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Genome-wide cross-trait analysis identified shared etiology between Alzheimer's disease and migraine

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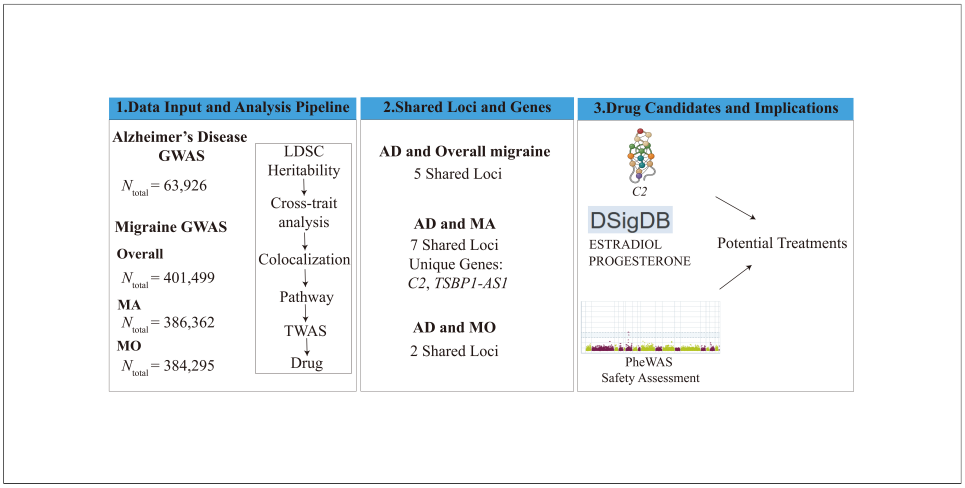

Abstract

Aim: Alzheimer's disease (AD) and migraine are both common and heritable neurological disorders. Epidemiological studies repeatedly report an association between migraine and an increased risk of AD. However, whether this co-occurrence reflects shared molecular etiology remains unclear.

Methods: We integrated large-scale genome-wide association study (GWAS) summary statistics, AD (N_{case} = 21,982 and $N_{control}$ = 41,944), overall migraine (N_{case} = 26,894 and $N_{control}$ = 374,605), migraine with aura (MA, N_{case} = 11,757 and $N_{control}$ = 374,605), and migraine without aura (MO, N_{case} = 9,690 and $N_{control}$ = 374,605), to perform genome-wide cross-trait meta-analysis (CPASSOC), functional annotation and transcriptome-wide

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association studies (TWAS) to elucidate the genetic etiology between AD and migraine in detail.

Results: Genome-wide cross-trait analysis revealed that 11 independent suggestive shared loci ($P_{CPASSOC} < 5 \times 10^{-8}$ and $P_{single\text{-}trait} < 0.05$) and 3 significant shared loci ($P_{CPASSOC} < 5 \times 10^{-8}$ and $P_{single\text{-}trait} < 5 \times 10^{-3}$) for AD and migraine, with substantial subtype specificity. In addition, after global false discovery rate (FDR) correction across 49 tissues, we identified *C2* as a highly significant shared pleiotropic gene in the brain cerebellar hemisphere, and *TSBP1-AS1* in the thyroid for AD and MA. Finally, drug-target prioritization highlighted *C2* as a candidate therapeutic target, while PheWAS analysis revealed no significant associations between *C2* and major disease categories, supporting its limited phenotypic pleiotropy.

Conclusion: This study clarified the pleiotropic loci and shared genes underlying AD and migraine by integrating multi-omics. These findings provide important insights into the molecular mechanisms between AD and migraine, and potential candidate genes for further functional validation.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and a progressive neurodegenerative disorder.[1]. Its clinical manifestations are diverse, mainly including cognitive impairment, mental and behavioral symptoms, and deterioration of social life functions[1]. There are currently limited effective medications available for the treatment of AD. More than 55 million people worldwide are living with dementia, with AD accounting for approximately 60%-70% of cases[2]. The disease progresses from mild to severe, and the symptoms of patients gradually worsen, causing significant impacts on patients and their families[2].

The pathogenesis of AD is extremely complex. It is currently believed to be caused by the combined effects of various factors such as genetics and environment[3]. According to estimates from some studies, genetic factors account for 60%-80% of the risk of developing Alzheimer's disease[4,5]. The *APOE* gene on chromosome 19q region, is considered to be the strongest risk factor for late-onset AD[6,7]. The *APOE* gene has three common alleles (ε2, ε3, and ε4). *APOE* ε2 has a protective effect against the risk of developing Alzheimer's disease, while ε4 can increase the risk of the disease[5].

With the emergence of the technology of genome-wide association analysis (GWAS), many single-nucleotide polymorphisms (SNPs) associated with AD were identified by utilizing this approach. Through a two-stage meta-analysis of previously published GWAS data, 19 loci were found to be significantly contributing to AD, among which 11 loci were newly discovered[8]. A GWAS based on 1,126,563 individuals identified 7 new loci associated with late-onset AD, and further proved that immunity and metabolism play a key role in the disease development[9]. A large-scale meta-analysis for late-onset AD has confirmed the 20 previously discovered loci and has also identified 5 new loci (*IQCK*, *ACE*, *ADAM10*, *ADAMTS1*, and *WWOX*). In addition, immunity, lipid, and protein metabolism pathways are identified to be relevant to the development of AD[10]. Based on clinically diagnosed/proxy AD patients and normal controls, 42 new loci were identified by a two-stage GWAS. The amyloid/tau pathways and microglia were highlighted by pathway enrichment analyses[11]. These identified significant loci could provide insights into the pathological mechanisms of AD.

Migraine is a common chronic neurovascular disorder with a strong genetic predisposition[12,13]. At present, the prevalence of migraine worldwide is approximately 15%[14]. The incidence rate of migraine varies between men and women, approximately threefold more prevalent in women[14]. According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), migraine can be classified into two major subforms, migraine with aura (MA) and migraine without aura (MO), based on the presence or absence of focal

neurological symptoms that precede or accompany the headache[15]. MA and MO differ in prevalence, genetics, and pathophysiology. MA shows stronger heritability and over-representation of cortical spreading depression, whereas MO is more polygenic and vascular-risk-related[15,16]. To date, the pathophysiological mechanism of migraine has not yet been fully elucidated.

Some GWAS have begun to be used to identify the genetic factors of migraine disease. The genetic variant rs1835740 on chromosome 8q22.1 was identified to be associated with migraine in European ancestry by GWAS[17]. Three associated loci for common migraine were further identified in the general population[18]. The first GWAS of MO was conducted and found several susceptibility loci[19]. Based on 59,674 cases and 316,078 controls, a meta-analysis of GWAS identified the 38 susceptibility loci associated with migraine[20]. Eight novel susceptibility loci were found for the onset age of migraine of Han ethnicity in Taiwan, China[21]. A recent large-scale GWAS found 123 loci and subtype-specific associated alleles, and these genetic variants are mainly enriched in vascular and central nervous system cell types[16]. These results can provide important evidence for understanding the genetic basis of migraine.

