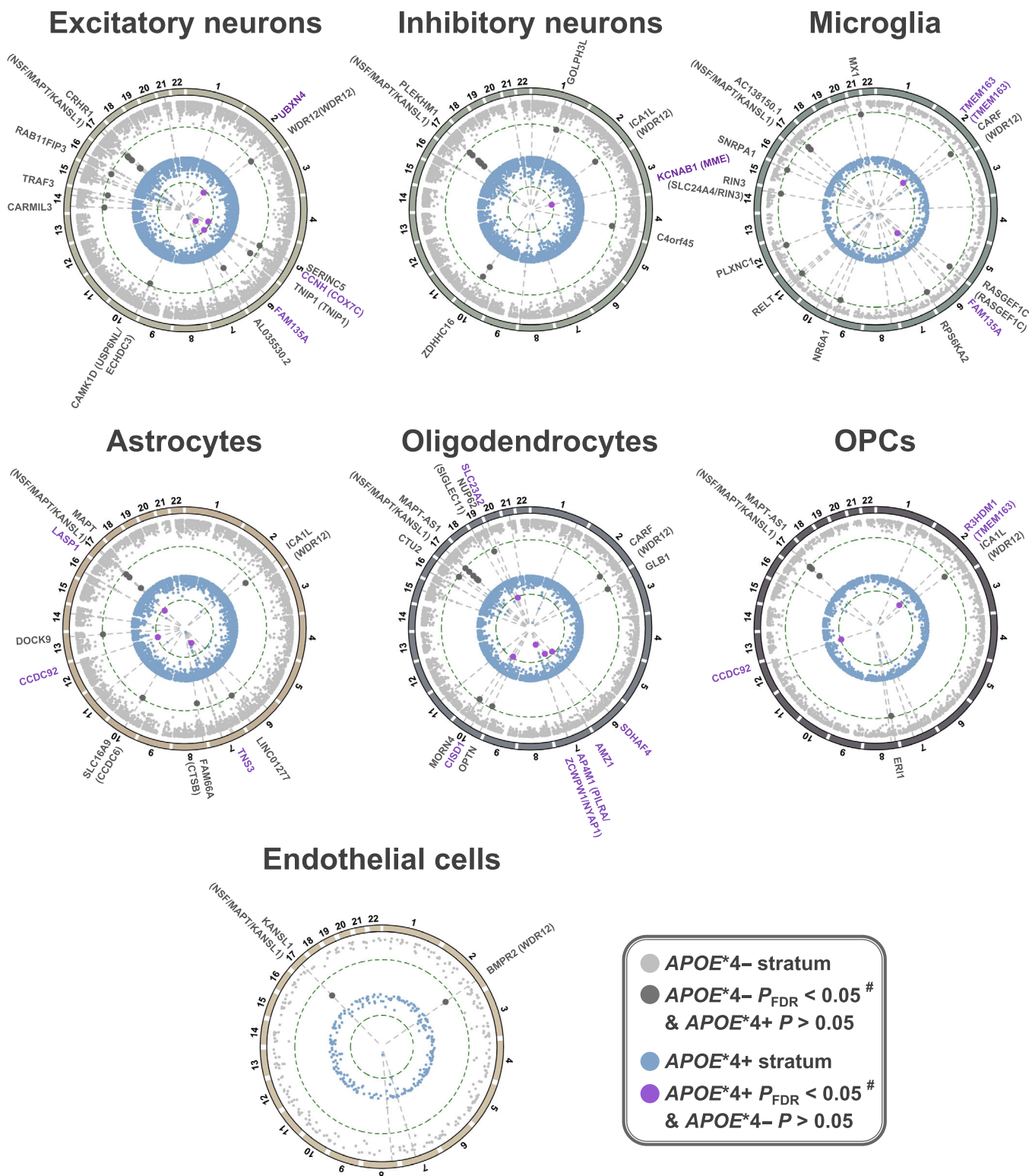


FIGURE 2 $APOE^*4$ -stratified cell-type-specific transcriptome-wide association study (cTWAS) findings. For each cell type, a circos plot is shown, depicting $APOE^*4-$ findings on the outer layer and $APOE^*4+$ findings on the inner layer. The radial axes indicate the $-\log_{10}(p \text{ value})$, i.e., significance of gene association, with increasing significance toward the center of the plots. Dashed circular lines indicate $p_{FDR} < 0.05$ thresholds. Significant associations that displayed evidence of $APOE^*4$ specificity (dotted lines show alignment across $APOE^*4$ strata) are labeled with unique colors (see legend) and their respective gene names, including further gene annotation if they fell within known AD risk loci (genes between parentheses). If multiple genes were located within the same locus (within a 1 Mb window), only the top significant gene is labeled in the outer track.

