

ORIGINAL RESEARCH ARTICLE

Discovering genes associated with multiple sclerosis through cross-tissue integrative transcriptome-wide association studies

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Abstract

Genome-wide association studies (GWASs) have identified over 200 loci associated with multiple sclerosis (MS), yet these loci explain only a fraction of the genetic risk. Integrating GWAS with expression quantitative trait loci through transcriptome-wide association studies (TWAS) provides a powerful approach to pinpointing candidate genes underlying complex traits. We performed a TWAS using FUSION with Genotype-Tissue Expression version 8 expression weights, based on meta-analyzed summary statistics from large-scale MS GWAS datasets (5263 cases and 83,167 controls). To refine candidate genes and assess causality, we applied conditional analysis, Bayesian colocalization, summary-data-based Mendelian randomization (SMR), and fine-mapping strategies. TWAS identified 403 candidate genes, of which 15 were further supported by SMR analysis. Six of these genes (*HLA-G*, *HLA-J*, *HLA-DRB1*, *TAP2*, *HLA-C*, and *HLA-B*) overlapped with previously reported MS loci, and nine additional genes (e.g., *MICF*, *USP8P1*, *PSORS1C3*, *HCG24*, and *HLA-DQB1-AS1*) represented novel candidates requiring further validation. Through the integration of transcriptomic and GWAS data, our study unveiled established and novel genetic contributors to MS. These findings deepen our understanding of MS pathogenesis and highlight high-priority targets for future functional and therapeutic studies.

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1. Introduction

Multiple sclerosis (MS) is a chronic and enduring neurological condition affecting the central nervous system. It is characterized by an unpredictable course and a diverse range of clinical manifestations.¹ MS stands as a leading cause of disability among young adults² and has the potential to result in persistent disability and reduced life expectancy.³ In 2019, there were a reported 59,345 new cases of MS and 22,439 fatalities worldwide attributed to this condition. The prevalence, mortality, and disability-adjusted life years associated with MS have shown an upward trajectory.⁴ Furthermore, MS exerts a significant burden on both individuals and society, profoundly impacting daily and occupational functioning, with this impact intensifying as disability

progresses and the overwhelming burden of fatigue takes hold.⁵

In recent years, genome-wide association studies (GWASs) have proven highly effective in identifying common single-nucleotide polymorphism (SNP)-based variants that exert moderate to significant influences on phenotypic outcomes. The ImmunoChip custom genotyping array identified 135 regions potentially linked to MS in 14,498 cases and 24,091 controls. In the subsequent replication phase, an additional 48 susceptibility variants were identified in 80,094 individuals of European descent, culminating in the confirmation of 110 risk variants at 103 distinct loci.⁶ A genome-wide meta-analysis⁷ unearthed three additional loci associated with the development of MS. Although the heritability of MS is estimated at 19%, GWAS have unveiled numerous genetic variants associated with the condition.⁸ MS susceptibility has been linked to over 200 loci, explaining nearly 50% of its hereditary component.⁹ The estimated heritability of MS in twin pairs was found to be 0.64 (0.36–0.76), with a shared environmental component of 0.01 (0.00–0.19).¹⁰ Nevertheless, familial risk varies across different populations, and some studies suggest that variations in population risk can be predominantly ascribed to environmental factors rather than genetic factors.¹¹ For example, Kular and Jagodic¹² concluded that approximately 30% of the modified genes observed in peripheral immune cells of progressive MS patients were also present in brain tissues, indicating a shared impact on neuronal functions. In addition, they discussed potential mechanisms responsible for the shared epigenetic patterns between blood and brain, implicating genetic regulation and external factors such as smoking and aging. Genetic variants identified through GWAS do not offer clear biological mechanisms or functional consequences. Epigenetics holds promise in shedding light on clinically significant mechanisms implicated in disease progression, potentially opening new avenues for treating progressive MS patients in the future.¹²

Transcriptome-wide association studies (TWASs) leverage expression quantitative trait loci (eQTL) data alongside individual-level genotype information or GWAS summary data to explore the relationship between gene expression levels and complex traits or diseases.¹³ This powerful approach helps overcome key GWAS limitations by providing a functional context for non-coding variants and boosting statistical power to detect associations.^{14–16} While previous TWAS analyses in complex diseases have successfully identified immune-related pathways and candidate genes,¹⁷ our study expands on these efforts by leveraging a substantially larger, meta-analyzed GWAS dataset for MS. This increased statistical power, combined with a comprehensive multi-tissue eQTL panel from

Genotype-Tissue Expression (GTEx), enhances our ability to detect novel gene associations and refine signals within known risk loci, providing a more detailed transcriptome-wide view of MS susceptibility.