Both AD and migraine are severe neurological disorders. Several prospective studies have indicated that migraine is associated with an increased risk of all-cause dementia in different ancestry cohorts[22-27]. Different subtypes of migraine have different effects on dementia, and MA has a much greater impact on dementia compared with MO[24-26]. In addition, compared with men, migraine in women has been associated with a higher risk of dementia[28]. By using bidirectional two-sample Mendelian randomization (MR), a recent study suggested a potential causal association between migraine and AD[29]. Collectively, these studies suggest that there is a shared genetic architecture between AD and migraine. However, MR analyses rely on strict methodological assumptions, such as no horizontal pleiotropy, highlighting the need for further genetic and mechanistic dissection.

Large-scale GWAS have identified several significant risk loci for AD and migraine, which provides an opportunity to dissect their genetic relationship. To address this gap, we integrated genome-wide cross-trait meta-analysis, transcriptome-wide association analysis (TWAS), colocalization, pathway enrichment, drug-target prioritization, and phenome-wide association analysis (PheWAS) to systematically characterize the shared genetic architecture between AD and migraine.

METHODS

AD GWAS dataset

The AD GWAS summary statistics were obtained from a large-scale meta-analysis[10]. In stage 1, 11,480,632 SNPs of 21,982 AD cases and 41,944 cognitively normal controls were genotyped and imputed first, and then meta-analysis was conducted to identify the 12 significant loci. In stage 2, the authors genotyped 11,632 variants on the I-select chip and tested the association in an independent sample set, which is composed of 8,362 AD cases and 10,483 normal controls. For the variations that the I-selected chip failed to accurately capture, stage 3A (N = 11,666) and 3B (N = 30,511) analyses were further performed. In this study, we adopted the stage 1 results of the AD meta-analysis. The International Genomics of Alzheimer's Project (IGAP) was releasing this summary data with the accession number: NG00075.v1. We can download the *P*-values only summary statistics from https://dss.niagads.org/open-access-data-portal/#NG00075. Complete GWAS summary data were obtained upon application.

Migraine GWAS dataset

The migraine GWAS summary statistics were obtained from the FinnGen initiative, which is a large-scale genomic research project with 500,000 Finnish individuals[30]. Here, we used the R12 version of the GWAS datasets released in 2024. The GWAS summary statistics of overall migraine, MA, and MO were conducted

on genotyped 21,325,483 variants of 26,894 cases and 374,605 controls, 21,325,193 variants of 11,757 cases and 374,605 controls, and 21,325,144 variants of 9,690 cases and 374,605 controls, respectively. The above GWAS summary datasets are freely available at https://storage.googleapis.com/finngen-public-data-r12/summary_stats/release/finngen_R12_G6_MIGRAINE.gz, https://storage.googleapis.com/finngen-public-data-r12/summary_stats/release/finngen_R12_G6_MIGRAINE_WITH_AURA.gz, https://storage.googleapis.com/finngen-public-data-r12/summary_stats/release/finngen_R12_G6_MIGRAINE_NO_AURA.gz, respectively.

Genotype-tissue expression (GTEx) V10 RNA-seq data

In this study, we utilized the GTEx V10 RNA-seq data to plot the gene expression in specific tissues. The GTEx project aims to investigate the relationship between genetic variation and gene expression in multiple healthy human tissues. The GTEx RNA-seq V10 dataset can be accessed from https://www.gtexportal.org/.

Data preprocessing and quality control

We carried out preprocessing on the downloaded GWAS datasets according to the following process. Firstly, we unified the reference genome of all GWAS data to genome reference consortium human build 37 (GRCh37)/hg19. For datasets utilizing other reference genomes, the liftOver tool was used to convert coordinates to GRCh37. Secondly, the non-standard SNPs lacking an "rs" prefix were excluded. Thirdly, we only kept the SNPs with single-nucleotide variants and filtered indels. Finally, the SNP with minor allele frequency (MAF) ≥ 0.01 in autosomes would be considered for subsequent analysis. These quality control procedures can ensure that all GWAS follow a unified standard and minimize bias to the greatest extent in the subsequent analysis process.

To ensure the robustness and reproducibility of our findings, several quality control measures were implemented. Firstly, potential bias arising from sample overlap between the AD (IGAP) and migraine (FinnGen) cohorts was assessed using the LDSC intercept. The intercept values were consistently close to 1.0, suggesting that the influence of sample overlap or residual population stratification was minimal. Secondly, linkage disequilibrium (LD) was estimated using the European ancestry reference panel from the 1000 Genomes Project Phase 3, ensuring consistency with the underlying GWAS datasets. Finally, multiple testing was rigorously controlled. A false discovery rate (FDR) correction was applied to the TWAS analyses, and a genome-wide significance threshold of $P < 5 \times 10^{-8}$ was adopted for the cross-trait meta-analysis to limit false-positive findings.

Genome-wide heritability

We used the linkage disequilibrium score regression (LDSC) to estimate the genome-wide heritability for every trait using only GWAS summary statistics, without requiring individual-level genotype data[31].

Cross-phenotype association

In order to obtain the shared genetic variants for multiple traits, we then conducted a cross-trait GWAS meta-analysis using the cross-phenotype association (CPASSOC)[32]. CPASSOC is a cross-trait association analysis method based on summary statistics, which is used to simultaneously test whether a genetic variation is significantly correlated with multiple traits. The assumption is that if a certain SNP is associated with multiple traits, its cross-trait combined effect should be significantly stronger than that of any single trait.

CPASSOC provides two algorithms, Shom and Shet[32]. Shom employs a fixed effect model, assuming that the effect size of the SNP is exactly the same for each trait. This model is suitable for traits with highly consistent effect sizes. Shet allows SNPs to have heterogeneity in their genetic effects for different traits (with different directions or magnitudes). Through random-effect meta-analysis, Shet gives higher weights to traits with

large effects, reducing the interference from traits with small effects or heterogeneity. Thus, in the practical research where heterogeneity of effects is widespread, Shet becomes a more reliable choice for cross-trait meta-analysis. To formally justify this, Cochran's *Q* test was applied to confirm significant heterogeneity across the top loci, supporting the use of the Shet random-effects model.

After cross-trait meta-analysis, a number of genetic variants shared by two traits were identified. To further ascertain the independent pleiotropic SNPs, we used the PLINK1.9 to clump the SNPs by using the parameter "-clump-p1 5e-8 -clump-p2 1e-5 -clump-r2 0.001 -clump-kb 500". In this clumping process, the genetic variant with the lowest *P* value within each LD block was selected as the index SNP. SNPs that simultaneously meet the criteria of *P* value less than 5×10^{-8} after meta-analysis and a *P* value less than 0.05 for single trait are considered as suggestive pleiotropic loci[33]. To rigorously control for false positives and asymmetric chance associations, loci were declared as significant pleiotropic regions only if they simultaneously met a highly stringent cross-trait genome-wide significance threshold ($P_{CPASSOC} < 5 \times 10^{-8}$) and a strict single-trait threshold of $P < 5 \times 10^{-3}$ for both underlying phenotypes. In order to further obtain the function annotation of pleiotropic loci, we adopted the variant effect predictor (VEP) tool to obtain the nearest gene based on physical proximity[34]. In addition, 3DSNP was used to obtain the regulated target gene based on chromatin three-dimensional interactions[35].