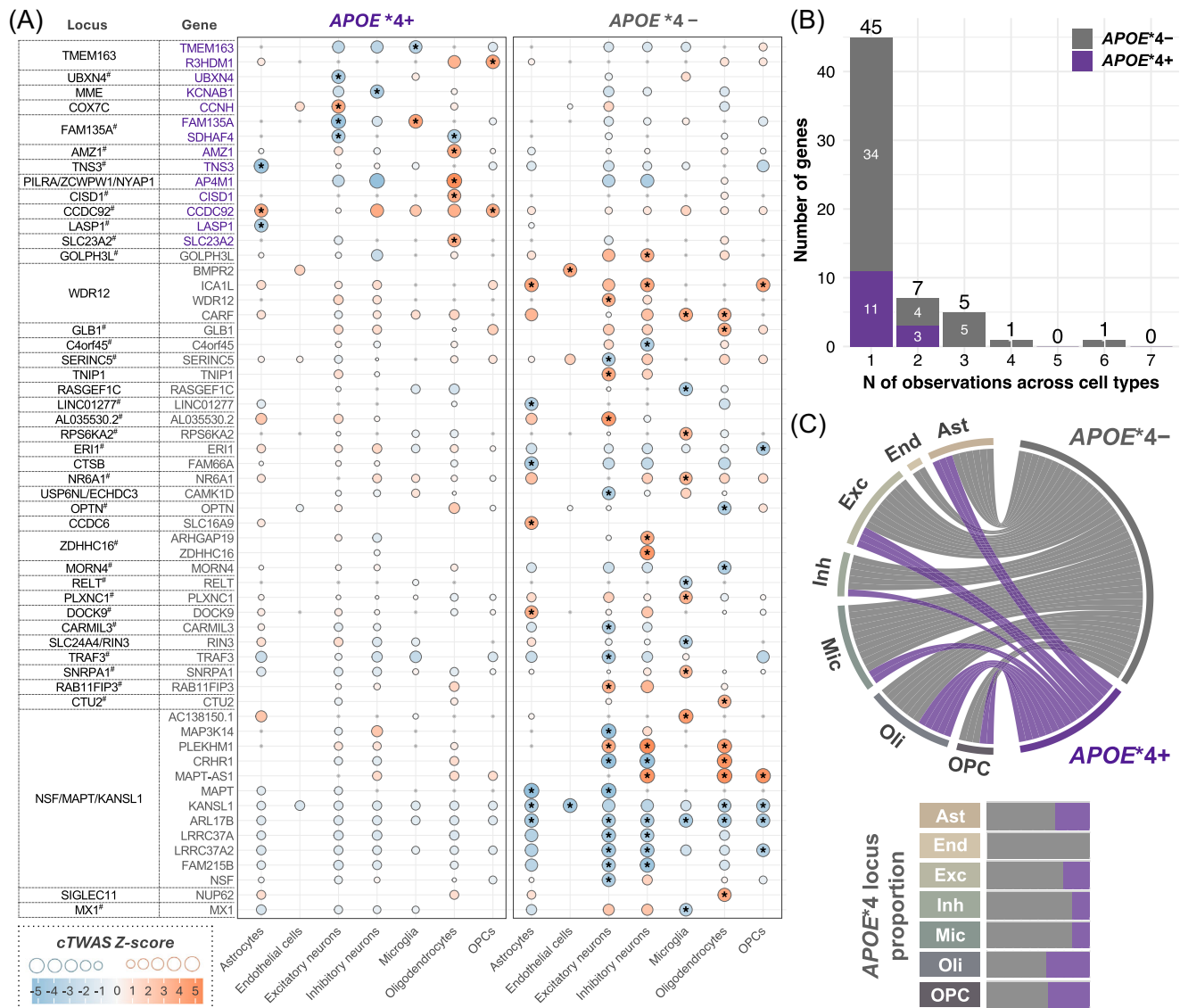


FIGURE 3 Cell-type-specificity of *APOE**4 stratified cTWAS results. (A) Dot matrix visualizes all significant cTWAS genes that passed *APOE**4 specificity criteria in at least one cell type. Dot sizes and color intensities indicate Z-scores, reflecting gene associations with AD. Red colors (positive Z-scores) and blue colors (negative Z-scores) respectively indicate that higher or lower gene expression levels increase AD risk. Asterisks (*) denote genes specific to *APOE**4 non-carriers (*APOE**4–) or *APOE**4 carriers (*APOE**4+). Gray dots represent genes with available eQTL data but lacking gene expression weight files and thus were not tested in cTWAS (reflecting low heritability). Genes are labeled on the y-axis and grouped by locus; novel loci are marked with (#). (B) The distribution of respective gene observations across cell-types is shown, indicating that most genes were observed in only one cell-type. (C) Chord diagram (left) illustrates AD risk loci across *APOE**4 and cell-type groups, while the matching distributions are visualized in bar graphs (right). Notably, Oligodendrocytes showed the highest proportion of *APOE**4+ risk modifying loci.