In our quest to identify gene regulatory risk loci associated with MS, we conducted TWAS using MS GWAS summary statistics sourced from the UK Biobank and FinnGen. In addition, we performed conditional analyses on all significant TWAS associations to ascertain the co-significant TWAS genes, which serve as driver genes for each risk locus. To further delineate these associations, we employed summary data-based Mendelian randomization (SMR). A visual representation of our approach is presented in Figure 1.

2. Methods

2.1. Study cohort

This study utilized genome-wide summary statistics from multiple large-scale GWAS datasets, including:

- (i) MS GWAS summary data from the UK Biobank results (<https://www.leelabsg.org/resources>), as reported by Zhou *et al.*¹⁸
- (ii) MS GWAS summary data from the FinnGen research project (<https://r9.finnngen.fi>), where MS cases were defined using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision diagnostic codes
- (iii) Thirteen tissue-specific SNP-weight reference panels from the GTEx project,¹⁹ representing multiple brain regions (cerebellar hemisphere, cerebellum, brain cortex, frontal cortex, hippocampus, hypothalamus,

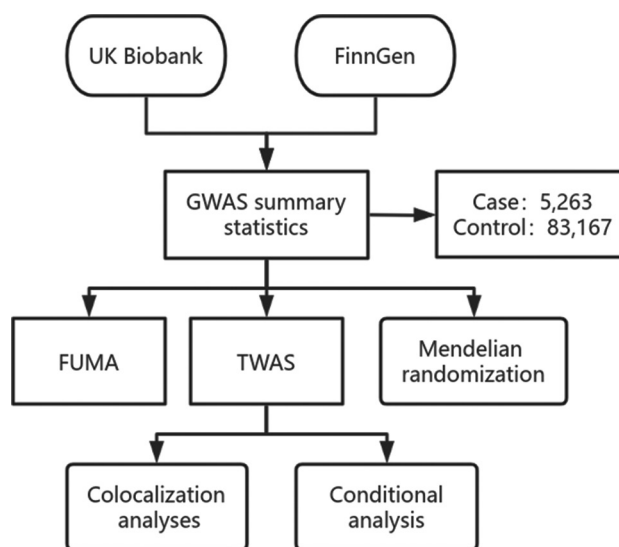


Figure 1. Schematic workflow of this study
Abbreviations: GWAS: Genome-wide association studies;
TWAS: Transcriptome-wide association studies.

nucleus accumbens, and basal ganglia including putamen and substantia nigra), as well as spinal cord and whole blood. These reference panels were obtained from the FUSION repository (<http://gusevlab.org/projects/fusion>)

- (iv) The linkage disequilibrium (LD) reference panels from the 1,000 Genomes Project, used for LD estimation and sourced from the FUSION website (<http://gusevlab.org/projects/fusion>).

2.2. Combination of GWAS summary statistics

Study-specific GWAS results from the UK Biobank and FinnGen datasets were combined using inverse-variance weighted meta-analysis conducted with METAL (<http://www.sph.umich.edu/csg/abecasis/metal>). SNPs with a minor allele frequency of $\leq 1\%$ were excluded from the meta-analysis. A Manhattan plot was generated using the *qqman* package in R.

2.3. Transcriptome-wide association study

Transcriptome-wide association study was performed using the FUSION pipeline with default parameters to identify genes whose genetically regulated expression was associated with MS risk. The LD structure between SNPs was accounted for using a reference panel from the 1,000 Genomes Project (Phase 3 European, $N = 489$). SNP weight sets were generated in FUSION using best linear unbiased predictor (BLUP), bayesian sparse linear mixed model (BSLMM), least absolute shrinkage and selection operator (LASSO), and top-SNPs, except where BLUP/BSLMM was excluded due to sample size or convergence issues. To control for multiple testing across tissues and weight models (70,283 features in total), a stringent Bonferroni correction threshold of $p < 7.11 \times 10^{-7}$ ($0.05/70,283$) was applied. This conservative correction ensured the robustness of findings and minimized false-positive associations. In addition, concordance of signals across different weight models was used as supplementary evidence for reliability.