Colocalization

Colocalization is a Bayesian statistical method to determine whether the association signals of two traits are driven by the same causal variant. For the independent pleiotropic loci, we then conducted colocalization analysis by using R package Coloc[36]. This approach provides five mutually exclusive hypotheses (H0-H4), and calculates the posterior probability (PP) through Bayesian factor: H0 (no association), H1 (only associated with trait 1), H2 (only associated with trait 2), H3 (two distinct variants associated with two traits), and H4 (one shared variant associated with two traits). We extracted the summary statistics of independent pleiotropic SNPs ±500 kb from two GWAS as the input to calculate the PP. Loci with PPH3 > 0.5 or PPH4 > 0.5 can be considered colocalized[37].

Pathway enrichment analysis

To capture the broad polygenic architecture of the shared genetic etiology, candidate genes for pathway enrichment analysis were mapped from variants meeting genome-wide significance ($P_{CPASSOC} < 5 \times 10^{-8}$) using positional mapping and expression quantitative trait loci (eQTL) mapping in GTEx V8 brain tissues by functional mapping and annotation of GWAS (FUMA)[38]. Pathway enrichment analysis was performed by web-based tool Metascape[39]. Redundant enriched terms were clustered, and statistical significance was strictly defined at a Benjamini-Hochberg FDR-corrected *P* value < 0.05. The pathway enrichment results were plotted using R.

Transcriptome-wide association studies

The shared SNPs between a pair of traits can be identified by cross-trait meta-analysis. Many genetic variation sites often participate in the progression of diseases and phenotypes by regulating the expression of genes. Therefore, we further identified the shared genes between the two traits by transcriptome-wide association studies (TWAS) using Fusion[40]. GTEx V8 expression weights for TWAS are provided from Fusion. In addition to whole blood and brain tissues, other tissues and organs of the organism also play a very important role in the development of the disease. Firstly, we conducted the TWAS in 49 tissues to identify the significant gene-tissue pairs for single trait. Then, we intersected the significant gene-tissue pairs of different traits to obtain the shared genes. Considering the extensive multiple testing burden across 49 evaluated tissues, we employed a highly conservative global FDR correction (Benjamini-Hochberg) simultaneously across all tissue-gene pairs to strictly minimize false-positive discoveries.

Genetic drug target analysis

To prioritize potential therapeutic drugs, we queried the Drug-Gene Interaction Database (DGIdb) and Drug Signatures Database (DSigDB) for Food and Drug Administration (FDA)-approved compounds whose targets overlap the shared genes, yielding a pharmacological landscape that could inform treatment strategies for both AD and migraine[41,42].

Phenome-wide association study

PheWAS systematically relates a given variant or gene to the full spectrum of phenotypic outcomes recorded in large biobanks, thereby revealing pleiotropic effects. Using the AstraZeneca PheWAS portal, which is built on UK Biobank exome and phenotype data, we surveyed the disease landscape linked to each drug-target gene to flag potential on- or off-target liabilities of the corresponding compounds[43].

Software and analysis pipelines

All computational analyses were performed utilizing publicly available software and established bioinformatics pipelines. The primary tools employed in this study include LDSC (https://github.com/bulik/ldsc) for heritability estimation, CPASSOC (https://hal.case.edu/~xxz10/zhu-web/) for cross-trait meta-analysis, PLINK 1.9 (https://www.cog-genomics.org/plink/) for linkage disequilibrium clumping, FUSION (http://gusevlab.org/projects/fusion/) for TWAS, and the R package coloc (https://cran.r-project.org/web/packages/coloc/) for Bayesian colocalization. The positional and eQTL mapping of genetic variants were performed using FUMA (https://fuma.ctglab.nl/). Pathway enrichment was conducted via the Metascape platform (https://metascape.org). Downstream statistical analyses and data visualizations were executed in R software (v4.3.0) using standard packages including ggplot2 and pheatmap. All analyses strictly adhered to the standard protocols and official tutorials provided by the respective software developers.

RESULTS

Genome-wide heritability of AD and migraine subtypes

We first calculated the SNP-based heritability for each trait by using univariate LDSC. The SNP-based heritability estimates for AD, overall migraine, MA, and MO are 0.0713, 0.0326, 0.0184, and 0.0177, respectively [Supplementary Table 1].

Global effect size correlation assessment between AD and migraine cohorts

To explicitly address potential systematic biases arising from population heterogeneity between the IGAP and FinnGen cohorts, we assessed the global effect size (BETA) correlations using variants not expected to be associated with either trait. Specifically, we filtered for background null variants (single-trait $P > 0.05$ in both corresponding datasets) and randomly downsampled to 50,000 SNPs per comparison to plot their aligned effect sizes. We observed near-zero overall correlations across all comparisons (AD and overall migraine: $R = -3.0 \times 10^{-5}$, $P = 0.99$; AD and MA: $R = 0.0051$, $P = 0.26$; AD and MO: $R = 0.019$, $P = 2.3 \times 10^{-5}$; Figure 1). Although the correlation for the AD and MO pair reached nominal statistical significance due to the large number of evaluated variants, the absolute magnitude of the correlation coefficient remained biologically negligible. The absence of pervasive, directional genomic correlation among these null variants confirms that macroscopic methodological confounders, such as unadjusted population stratification or cryptic sample overlap, do not artificially inflate the genetic overlap. Collectively, these findings indicate that the cross-trait associations identified in the subsequent analyses are unlikely to be driven by systematic methodological artifacts, thereby increasing confidence in the robustness of the detected signals.

Pleiotropic loci identified by cross-trait meta-analysis

Several studies have shown that migraine is significantly associated with an increased risk of developing dementia in different ancestry cohorts[22-27]. In addition, MR study demonstrated that migraine has a significant causal effect on AD[29]. Therefore, we performed genome-wide cross-trait meta-analysis to identify the pleiotropic loci shared by two traits by CPASSOC.