*APOE**4+), through sensitivity analyses in which we adjusted discovery thresholds or downsampled *APOE**4– GWAS to match power with *APOE**4+ GWAS, we confirmed this observation was driven by the larger power in *APOE**4– analyses rather than reflecting a potential biological effect (Figures S8 and S9).

Candidate genes from cTWASs were next subjected to six gene prioritization analyses (Table S12–S18; Figure S10) summarized in Figure 4A and Table S19 (findings excluding *MAPT* locus: Figure S11, Table S20). Overall, 11/17 *APOE**4+ (Figure 4B) and 33/67 *APOE**4– cell type-gene pairs (Figure S12A) were supported by more than half of the prioritization analyses. The druggability of

these prioritized genes and their connected AD-related genes is presented in Table S21. Using these gene sets, we identified 106 and 786 enriched compounds or drugs in *APOE**4+ and *APOE**4– strata, respectively (Table S22). In *APOE**4– analyses, *TRAF3* and *MAPT* displayed the most numerous compound or drug interactions, and both displayed highly concordant *APOE**4 heterogeneity across ADGC+ADSP and UKB (Figure S7), marking them as promising targets. In extended analyses excluding the *APOE**4– prioritized gene *TRAF3*, which had extensive AD-gene-drug interactions, 101 compounds remained significantly enriched in *APOE**4– analyses, and *MAPT* remained the gene with the most compound