2.4. Bayesian colocalization

To determine if GWAS SNPs co-occur with eQTLs, the COLOC package in R (<https://cran.r-project.org/web/packages/coloc/>; version 5.1.0) was used for Bayesian colocalization. This involved combining all associations with PTWAS < 0.05 within a 1-megabase (Mb) range.²⁰ The Bayesian colocalization method assesses the posterior probability (PP) to determine whether the connection between two outcomes (GWAS and eQTL signals) within a locus is due to a shared causal variable or strong LD variation. COLOC evaluates five hypotheses: PP0, PP1, PP2, PP3, and PP4, with the primary aim being to establish if the GWAS and eQTL signals align with shared causal

variants (i.e., PP4). A high PP (PP4 $> 80\%$) indicates that GWAS and eQTL signals coincide.

2.5. Conditional analysis

To detect various significant features within a specific region or identical features across different tissues, a conditional analysis was conducted to identify independent features under specific conditions. The process also assessed how much GWAS signal remained after accounting for correlations. This approach identified jointly significant features and marginally significant features. Furthermore, it assessed the extent to which GWAS associations within each genetic region could be explained by the functional connectivity identified in the TWAS. To evaluate the association between characteristics in the SNP weight collection and among different groups, the eQTL weights were randomly altered, and the empirical association metrics for the GWAS effect condition were recalculated through fusion. In this study, 1,000 permutation tests were conducted for each TWAS gene, with a significance level set at $p < 0.05$.^{21,22}

2.6. Summary data-based Mendelian randomization

To explore whether MS SNP associations were mediated through expression, an SMR analysis was performed.²³ This method examined the correlation between GWAS and eQTL summary statistics, utilizing a Mendelian randomization framework to infer causality. The Heterogeneity in Dependent Instruments (HEIDI) test was additionally employed to distinguish between causality (or pleiotropy) and linkage, where feasible based on available data.²³ An SMR association passing the HEIDI test with low heterogeneity ($p > 0.05$) indicates alignment of the data with the MS-associated SNP, signifying differences in gene expression between the risk and protective alleles. The analysis incorporated quality-controlled MS GWAS summary statistics, along with an LD reference derived from imputed genotype data from the GWAS of MS conducted by Zhou *et al.*¹⁸ and FinnGen. eQTL data from GTEx v8²⁴ and additional relevant MS tissues (BrainMeta, Westra, and CAGE eQTL data) were used for the analysis of expression data.

The first set of additional relevant MS tissues was from the BrainMeta samples, previously meta-analyzed by Qi *et al.*²⁵ (effective sample size of 1194). The second set was from the study conducted by Westra *et al.*,²⁶ the largest eQTL meta-analysis in peripheral blood samples of 5311 European healthy individuals. The third set was from the study conducted by Luke,²⁷ an eQTL meta-analysis in peripheral blood samples of 2765 European individuals. The CAGE eQTL results provided finer coverage than those of Westra *et al.*²⁶'s study. The fourth set was the

version 8 release of the GTEx eQTL/sQTL summary data ($n = 73\text{--}670$),²⁸ which included amygdala, anterior cingulate cortex (Brodmann area [BA]24), caudate basal ganglia, cerebellar hemisphere, cerebellum, cortex, frontal cortex (BA9), hippocampus, hypothalamus, nucleus accumbens, basal ganglia (including substantia nigra and putamen), spinal cord cervical C1, and whole blood.

Significant probes for the SMR analysis were chosen based on a stringent Bonferroni-corrected threshold for SMR p -values ($0.05/n_{\text{probes}}$). In addition, the HEIDI test was employed, with a significance threshold set at p -value higher than 0.05. The combined use of both SMR and HEIDI methods is considered optimal for prioritizing loci for further functional investigation, which provided that the study possesses sufficient statistical power and adheres to conservative thresholds.

To visualize the overlap of genes identified through different analyses, a Venn diagram was generated using the matplotlib-venn library in Python 3.

3. Results

3.1. GWAS meta-analysis

A total of 5263 patients with MS and 83,167 controls of European ancestry were included in the study.

A Manhattan plot (Figure 2) was constructed using the combined GWAS summary statistics, revealing three significant loci (*C6orf10*, *CLN8*, and *CLEC16A*), consistent with previous GWAS studies.^{29,30} To further characterize these findings, we identified lead SNPs for each genomic risk locus (Table S1) and compiled a comprehensive list of all independent significant SNPs (Table S2). Subsequently, to explore the potential biological mechanisms, all variants within these genomic risk loci were subjected to extensive functional annotation, with detailed results presented in

Table S3. This annotation provided the foundational data for prioritizing candidate genes.