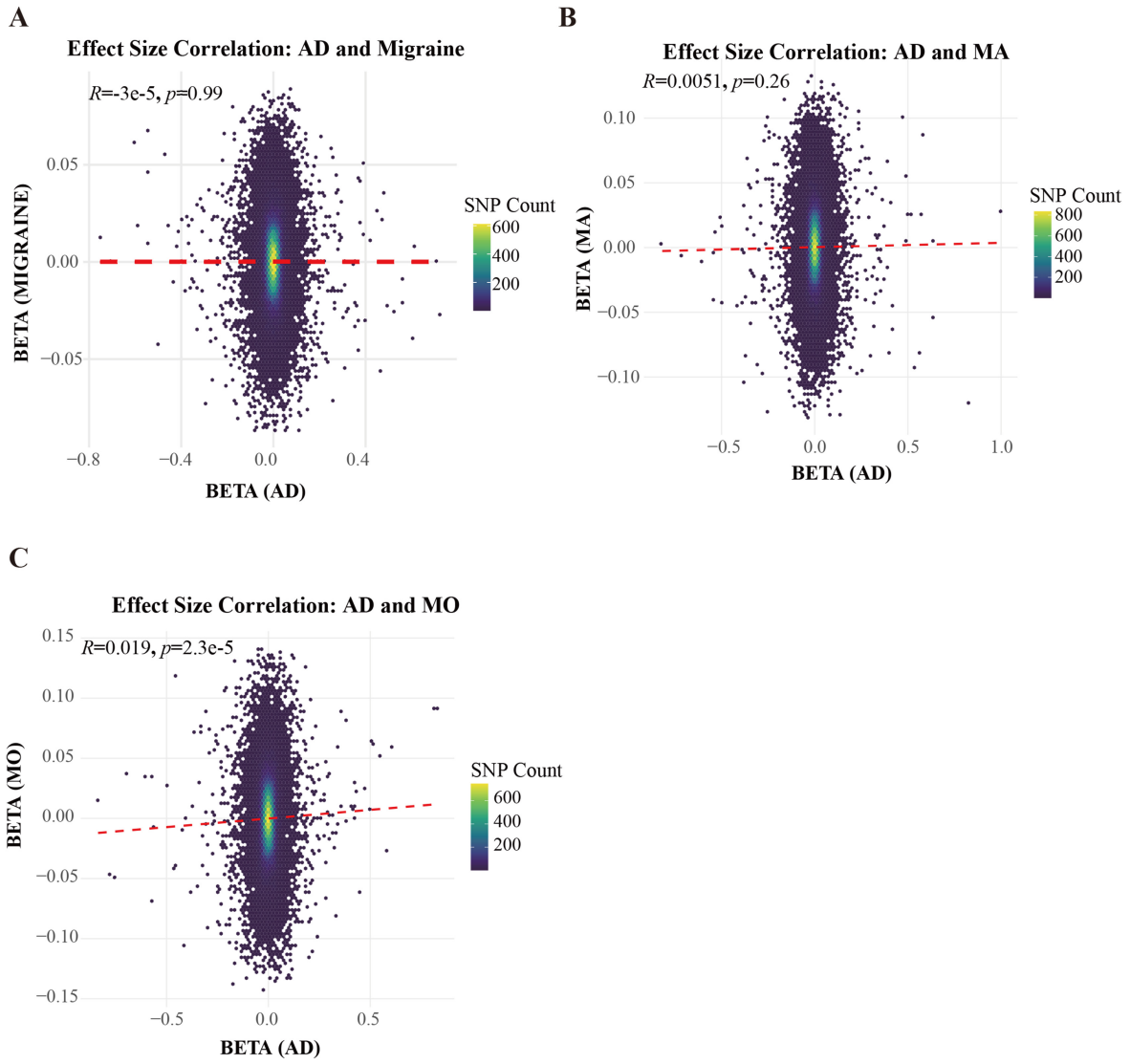

Figure 1. Global effect size correlations between AD and migraine subtypes. (A-C) Hexbin density scatter plots illustrating the distribution of aligned variant effect sizes for AD (x-axis) against (A) overall migraine, (B) MA, and (C) MO (y-axis). To assess systematic biases, the analyses were strictly restricted to background variants not significantly associated with either trait (single-trait $P > 0.05$ for both AD and the respective migraine phenotype), with 50,000 SNPs randomly down-sampled for visualization. The color gradient indicates the number of SNPs within each hexagonal bin. Red dashed lines represent the linear regression fit. Pearson correlation coefficients (R) and nominal P-values are provided for each comparison. AD: Alzheimer's disease; MA: migraine with aura; MO: migraine without aura; SNPs: single-nucleotide polymorphisms.

AD and overall migraine

As for the AD and overall migraine trait pair, we identified 4 suggestive independent shared loci and 1 significant shared locus after clumping by PLINK [Figure 2A and Supplementary Table 2]. The significant shared locus rs76968534 was identified under stringent dual-threshold criteria ($P_{CAPSSOC} < 5 \times 10^{-8}$, $P_{single\text{-}trait} < 5 \times 10^{-3}$). The significant locus rs76968534 is located in an intergenic region. Among the suggestive loci, rs117310449 ($P_{CPASSOC} = 4.20 \times 10^{-46}$) is in close proximity to genes *PVRL2*, *TOMM40*, and *CTB-129P6.4*. *PVRL2* plays a key role in immune response and is associated with the development of AD[44-47]. *TOMM40* is closely related to neuroinflammation and AD[45,47,48]. *CTB-129P6.4* is associated with the risk of intracerebral hemorrhage and AD[49,50]. The other suggestive locus (index SNP: rs3851179, $P_{CPASSOC} = 2.02 \times 10^{-15}$) is near the gene *RNU6-560P*, which is a non-coding gene associated with AD[51,52]. The other suggestive locus (index SNP: rs10909892, $P_{CPASSOC} = 9.81 \times 10^{-10}$) is close to the gene *PRDM16*. This gene is expressed in astrocytes and downregulated in AD patients[53].

AD and MA

We identified 5 suggestive independent pleiotropic loci and 2 significant pleiotropic loci for AD and MA [Figure 2B and Supplementary Table 3]. The loci rs9271060 (near *HLA-DRB1*, *CR753309.2*, *CR753835.1*) and rs79254581 were shared by AD and MA. The suggestive shared locus (index SNP: rs8106813, $P_{CPASSOC} = 9.06 \times 10^{-20}$) is close to the gene *APOC1P1*. It plays a crucial role in the development of AD risk[54]. The next locus (index SNP: rs3740688, $P_{CPASSOC} = 5.54 \times 10^{-11}$) is near the *SPI1*, which is a risk gene for AD. rs16035 (near *CACNA1A*) and rs11767557 (near *EPHA1*, *EPHA1-AS1*) were shared by AD and MA. *CACNA1A* is mainly expressed in the nervous system and associated with hemiplegic migraine[55,56]. *HLA-DRB1*, *EPHA1*, and *EPHA1-AS1* are risk factors for AD[57-59].

AD and MO

As for the AD and MO trait pair, we identified 2 independent suggestive shared loci [Figure 2C and Supplementary Table 4]. The suggestive locus (index SNP: rs3851179, $P_{CPASSOC} = 2.21 \times 10^{-16}$) is close to the gene *RNU6-560P*, which is closely linked with AD risk[60]. Although two suggestive loci were initially identified, neither satisfied our more stringent locus-level filtering criteria, leaving no robust shared loci for downstream analyses.

Colocalization analysis supports shared causal variants at specific loci

The purpose of colocalization is to distinguish whether the associated signals of two traits are driven by the same causal variant or by different but linked variants. We found that 1 shared locus (index SNP: rs76968534) between AD and overall migraine demonstrated strong posterior probabilities for a single shared causal variant (PPH4 > 0.5), pointing to a shared causal variant [Figure 3A and Supplementary Table 5]. As for the AD and MA, the critical locus (rs9271060) exhibited a high PPH3 (> 0.5), reflecting distinct but tightly correlated regulatory variants driving the two traits independently within the same genetic region, while rs79254581 was colocalized at the same genetic variant (PPH4 > 0.5) [Figure 3B and C, Supplementary Table 6].