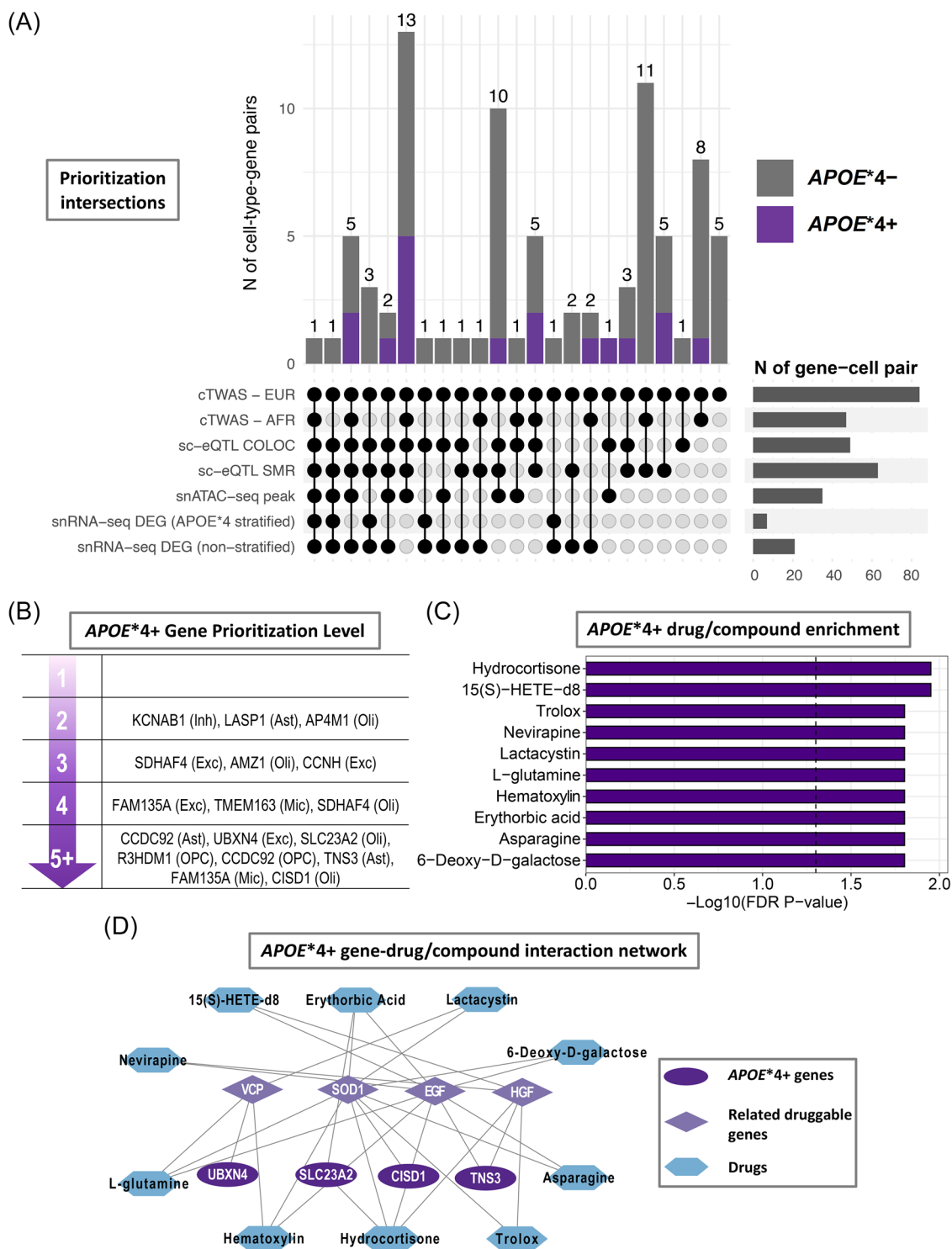


FIGURE 4 $APOE^*4$ -stratified gene and drug target prioritization. (A) The UpSet plot summarizes the European cTWAS significant cell type-gene pairs with their varying supporting gene prioritization findings, arranged highest to lowest supporting observations from left to right. (B) The schematic indicates cell type-gene pairs with increasing levels of gene prioritization support in $APOE^*4+$ stratum. (C) Compound and drug enrichment results for $APOE^*4+$ specific genes (with prioritization level ≥ 4) and their interacting AD-related, druggable genes. The bar graph shows the top 10 FDR significant (vertical dotted line) compounds and drugs. (D) Gene-drug interaction network matching to (C), including $APOE^*4+$ cTWAS genes and their interacting AD-related genes that were connected to the top 10 enriched compounds or drugs.

connections (Table S22). Further, the top 10 *APOE**4+ compounds and their gene interactions highlighted promising drug targets, including *TNS3*, *CISD1*, *SLC23A2*, and *UBXN4* (Figure 4C,D; *APOE**4– findings: Figures S12B–E). Of these four, *TNS3* and *CISD1* displayed the strongest concordance of *APOE**4 heterogeneity across ADGC+ADSP and UKB (Figure S7). Higher *TNS3* expression in astrocytes was protective of AD in *APOE**4+ subjects, and its lead genetic signal fell within a distinct astrocyte snATAC-seq peak (Figure S13A). Higher *CISD1* expression in oligodendrocytes increased AD risk in *APOE**4+ subjects. Leveraging independent plasma proteomics data, we additionally replicated the observation that plasma *CISD1* levels were significantly increased in *APOE**4+ (but not *APOE**4–) AD cases versus controls (Table S23; cf. Supplementary Methods).