3.2. Transcriptome-wide association study

A TWAS was conducted using FUSION to identify genes associated with MS. Across all tested tissues, 403 significant gene-trait associations were identified (Table S4), corresponding to 98 distinct genes. To assess the potential inflation of association statistics and validate these findings, a permutation test was performed by randomly shuffling the quantitative trait locus weights. Post-permutation analysis indicated that a substantial portion of these genes (46 distinct genes) retained their significance, affirming the authenticity of the associations and ruling out chance occurrences.

3.3. Conditional and joint analyses

Conditional and joint analyses were conducted to evaluate the independence of TWAS signals, particularly at loci overlapping with GWAS associations. The analyses demonstrated that several signals were predominantly driven by specific expression features. For example, ENSG00000253982.1 (*CLN8-AS1*) explained most of the association at the *CLN8* locus (lead SNP rs1536776, GWAS $p = 2.4 \times 10^{-7}$; conditioned $p = 0.054$; variance explained = 0.848; Figure S1). Similarly, ENSG00000262222.1 accounted for the majority of the signal at another locus (lead SNP rs1536776, GWAS $p = 4.3 \times 10^{-8}$; conditioned $p = 0.015$; variance explained = 0.802; Figure S2).

Overall, four genomic regions (± 0.5 Mb windows) were identified as harboring multiple significant features. Joint analysis revealed 26 conditionally independent associations across 23 unique genes, while 378 associations were marginally significant (95 unique genes; Table S5).

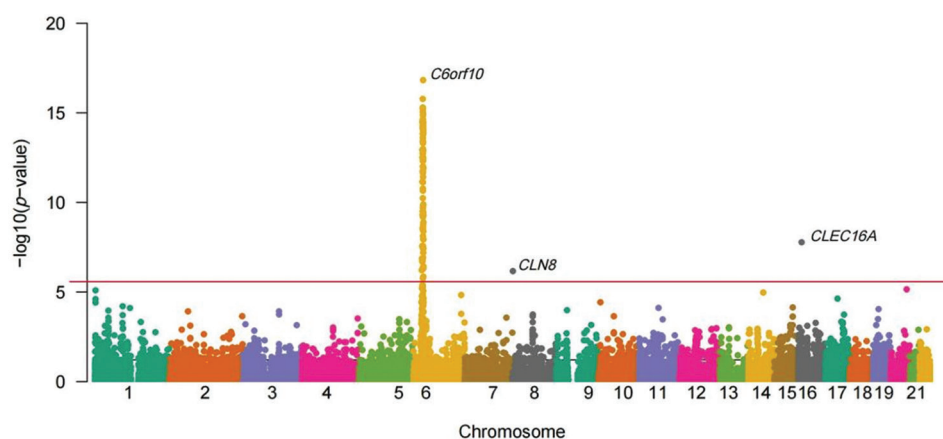


Figure 2. Manhattan plot for the combined genome-wide association studies summary statistics

These findings suggest that most observed signals were attributable to co-expression with a smaller set of independent features. The proportion of GWAS variance explained by gene expression within each region ranged from 0.802 to 0.985 (median = 0.882), indicating substantial mediation of GWAS associations by expression regulation.

3.4. Colocalization and summary data-based Mendelian randomization validation

To further assess causality, SMR was applied to integrate MS GWAS and GTEx v8 eQTL data. Across 16 tissues, 15 genes showed significant associations with MS (SMR $p < 0.05$ /number of probes), with no evidence of heterogeneity in the eQTL instruments (HEIDI $p > 0.05$). Tissue-specific probe counts, multiple-testing thresholds, and full HEIDI results are summarized in Table S2, while detailed statistics for significant SMR associations are provided in Table S6. These signals prominently included HLA-related genes (e.g., *HLA-B*, *HLA-C*, *HLA-DRB1*, *HLA-DQB1-AS1*, and *HLA-G*), several of which (*HLA-DRB1*, *HLA-B*, and *HLA-C*) overlapped with FUSION-TWAS findings. Integration with functional mapping (positional, eQTL, and chromatin interaction data; Table S7) offered convergent support. A Venn diagram (Figure 3) shows that all SMR-supported genes were a subset of the 403 TWAS-positive genes, refining the list to a smaller group with stronger evidence for causal involvement in MS. These results corroborate prior associations of MS with *HLA-DRB1* (including links to Epstein–Barr virus and *HLA-DRB1*1501*) as well as *HLA-B* and *HLA-C*.^{31–34}