Pathway enrichment analysis highlights biological mechanisms

Based on the annotated genes from the genome-wide significant cross-trait loci, we performed pathway enrichment analysis. After rigorous Benjamini-Hochberg FDR correction (q-value < 0.05), the significantly enriched pathways for AD and overall migraine/MA were highly concentrated in neuro-immune regulation, lipid metabolism, and amyloid pathology. The most significantly enriched biological processes included the regulation of amyloid-beta clearance and cholesterol transport and efflux. Furthermore, robust enrichment was observed in immune-related cascades, notably the regulation of complement-dependent cytotoxicity [Figure 4A and B, Supplementary Tables 7 and 8]. Importantly, consistent with our stringent locus-level analyses, which identified no robust shared loci between AD and MO, downstream pathway enrichment analysis was inherently not applicable and thus intentionally not pursued for the MO subtype.

TWAS identifies shared genes between AD and migraine

We performed TWAS to identify the shared genes between AD and migraine, including its subtypes, in 49 tissues. Firstly, the shared genes related to single trait were identified in different tissues. Then, we obtained the shared genes between two traits by intersecting the single-trait associated genes according to different tissues. For AD and MA, following a conservative global FDR correction across all 49 tissues, the complement component 2 (*C2*) gene emerged as a highly robust pleiotropic driver specifically within the central nervous system (Brain Cerebellar Hemisphere). *TSBP1-AS1* was significant in thyroid tissue [Table 1].

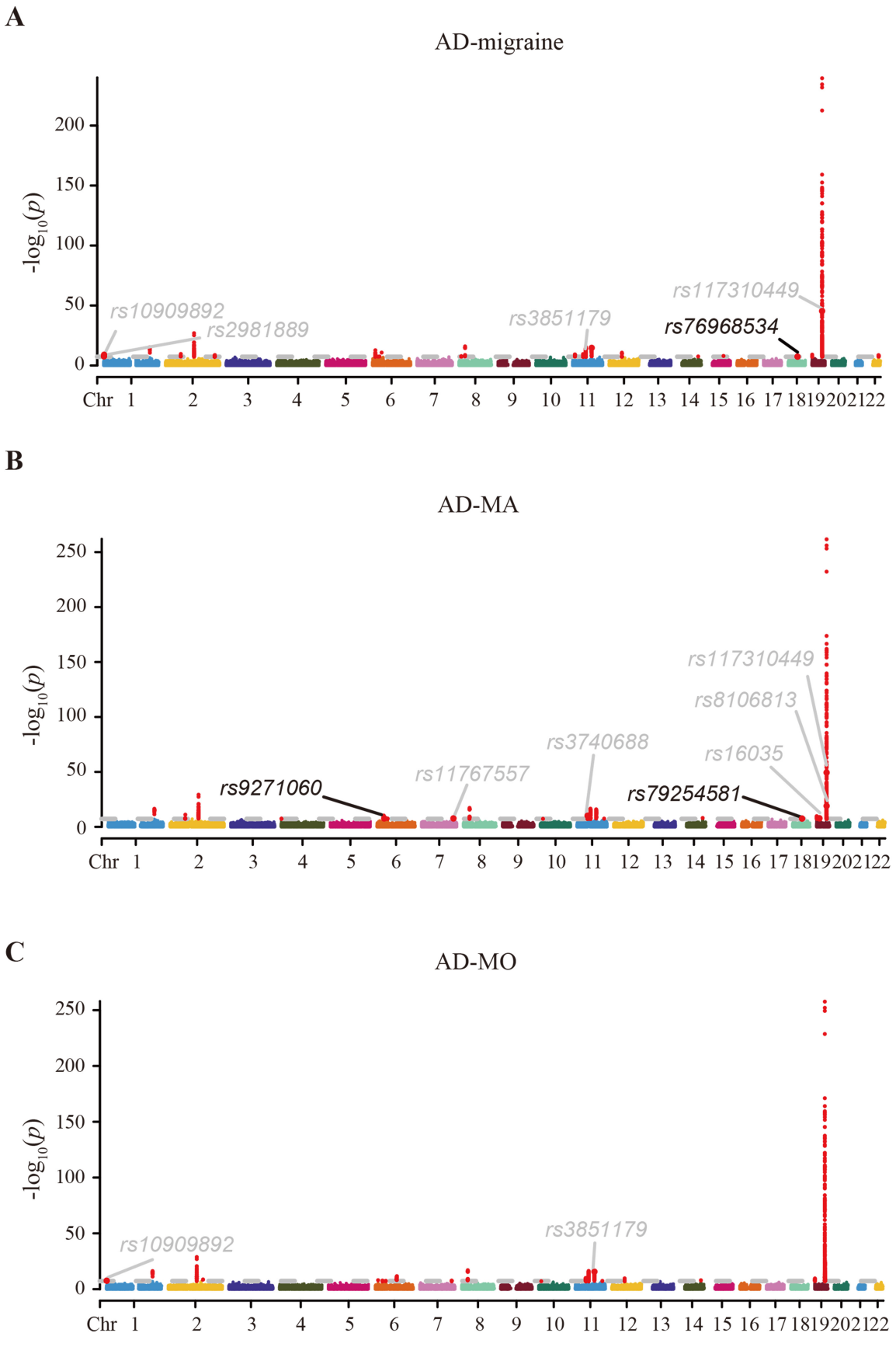

Figure 2. Shared genetic loci between AD and migraine phenotypes identified by CPASSOC. (A-C) Manhattan plots displaying the cross-trait genome-wide association signals for (A) AD and overall migraine, (B) AD and MA, and (C) AD and MO. The y-axis represents the -log10-transformed *P*-values derived from the CPASSOC analysis across the autosomes. Lead SNPs for the identified loci are annotated. Black text indicates significant shared loci, defined by a stringent cross-trait genome-wide significance threshold ($P_{CPASSOC} < 5 \times 10^{-8}$) and a

strict single-trait threshold of $P < 5 \times 10^{-3}$ for both underlying phenotypes. Grey text denotes suggestive shared loci, defined by the cross-trait genome-wide significance threshold ($P_{CPASSOC} < 5 \times 10^{-8}$) and a single-trait threshold of $P < 0.05$ for both underlying phenotypes. Red dots indicate SNPs surpassing the cross-trait genome-wide significance threshold in the respective CPASSOC analysis. AD: Alzheimer's disease; MA: migraine with aura; MO: migraine without aura; SNPs: single-nucleotide polymorphisms.