Finally, we more closely inspected findings at the *MAPT* locus for which the association was biased toward *APOE**4– subjects. The gene prioritization efforts in a prior *APOE**4-stratified GWAS by Jun et al. had nominated *KANSL1* rather than *MAPT* as the candidate causal gene at this locus.²³ In contrast, we identified 13 candidate causal genes (including *KANSL1*) and observed the strongest effect sizes for *MAPT* (astrocytes, excitatory neurons) and its anti-sense RNA, *MAPT-AS1* (inhibitory neurons, oligodendrocytes, oligodendrocyte precursor cells). Four of these cell type–gene pairs were confirmed by more than half (≥ 4) of gene prioritization analyses, with the excitatory neuron–*MAPT* pair supported by only 3. While colocalization PP4 results for *MAPT*/*MAPT-AS1* were only suggestive, visual inspection confirmed strong colocalization (cf. Figure S5), which reflects challenges conferred by the complex genetic LD structure at the *MAPT* locus.⁵⁷ Surprisingly, the cTWAS effect directions indicated that increased *MAPT* (and decreased *MAPT-AS1*) levels were protective of AD. Fujita et al. previously reported that most astrocyte and excitatory neuronal sc-eQTL findings in the ROSMAP cohort – used in our cTWAS – had concordant effect directions with those observed in induced pluripotent stem cell-derived astrocytes and neurons, except a few notable ones, including *MAPT*.²⁷ To confirm the robustness of this observation, we queried findings from the recent SingleBrain resource,⁶⁰ which reprocessed data from Fujita et al. and three other snRNA-seq datasets – doubling sample sizes for sc-eQTL analyses – and observed replications across all datasets for all cell type–gene pairs except *MAPT* in excitatory neurons (Table S24). We further verified that the top (protective) *APOE**4– AD and (expression increasing) *MAPT* sc-eQTL signals fell on the large H2 inversion haplotype that has historically been associated with protection against AD (Table S25).⁵⁷

4 | DISCUSSION

Our *APOE**4-stratified GWAS identified many loci previously associated with AD in non-stratified AD GWASs (Figure S2),^{16,17} confirming the robustness of our genetic findings. Compared to prior *APOE**4-stratified AD GWASs by Jun et al. and Madrid et al.,^{23,24} in which effective sample sizes ranged from 18,130 to 23,412 in respective *APOE**4 strata, our GWAS was better powered with effective sample sizes of 38,608 and 50,752 in *APOE**4+ and *APOE**4– subjects, respectively.

By leveraging our novel GWAS results to perform *APOE**4-stratified cTWAS, we further identified 13 known and 29 novel AD risk loci whose associations depended on *APOE**4 status and for which we could nominate candidate causal cell type–gene pairs. Excitatory neurons, microglia, and oligodendrocytes were the most implicated cell types by cTWAS, each respectively linked to 12 AD genetic loci displaying *APOE**4 heterogeneity. However, microglia had the fewest heritable genes – a prerequisite for gene inclusion in cTWAS – compared to excitatory neurons or oligodendrocytes (~40%), suggesting a relative enrichment of microglial genes (Table S8 and S9). This is consistent with prior reports that many AD genes are expressed by microglia.^{28,29,61,62} Interestingly, oligodendrocytes displayed the largest proportion of *APOE**4+ genes, which remained robust even when applying stricter gene prioritization filters (Figures S14 and S15). The relevance of oligodendrocytes in AD pathogenesis is increasingly recognized,⁶³ with recent work showing that *APOE**4 impairs myelination by dysregulating cholesterol metabolism in oligodendrocytes.¹¹

Beyond prior published studies, at the time of writing, a preprint by Thomassen et al. presents another novel *APOE**4-stratified GWAS that is larger than ours, using the same plus other cohorts.⁶⁴ At first glance, few genes or loci overlap across our studies, except the *MAPT* locus, which also showed evidence of an *APOE**4– bias in Thomassen et al. However, our studies importantly differ in their design. First, Thomassen et al. used fewer subjects in UKB since they did not leverage proxy cases. Second, and most importantly, Thomassen et al. focus on reporting genome-wide significant variants in *APOE**4-stratified GWAS, whereas we performed an *APOE**4-stratified GWAS and subsequently an *APOE**4-stratified cTWAS to amplify the discovery power of subthreshold AD genetic signals and enable gene prioritization. We provide a detailed comparison to their study in the Supplementary Discussion; in summary, we found that our data supported several of the *APOE**4 heterogeneous loci they reported (although some were also discrepant), while differences in study design likely explain why they did not identify the same loci as us. Overall, we conclude our two studies provide complementary insights into *APOE**4-stratified risk genes.