3.5. Overlap of TWAS candidate genes, SMR-supported genes, and COLOC genes

Transcriptome-wide association study identified 403 significant associations, corresponding to 95 unique

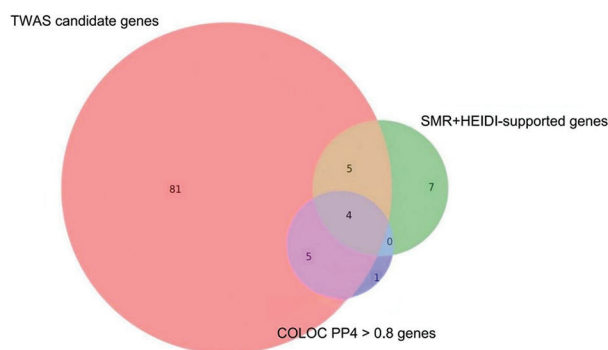


Figure 3. Three-set Venn diagram of Table S8 showing the overlap and unique components among TWAS candidate genes, SMR+HEIDI-supported genes, and COLOC (PP4>0.8) genes

Abbreviations: HEIDI: Heterogeneity in Dependent Instruments; PP: Posterior probability; SMR: Summary-data-based Mendelian randomization; TWAS: Transcriptome-wide association studies.

candidate genes (Table S8). Among these, 16 genes were further supported by SMR with HEIDI testing, and 10 genes showed evidence of colocalization with GWAS signals (COLOC PP4 > 0.8). A three-set Venn diagram (Figure 3) displays the overlap and unique components among TWAS candidate genes, SMR-supported genes, and COLOC genes. Notably, several HLA genes (e.g., *HLA-DRB1*, *HLA-DQB1*, *HLA-C*, and *HLA-B*) were consistently highlighted across TWAS, SMR, and COLOC. In contrast, a subset of genes, such as *MICF*, *HCG24*, and *HCG27*, was identified exclusively through TWAS.

4. Discussion

The GWAS approach has greatly advanced our understanding of MS genetics, identifying over 200 autosomal susceptibility variants outside the major histocompatibility complex (MHC), as well as 32 within the extended MHC and one on chromosome X.⁸ A major challenge in GWAS, however, lies in the extensive LD within risk loci, which complicates pinpointing the causal variants.²⁹ To address this, our study adopted a gene-centric approach integrating European MS GWAS summary statistics with GTEx v8 eQTL data. Through FUSION analysis, we identified 403 genes, of which 15 were further validated using SMR. Six of these genes (*HLA-G*, *HLA-J*, *HLA-DRB1*, *TAP2*, *HLA-C*, and *HLA-B*) have been well established in MS,^{33–37} while nine represent novel candidates identified through SMR analysis, warranting functional characterization.

Our results reinforce the central role of HLA variants in MS.³⁸ Among these, *HLA-DRB1*1501* remains the strongest genetic risk allele, conferring a threefold increased risk across populations.¹² Although its precise mechanism remains unclear, accumulating evidence points toward altered antigen presentation and epigenetic regulation. For example, Kular and Jagodic¹² demonstrated allele-specific methylation patterns influencing *HLA-DRB1* expression and identified a protective variant (rs9267649) linked to increased methylation and reduced expression, suggesting DNA methylation may mediate HLA-driven risk. This highlights the complex interplay between genetic and epigenetic mechanisms in MS susceptibility.

We also observed independent associations at MHC class I loci, particularly *HLA-B* and *HLA-C*. Prior studies reported inconsistent results across populations: some alleles (e.g., *HLA-B*44:02* and *HLA-B*27:05*) were protective,^{39,40} while others (e.g., *HLA-B*07:02*) conferred increased risk in African Americans.⁴¹ In contrast, *HLA-B*44* alleles exerted a global negative effect in a European cohort.³³ These population-specific differences underscore the genetic heterogeneity of MS and emphasize the need for replication

in diverse cohorts. Importantly, our findings suggest that multiple class I loci may contribute to MS pathogenesis beyond the established *HLA-DRB1* effects.