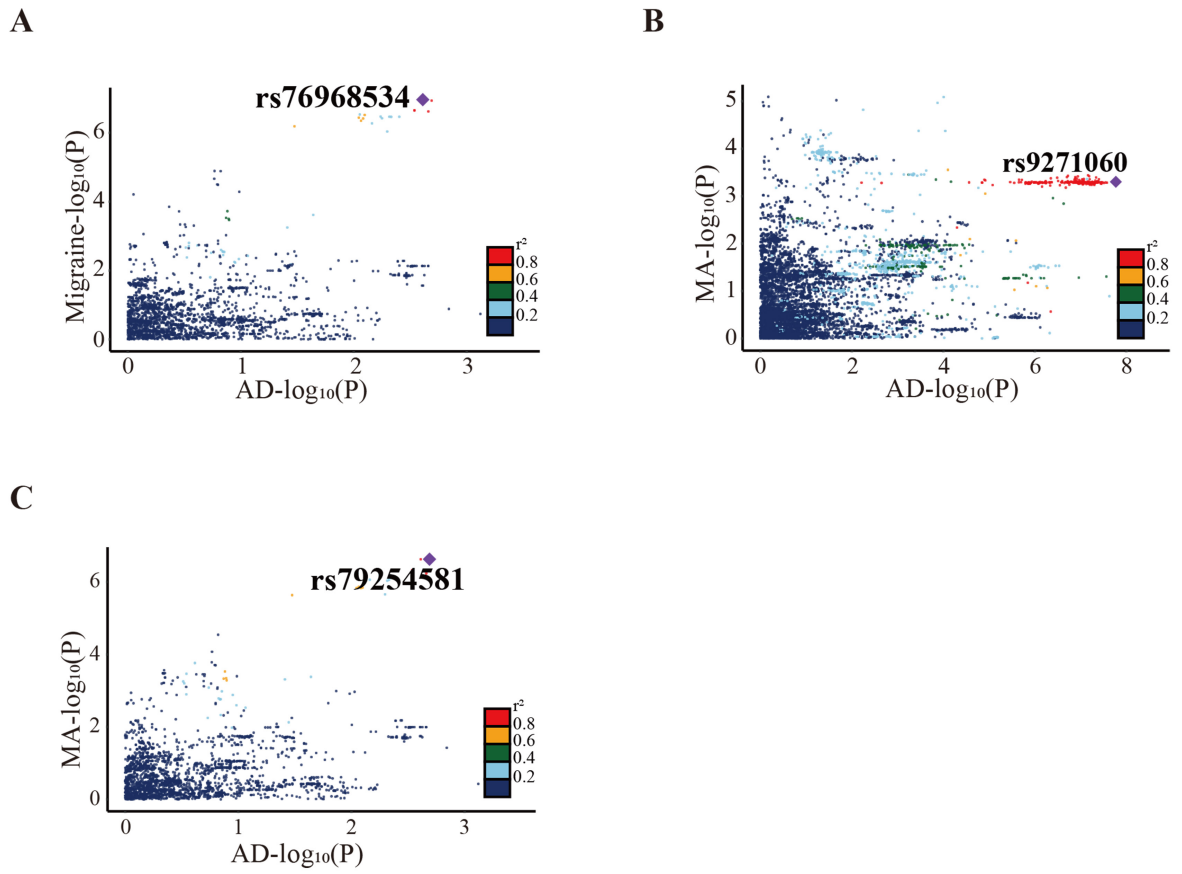

Figure 3. LocusZoom plots of identified pleiotropic loci by the R package LocusCompareR. (A) The plots of pleiotropic loci between AD and migraine; (B and C) The plots of pleiotropic loci between AD and MA. The horizontal axis presents -$\log_{10}$ *P* values from AD GWAS, and the vertical axis indicates -$\log_{10}$ *P* values from migraine or MA GWAS. AD: Alzheimer's disease; MA: migraine with aura.

Tissue-specific expression for shared genes

We obtained the 2 shared genes between AD and MA. In order to further explore the expression in different tissues, we further quantitatively characterized gene expression using the GTEx V10 data.

According to the results, we found that the *C2* gene is highly expressed in liver and lung tissues, and it is also expressed in the cerebellar hemisphere of the brain [Figure 5 and Supplementary Table 9]. *TSBP1-AS1* is highly expressed in brain spinal cord (cervical c-1), with relatively lower expression across other tissues, including the thyroid [Figure 5 and Supplementary Table 9].

Genetic drug target analysis identifies the potential therapeutic candidates

After identifying the shared genes between AD and migraine subtypes, we further identified potential target genes. Based on TWAS prioritization, *C2* and *TSBP1-AS1* were carried forward for downstream drug-target analyses.

Then, we made full use of DGIdb and DSigDB to obtain FDA-approved drugs for these target genes. According to DSigDB, there are two drugs (ESTRADIOL and PROGESTERONE) with reported gene

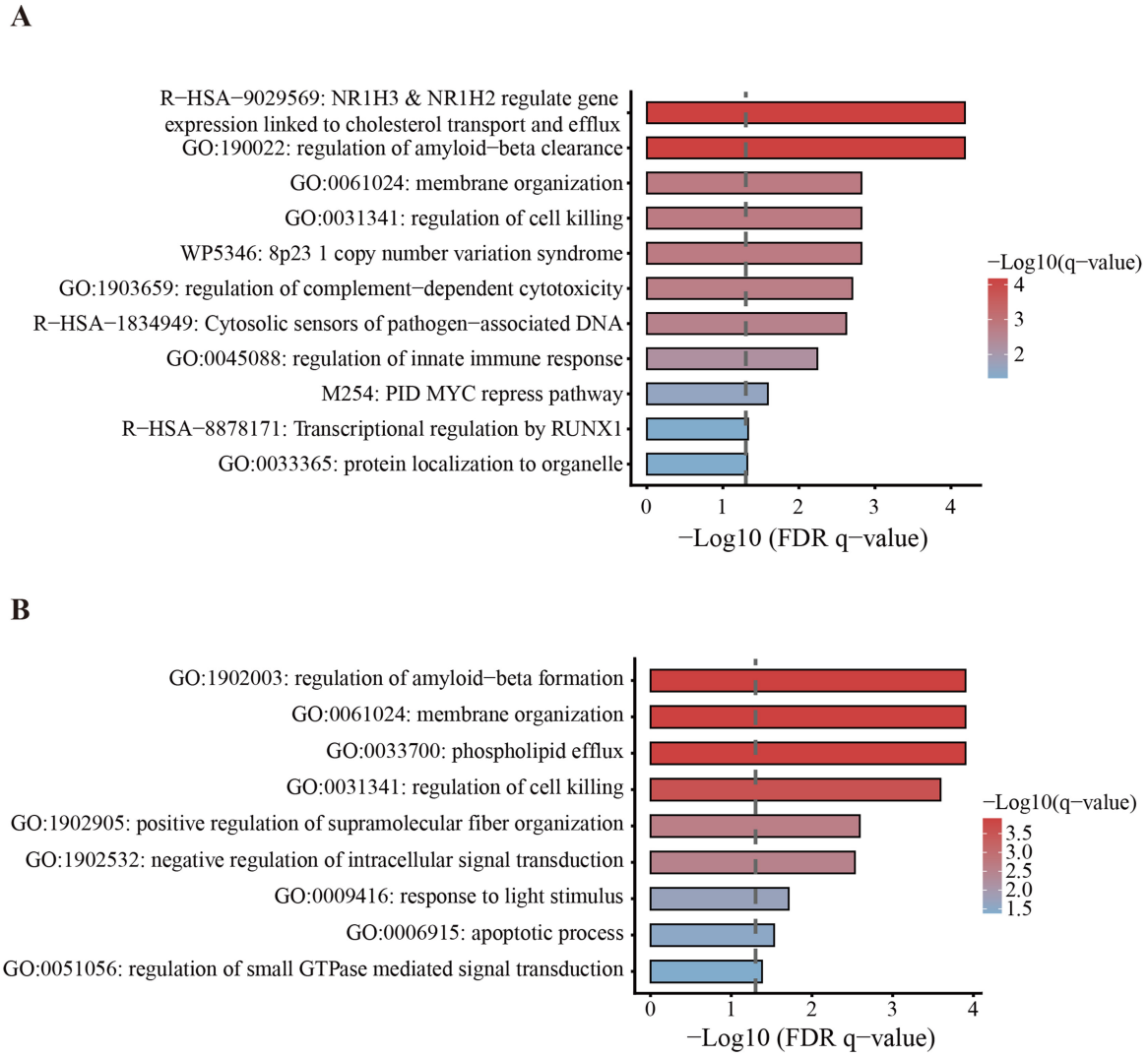

Figure 4. Pathway enrichment analysis based on the annotated genes for AD and migraine, as well as MA, by Metascape. (A) The top 11 clusters with representative enriched terms based on annotated genes between AD and migraine; (B) The top 9 clusters with representative enriched terms based on annotated genes between AD and MA. AD: Alzheimer's disease; MA: migraine with aura; FDR: false discovery rate.