It is notable that in our study and those of Thomassen et al.⁶⁴ and Jun et al.,²³ the *MAPT* locus was consistently identified to be more strongly associated with AD in *APOE**4– subjects. Across our analyses, we provided evidence that *MAPT* was the most likely causal gene candidate at this locus and that genetic regulation of *MAPT* expression across different brain cell types had a stronger impact on AD risk in *APOE**4– versus *APOE**4+ subjects but surprisingly revealed a protective role for increased *MAPT* expression (cf. Results). While the origin of this observation remains unclear, it will represent an important topic of investigation for future studies. It should still be considered that multiple genes at the *MAPT* locus may be causal to AD.⁵⁷ Notably, *KANSL1* remains a strong candidate as it is the KAT8 Regulatory NSL Complex Subunit 1 that regulates KAT8, which has been implicated by multiple prior AD GWASs.¹⁶

We further focused on cTWAS genes with strong prioritization support and assessed which of these constituted promising drug targets. In *APOE**4– subjects, *TRAF3* was identified in excitatory neurons, and its underlying genetic signal represented an independent association

from the novel genome-wide significant *APOE**4– GWAS signal at *TECPR2* within the same locus (Figure S5.24). *TRAF3* displayed extensive connections with known, druggable AD genes, and while *TRAF3* is primarily tied to immune cell function, it has also been implicated in mediating neuronal apoptosis,⁶⁵ corroborating its potential as a drug target for AD. Top *APOE**4+ drug targets included *TNS3* (astrocytes), *CISD1* and *SLC23A2* (oligodendrocytes), and *UBXN4* (excitatory neurons). *UBXN4* may impact AD through its role in endoplasmic reticulum protein degradation, while *SLC23A2* (also known as *SVCT2*) is a vitamin C co-transporter that may affect AD through its role in oligodendrocyte myelination.⁶⁶ It should be noted that the *APOE**4+-biased effect of *SLC23A2* appeared more driven by UKB such that this gene should be considered less robust, with additional replication warranted. A recent study implicated *TNS3* in microglial gene networks in glioblastoma and AD and reported an inverse correlation between *TNS3* and *APOE* expression levels.⁶⁷ This complements our observation of a protective effect of increased astrocyte *TNS3* levels in *APOE**4+ subjects and may corroborate the emerging consensus to reduce *APOE* levels in *APOE**4+ subjects to counter AD risk.³ Further, *TNS3* interacts with AD-related druggable genes *EGF* and *HGF*, which in turn interact with *EGFR* (Figure S13B), a gene that was recently implicated in AD through a GWAS¹⁶ and itself shows strong potential as a dual drug target for cancer and AD.⁶⁸ For *CISD1*, we replicated its *APOE**4+-specific AD risk-increasing effect from cTWAS in an independent plasma proteomics dataset in which higher *CISD1* levels were associated with AD risk solely in *APOE**4+ subjects. *CISD1* encodes an outer mitochondrial membrane protein that plays an important role in regulating oxidation.⁶⁹ Additionally, *CISD1*, as well as its connected druggable gene *SOD1*, is linked to ferroptosis, which is increasingly implicated in microglial AD pathogenesis.^{61,70,71} Importantly, *SOD1* is a hallmark gene in amyotrophic lateral sclerosis (ALS), and while there is no direct link between AD and ALS, our findings suggest that converging mechanisms such as oxidative stress and protein misfolding may pinpoint drug repurposing opportunities for both diseases. Finally, we identified compounds or drugs that were significantly enriched in the prioritized gene sets. While these findings should be considered preliminary as they lack orthogonal evidence to validate drugs or target specificity, they enable hypothesis generation of potential differential therapeutic avenues across subjects with or without *APOE**4. Among top compounds, hydrocortisone and Trolox implicated oxidative stress and inflammation as biological targets that may confer increased benefit in *APOE**4+ versus *APOE**4– subjects. Considering that elevated endogenous cortisol has been linked to increased AD risk,⁷² the enrichment of hydrocortisone likely reflects a gene signature that aligns with reducing cortisol as a therapeutic target. Similarly, Trolox, an analog of vitamin E, may protect against AD by reducing oxidative stress.⁷³

5 | LIMITATIONS

Despite the large size of our GWAS, the lower power in *APOE**4+ analyses reduced the number of possible *APOE**4+ gene discoveries.