In comparison with previous integrative studies of MS genetics, our work provides several distinct advances. Earlier efforts have typically focused on single data layers or tissue types, such as SMR-based prioritization of druggable targets in peripheral blood,⁴² network-based integration of GWAS with transcriptomic alterations in normal-appearing white matter,⁴³ and proteome-wide association analyses linking genetic risk to altered brain protein abundance.⁴⁴ By contrast, our study adopted a cross-tissue TWAS framework, systematically evaluating genetic effects across multiple MS-relevant tissues rather than restricting analyses to one biological context. Moreover, we combined multiple complementary post-TWAS approaches—including conditional analysis, Bayesian colocalization, SMR, and fine-mapping—to refine causal inference and reduce false positives. Finally, while corroborating well-established HLA risk genes, we also identified nine novel candidates, including long non-coding RNAs (lncRNAs) and pseudogenes, that have not been emphasized in prior integrative analyses. These features extend previous work and highlight the added value of a multi-layered, cross-tissue analytic strategy for uncovering novel contributors to MS pathogenesis.

Beyond classical HLA genes, our SMR analysis highlighted several novel candidates. For example, *PSORS1C3*, implicated in glucocorticoid receptor signaling and psoriasis susceptibility,⁴⁵ may point to shared inflammatory pathways across autoimmune diseases. *USP8P1*, a pseudogene of *USP8*, could potentially regulate T-cell receptor recycling and regulatory T-cell stability.⁴⁶ Furthermore, we identified *HLA-DQB1-AS1*, an MHC-region lncRNA, which is increasingly recognized as a regulator of local gene expression.^{47,48} These findings expand the current view of the MHC from protein-coding genes alone to a broader regulatory network involving non-coding elements. Although less is known about other candidates, such as *MICF* and *STK19P*, their prioritization suggests that they may represent novel biological pathways involved in MS risk.

Collectively, our study provides additional evidence that both classical HLA alleles and non-HLA loci contribute to MS susceptibility. More importantly, the identification of novel candidate genes, particularly lncRNAs and pseudogenes, opens new avenues for mechanistic and therapeutic exploration. Future functional studies are warranted to translate these associations into biological insight and potential clinical applications.

Despite these advances, several limitations must be

acknowledged. First, our analysis relied primarily on GWAS summary statistics from individuals of European ancestry (UK Biobank and FinnGen). Given the known differences in allele frequencies and LD structures across populations, our findings may not generalize to non-European groups. In African Americans, genetic studies have validated several previously established MS risk loci and highlighted population-specific HLA alleles, such as *HLA-DRB1*15:03*, with distinct effect sizes, although no novel genome-wide loci have been discovered. In contrast, East Asian populations have been studied only in small-scale or candidate-gene settings, and comprehensive genome-wide data remain scarce.^{49,50} Validation in multi-ethnic cohorts will therefore be essential for developing equitable diagnostic and therapeutic strategies. Second, our analysis did not stratify MS by clinical subtypes, such as relapsing-remitting MS or primary progressive MS. Although substantial genetic overlap exists, evidence suggests that subtype-specific risk factors may influence disease course.⁵¹ Future subtype-stratified or quantitative phenotype-based analyses (e.g., age of onset and lesion burden) may provide deeper insights. Finally, although our integrative approach yielded robust candidate genes, statistical associations alone cannot establish causality. Experimental validation is required, for example, through clustered regularly interspaced short palindromic repeats–CRISPR-associated protein 9 (CRISPR-Cas9)-mediated editing in immune cells, or knockout mouse models in experimental autoimmune encephalomyelitis. Such functional studies will be critical to confirm mechanistic roles for candidates such as *PSORS1C3*, *USP8P1*, and MHC-region lncRNAs, ultimately bridging the gap from genetic association to biological mechanism.

5. Conclusion

The present study underscores the substantial genetic and transcriptomic alterations associated with MS. Our research has not only unveiled novel connections but also elucidated the modifications in genetic and transcriptomic profiles that influence previously identified risk genes. Among the 15 genes detected by SMR, six (*HLA-G*, *HLA-J*, *HLA-DRB1*, *TAP2*, *HLA-C*, and *HLA-B*) have already been linked to MS in previous studies. Remarkably, three of them (*HLA-DRB1*, *HLA-B*, and *HLA-C*) overlap with the unique genes identified through the FUSION analysis. In addition, several genes with potential roles in MS pathogenesis (*MICF*, *USP8P1*, *PSORS1C3*, *HCG24*, *XXbac-BPG299F13.17*, *HCG27*, *STK19P*, *CTD-2336O2.1*, and *HLA-DQB1-AS1*) were identified, although further validation is required. These findings underscore the effectiveness of TWAS as a statistical technique for discerning genes with both minor and substantial roles in MS. Collectively, our findings provide a foundation for

functional validation studies and may ultimately guide the identification of molecular mechanisms and therapeutic targets in MS.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Xiaoyun Zhang