Table 1. The shared genes between AD and MA revealed by TWAS

Ensembl gene ID	Gene symbol	Tissue	CHR	AD				MA			
				Best.GWAS.ID	TWAS.Z	*P*	P.fdr	Best.GWAS.ID	TWAS.Z	*P*	P.fdr
ENSG00000166278.14	*C2*	Brain_Cerebellar_Hemisphere	6	rs3134954	-4.1544	3.26E-05	0.017	rs429150	-4.258	2.06E-05	0.038
ENSG00000225914.1	*TSBP1-AS1*	Thyroid	6	rs9270856	-3.9792	6.91E-05	0.027	rs429150	-4.608	4.06E-06	0.019

AD: Alzheimer's disease; MA: migraine with aura; TWAS: transcriptome-wide association study; CHR: chromosome.

associations. We did not obtain candidate small-molecule drugs or biologics for the target gene *TSBP1-AS1* from DGIdb and DSigDB. This is expected, as *TSBP1-AS1* is a long non-coding RNA (lncRNA), and current pharmacogenomic databases are heavily biased toward conventional protein-coding targets [Supplementary Table 10].

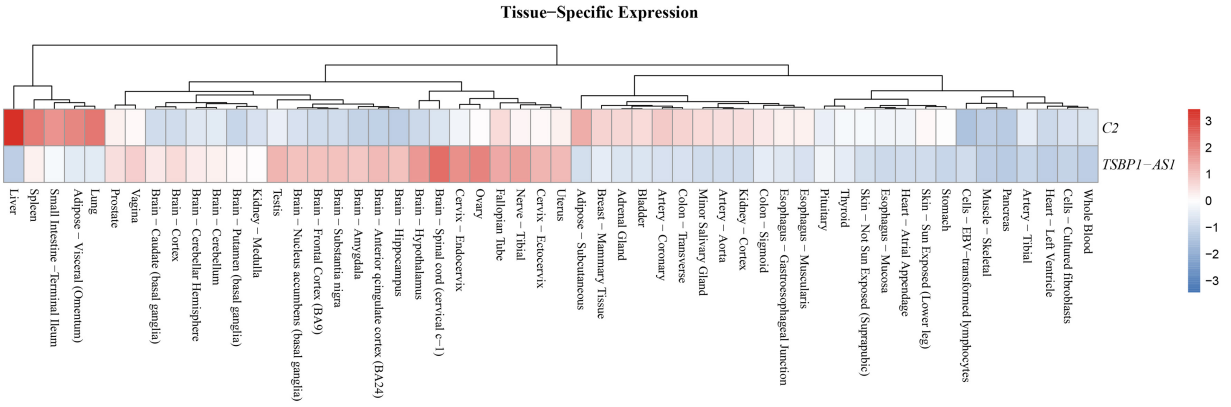

Figure 5. Tissue-specific expression profiles of *C2* and *TSBP1-AS1*. The heatmap illustrates the relative expression levels of the two shared genes across 54 human tissues derived from the GTEx database. Raw median TPM values were $\log_2$(TPM + 1) transformed and subsequently row-scaled (*Z*-score) to highlight the distribution pattern for each gene independently. The color gradient from blue to red represents relatively low to high expression levels. The top dendrogram denotes the hierarchical clustering of tissues based on expression similarity. TPM: Transcripts per million.

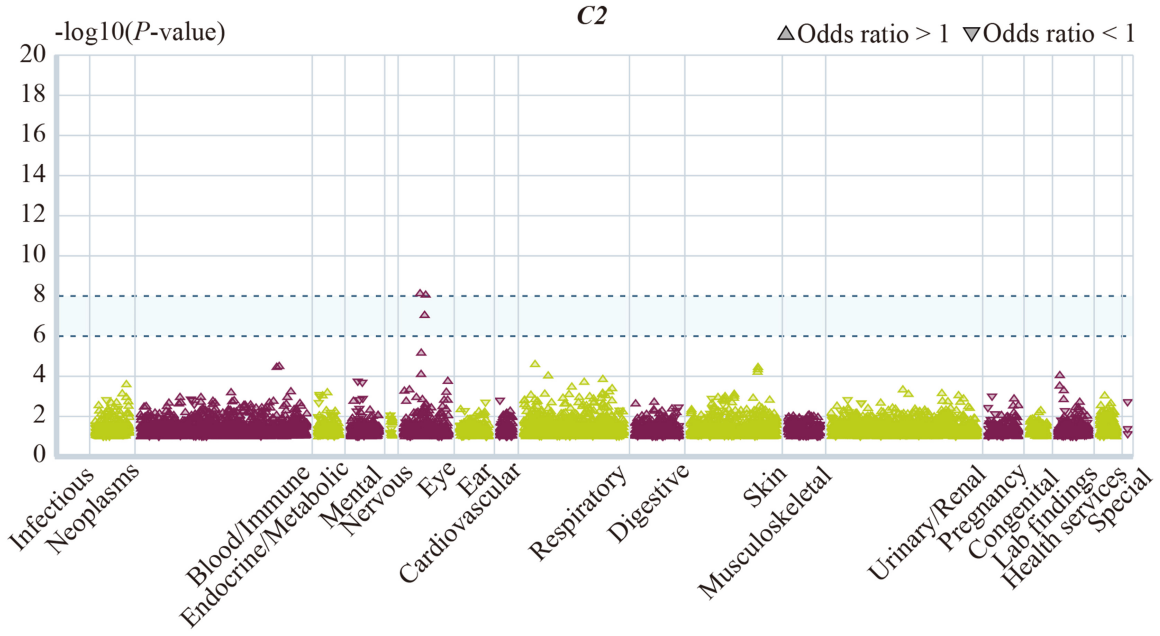

Figure 6. Phenome-wide association studies for the candidate gene target by AstraZeneca portal. The Manhattan plot for PheWAS based on *C2*. The first gray dotted lines represent the significance threshold in the Manhattan plots ($-\log_{10} P = 8$). The second gray dotted lines represent the suggestive threshold in the Manhattan plots ($-\log_{10} P = 6$). PheWAS: Phenome-wide association study.