Additionally, while we showed our findings appeared to display few signs of potential biases conferred by using proxy GWASs in UKB, the latter represented a large component of our GWAS's total sample size. The reliance on non-pathology verified AD phenotypes in proxy GWASs in UKB and even in clinically diagnosed AD phenotypes in ADGC and ADSP GWASs may lead to reduced specificity for AD. It will thus be important to integrate additional datasets into future *APOE**4-stratified GWASs, especially pathology-confirmed case-control cohorts, which will amplify power for cTWAS gene discoveries and help corroborate our current findings. Similarly, while the ROSMAP snRNA-seq dataset was large for sc-eQTL analyses, inclusion of other datasets will enable the detection of additional heritable genes to be assessed in cTWASs. We also performed AFR and Japanese GWASs, but sample sizes were relatively small and sc-eQTL data for cTWASs were not ancestry matched, such that larger multi-ancestry datasets are needed to better assess cross-ancestry consistency. As a result, our findings should currently be considered as mostly EUR-centric until additional validation opportunities become available. Regarding the cell specificity of our findings, it should be noted that while cTWAS implicates potential causal roles for cell type–gene pairs, the respective genes can still be involved in other cell types over the disease course. Further, our study used in silico approaches to nominate the most likely candidate causal genes such that experimental validation is warranted. On this note, it should further be considered that while we focused on cell-specific transcriptomics analyses, other tissues and gene regulatory features may also be relevant and could expand gene prioritization.

6 | CONCLUSION

We identified a set of *APOE**4-stratified genes that may be causal for AD through brain cell-type-specific mechanisms, prioritizing top genes for further interrogation. We additionally identified compounds that may be repurposed or shed light on therapeutic avenues for treating AD based on an individual's *APOE**4 status. Top identified compounds such as hydrocortisone and Trolox implicate oxidative stress and neuroinflammation as potential biological targets in *APOE**4+ individuals. Altogether, our study substantially expands current insights into the genetic architecture and molecular etiology of AD, while paving the way toward *APOE**4 genotype-tailored therapies.

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CONFLICT OF INTEREST STATEMENT

C.C. has received research support from GSK and Eisai. C.C. is a member of the scientific advisory board of Circular Genomics and owns company stock. C.C. is a member of the scientific advisory board of ADmit. The funding organizations and sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. No other authors have any conflicts of interest to report. Author disclosures are available in the [Supporting Information](#).

DATA AVAILABILITY STATEMENT

Data used in the APOE*4-stratified AD GWAS for European cohort and African mixed cohort are available upon application to:

- dbGaP (<https://www.ncbi.nlm.nih.gov/gap/>)
- NIAGADS (<https://www.niagads.org/>)
- LONI (<https://ida.loni.usc.edu/>)
- AMP-AD knowledge portal / Synapse (<https://www.synapse.org/>)
- Rush (<https://www.radc.rush.edu/>)
- NACC (<https://naccdata.org/>)
- UKB (<https://www.ukbiobank.ac.uk/>)

The specific data repository and identifiers for ADGC and ADSP data are indicated in Tables S1 and S2 of the supplement. Full APOE*4 GWAS summary statistics per ancestry are available at Zenodo (<https://doi.org/10.5281/zenodo.19896913>). The European ancestry summary statistics are additionally available in the GWAS Catalog under accession numbers GCST90838647 and GCST90838648.

TWAS gene weights and pseudobulk expression count matrices were generated as previously reported in Fujita et al., (<https://doi.org/10.1038/s41588-024-01685-y>). The underlying snRNA-seq data (raw UMI count matrices and cell-type annotations) are available from Synapse (<https://doi.org/10.7303/syn52335732>) upon application. Cell-type-specific eQTL summary statistics used in this study are available from Synapse (<https://doi.org/10.7303/syn52335732>). The scATAC-seq peak files used in this study were derived from Corces et al. (<https://doi.org/10.1038/s41588-020-00721-x>). The raw data are available in the Gene Expression Omnibus under accession number GSE147672. The GMT file for drug enrichment analysis was obtained from DSigDB (<https://dsigdb.tanlab.org/>).

CONSENT STATEMENT

The study protocol was granted an exemption by the Washington University Institutional Review Board because the analyses were carried out on “de-identified, off-the-shelf” data; therefore, additional informed consent was not required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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