Formal analysis: All authors

Investigation: All authors

Methodology: Xiaoyun Zhang

Writing—original draft: Zhen Liu

Writing—review & editing: Xiaoyun Zhang

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data used in this work are available from the corresponding author on reasonable request.

References

- Speil C, Rzepka R. Vaccines and vaccine adjuvants as biological response modifiers. *Infect Dis Clin North Am*. 2011;25(4):755-772.
doi: 10.1016/j.idc.2011.07.004
- Sadovnick AD, Ebers GC. Epidemiology of multiple sclerosis: A critical overview. *Can J Neurol Sci*. 1993;20(1):17-29.
doi: 10.1017/s0317167100047351
- Moransard M, Bednar M, Frei K, Gassmann M, Ogunshola OO. Erythropoietin reduces experimental autoimmune encephalomyelitis severity via neuroprotective mechanisms. *J Neuroinflammation*. 2017;14(1):202.
doi: 10.1186/s12974-017-0976-5
- Qian Z, Li Y, Guan Z, *et al*. Global, regional, and national burden of multiple sclerosis from 1990 to 2019: Findings of global burden of disease study 2019. *Front Public Health*. 2023;11:1073278.
doi: 10.3389/fpubh.2023.1073278
- Battaglia MA, Bezzini D, Cecchini I, *et al*. Patients with multiple sclerosis: A burden and cost of illness study. *J Neurol*. 2022;269(9):5127-5135.
doi: 10.1007/s00415-022-11169-w
- International Multiple Sclerosis Genetics C, Beecham AH, Patsopoulos NA, *et al*. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. *Nat Genet*. 2013;45(11):1353-1360.
doi: 10.1038/ng.2770
- Patsopoulos NA, Bayer Pharma MS, Edan G, *et al*. Genome-wide meta-analysis identifies novel multiple sclerosis susceptibility loci. *Ann Neurol*. 2011;70(6):897-912.
doi: 10.1002/ana.22609
- International Multiple Sclerosis Genetics C. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science*. 2019;365(6460):eaav7188.
doi: 10.1126/science.aav7188
- Kim W, Patsopoulos NA. Genetics and functional genomics of multiple sclerosis. *Semin Immunopathol*. 2022;44(1):63-79.
doi: 10.1007/s00281-021-00907-3
- Westerlind H, Ramanujam R, Uvehag D, *et al*. Modest familial risks for multiple sclerosis: A registry-based study of the population of Sweden. *Brain*. 2014;137(Pt 3):770-778.
doi: 10.1093/brain/awt356
- O'Gorman C, Freeman S, Taylor BV, *et al*. Familial recurrence risks for multiple sclerosis in Australia. *J Neurol Neurosurg Psychiatry*. 2011;82(12):1351-1354.
doi: 10.1136/jnnp.2010.233064
- Kular L, Jagodic M. Epigenetic insights into multiple sclerosis disease progression. *J Intern Med*. 2020;288(1):82-102.
doi: 10.1111/joim.13045
- Li B, Ritchie MD. From GWAS to Gene: Transcriptome-wide association studies and other methods to functionally understand GWAS discoveries. *Front Genet*. 2021;12:713230.
doi: 10.3389/fgene.2021.713230
- Dall'Aglio L, Lewis CM, Pain O. Delineating the genetic component of gene expression in major depression. *Biol Psychiatry*. 2021;89(6):627-636.
doi: 10.1016/j.biopsych.2020.09.010
- Huang S, Wang J, Liu N, *et al*. A cross-tissue transcriptome association study identifies key genes in essential hypertension. *Front Genet*. 2023;14:1114174.
doi: 10.3389/fgene.2023.1114174