PheWAS indicates no widespread pleiotropic effect

We have obtained the candidate therapeutic drugs for the potential gene targets. To evaluate the broader phenotypic associations of the prioritized target gene, we then conducted the PheWAS based on potential drug targets. According to the AstraZeneca PheWAS portal based on sequencing and phenotype data from the UK Biobank, the target gene *C2* was not significantly associated with infectious, neoplasms, blood/immune, endocrine/metabolic, mental, nervous, eye, ear, cardiovascular, respiratory, digestive, skin, musculoskeletal, urinary/renal, pregnancy, congenital, lab findings, health services, and special phenotypic categories [Figure 6]. This PheWAS result suggests that *C2* showed no significant associations across major disease categories. However, we caution that gene-level phenome associations act strictly as biological proxies and do not guarantee the clinical pharmacological safety of corresponding therapeutic compounds.

DISCUSSION

AD and migraine, including MA and MO, are common neurological disorders that impose a substantial socioeconomic burden worldwide. In this study, we integrated multiple complementary bioinformatic approaches to characterize the shared genetic architecture between AD and migraine, including its subtypes. Firstly, several pleiotropic loci between AD and overall migraine, as well as MA and MO, were identified by genome-wide cross-trait meta-analysis, followed by functional annotation. In addition, we identified the pleiotropic genes between a pair of traits by the TWAS method, which integrates GWAS data and eQTL to reveal the potential influence of gene expression on phenotype.

Shared genetic etiology at the locus and gene levels

We performed genome-wide cross-trait meta-analysis to identify the pleiotropic loci for a pair of traits, followed by functional annotation. As for AD and overall migraine, 4 independent suggestive shared loci and 1 significant shared locus were identified by CPASSOC. In addition, we found 5 suggestive pleiotropic loci and 2 suggestive pleiotropic loci for AD and MA. Consistent with previous epidemiological observations suggesting a stronger association between MA and dementia than MO, we identified more shared loci between AD and MA than between AD and MO[24-26]. Collectively, these findings support a shared genetic basis between AD and migraine at the locus level.

Furthermore, we identified the shared genes for AD and migraine, including their types, in 49 tissues by TWAS. At gene levels, we found the *C2* and *TSBP1-AS1* shared by AD and MA. *C2* is a serum glycoprotein and is part of the classical pathway of the complement system. It is associated with certain autoimmune diseases[61]. *TSBP1-AS1* is a lncRNA and is highly expressed in immune system cells[62]. Additionally, it was proven that *TSBP1-AS1* is shared by immune and bone diseases[63]. These genes were expressed in specific brain tissues, as well as peripheral tissues, including the liver and thyroid.

Systemic pleiotropy and tissue relevance

Regarding the associations identified in non-central nervous system (CNS) tissues, such as thyroid, we interpret these findings as a reflection of the systemic nature of pleiotropic genes. For example, *C2* is a fundamental component of the systemic immune system. While its primary disease relevance in this context is likely within the neuro-immune environment of the brain, its genetic signals are detectable across multiple tissues due to shared regulatory elements. In this study, we have prioritized the interpretation of results from CNS-pertinent tissues, such as cerebellum and basal ganglia, as they align more closely with the known pathophysiology of neurodegeneration and headache disorders.

A neuro-immune-vascular framework linking AD and migraine

Rather than positing a singular shared causal etiology, our refined colocalization and systems biology analyses reveal a highly complex genetic intersection between AD and MA. The identification of *C2* and *TSBP1-AS1* implicates immune-related mechanisms. *C2* participates in complement activation, whereas *TSBP1-AS1* may contribute to immune regulation through mechanisms that remain to be fully characterized. These pathways are implicated in AD-associated neuroinflammation, a hallmark of migraine pathophysiology. The lack of existing drugs targeting *TSBP1-AS1* likely reflects the historical focus on protein-coding genes. Nevertheless, the pleiotropic associations observed for *TSBP1-AS1* support its prioritization for future functional investigation and evaluation as a potential target for RNA-based therapeutics, including antisense oligonucleotides.

Taken together, these findings support a neuro-immune-vascular axis as a unifying framework, providing mechanistic insight into the reported epidemiological association between migraine and AD.

Limitations and future directions

Despite the integrative multi-omics framework employed in this study, several limitations should be acknowledged. First, to reduce potential bias arising from population stratification, our analyses were confined to GWAS summary statistics derived from European-ancestry cohorts (FinnGen and IGAP). Notably, the migraine data utilized the FinnGen cohort, which possesses a well-documented distinct population history and founder effect compared to the multi-cohort European IGAP dataset. While our LDSC intercept evaluations suggested minimal bias from cryptic sample overlap, this population heterogeneity represents a potential confounder. Future replication in independent, non-Finnish European cohorts is essential to independently validate these specific loci. Second, the shared risk genes identified in this study, including *C2* and *TSBP1-AS1*, were inferred through statistical and computational approaches. Although these findings provide important hypotheses, experimental validation remains necessary. In particular, functional studies in relevant cellular and animal models, such as clustered regularly interspaced short palindromic repeats (CRISPR)-based perturbation in neuronal or microglial systems, will be essential to establish causal roles and underlying biological mechanisms. Third, gene expression patterns across 54 tissues were characterized using bulk tissue data from GTEx data. While informative, such data may obscure cell-type-specific regulatory effects, particularly within complex structures such as the neurovascular unit. Future studies leveraging single-cell RNA sequencing or spatial transcriptomics will be critical to resolve these signals at higher resolution. Finally, our drug target and PheWAS analyses are strictly hypothesis-generating. And predicting therapeutic efficacy or safety from gene-level associations is inherently limited by unknown pharmacokinetic and off-target pharmacological variables.

Conclusion

In conclusion, our work has characterized the distinct and shared genetic correlations between AD and migraine in multiple aspects. Additionally, this study provides important insights for understanding the genetic etiology between the two traits. These findings are crucial to interpreting the molecular mechanisms of the disease and identifying potential therapeutic targets.

DECLARATIONS

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Authors' contributions

Conducted the experiment: Wang T, Wang W
Analyzed and plotted the results during the revision: Wang T, Fang C
Collected the data: Fang C, Liu Y
Wrote the initial manuscript: Wang T, Li J
Contributed to the overall study design: Li J, Zheng X
All authors participated in reviewing and modifying the manuscript.

Availability of data and materials

We used publicly available datasets in this study. AD GWAS datasets can be downloaded at https://dss.niagads.org/open-access-data-portal/#NG00075. The Migraine GWAS summary dataset was obtained from https://storage.googleapis.com/finngen-public-data-r12/summary_stats/release/finngen_R12_G6_MIGRAINE.gz, https://storage.googleapis.com/finngen-public-data-r12/summary_stats/release/finngen_R12_G6_MIGRAINE_WITH_AURA.gz, https://storage.googleapis.com/finngen-public-data-r12/summary_stats/release/finngen_R12_G6_MIGRAINE_NO_AURA.gz, respectively. The GTEx RNA-seq V10 dataset can be accessed from https://www.gtexportal.org/.

The datasets and materials generated and/or analyzed during the current study are available from the

corresponding author upon reasonable request.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool Gemini (version 3.1 Pro, released 2026-02-19) was used for language editing and formatting assistance. Additionally, some elements were initially generated using Gemini (version 3.1 Pro, released 2026-02-19) and subsequently modified by the authors for inclusion in the Graphic Abstract. The tools did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Supplementary Materials

Supplementary Materials

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