16. Lu M, Zhang Y, Yang F, *et al.* TWAS Atlas: A curated knowledgebase of transcriptome-wide association studies. *Nucleic Acids Res.* 2023;51(D1):D1179-D1187.
doi: 10.1093/nar/gkac821
17. Gusev A, Mancuso N, Won H, *et al.* Transcriptome-wide association study of schizophrenia and chromatin activity yields mechanistic disease insights. *Nat Genet.* 2018;50(4):538-548.
doi: 10.1038/s41588-018-0092-1
18. Zhou W, Nielsen JB, Fritsche LG, *et al.* Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. *Nat Genet.* 2018;50(9):1335-1341.
doi: 10.1038/s41588-018-0184-y
19. Consortium GT, Laboratory DA, Coordinating Center -Analysis Working G, *et al.* Genetic effects on gene expression across human tissues. *Nature.* 2017;550(7675):204-213.
doi: 10.1038/nature24277
20. Giambartolomei C, Vukcevic D, Schadt EE, *et al.* Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet.* 2014;10(5):e1004383.
doi: 10.1371/journal.pgen.1004383
21. Gusev A, Ko A, Shi H, *et al.* Integrative approaches for large-scale transcriptome-wide association studies. *Nat Genet.* 2016;48(3):245-252.
doi: 10.1038/ng.3506
22. Liao C, Laporte AD, Spiegelman D, *et al.* Transcriptome-wide association study of attention deficit hyperactivity disorder identifies associated genes and phenotypes. *Nat Commun.* 2019;10(1):4450.
doi: 10.1038/s41467-019-12450-9
23. Zhu Z, Zhang F, Hu H, *et al.* Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat Genet.* 2016;48(5):481-487.
doi: 10.1038/ng.3538
24. PredictDB Team (2021). GTEx v8 models on eQTL and sQTL. PredictDB. Available from: <https://predictdb.org/post/2021/07/21/gtex-v8-models-on-eqtl-and-sqtl/>
25. Qi T, Wu Y, Zeng J, *et al.* Identifying gene targets for brain-related traits using transcriptomic and methylomic data from blood. *Nat Commun.* 2018;9(1):2282.
doi: 10.1038/s41467-018-04558-1
26. Westra HJ, Peters MJ, Esko T, *et al.* Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nat Genet.* 2013;45(10):1238-1243.
doi: 10.1038/ng.2756
27. Lloyd-Jones LR, Holloway A, McRae A, *et al.* The genetic architecture of gene expression in peripheral blood. *Am J Hum Genet.* 2017;100(2):228-237.
doi: 10.1016/j.ajhg.2016.12.008
28. Consortium GT. The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science.* 2020;369(6509):1318-1330.
doi: 10.1126/science.aaz1776
29. Axisa PP, Hafler DA. Multiple sclerosis: Genetics, biomarkers, treatments. *Curr Opin Neurol.* 2016;29(3):345-353.
doi: 10.1097/WCO.0000000000000319
30. Mirzadeh Azad F, Malakootian M, Mowla SJ. IncRNA PSORS1C3 is regulated by glucocorticoids and fine-tunes OCT4 expression in non-pluripotent cells. *Sci Rep.* 2019;9(1):8370.
doi: 10.1038/s41598-019-44827-7
31. Sorosina M, Santoro S, Ferre L, *et al.* Risk HLA variants affect the T-cell repertoire in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm.* 2023;10(3):e200093.
doi: 10.1212/NXI.00000000000020093
32. Xiao D, Ye X, Zhang N, *et al.* A meta-analysis of interaction between Epstein-Barr virus and HLA-DRB1*1501 on risk of multiple sclerosis. *Sci Rep.* 2015;5:18083.
doi: 10.1038/srep18083
33. Lysandropoulos AP, Mavroudakakis N, Pandolfo M, *et al.* HLA genotype as a marker of multiple sclerosis prognosis: A pilot study. *J Neurol Sci.* 2017;375:348-354.
doi: 10.1016/j.jns.2017.02.019
34. Link J, Lorentzen AR, Kockum I, *et al.* Two HLA class I genes independently associated with multiple sclerosis. *J Neuroimmunol.* 2010;226(1-2):172-176.
doi: 10.1016/j.jneuroim.2010.07.006
35. Madigand M, Oger JJ, Fauchet R, Sabouraud O, Genetet B. HLA profiles in multiple sclerosis suggest two forms of disease and the existence of protective haplotypes. *J Neurol Sci.* 1982;53(3):519-529.
doi: 10.1016/0022-510x(82)90248-9
36. Middleton D, Megaw G, Cullen C, Hawkins S, Darke C, Savage DA. TAP1 and TAP2 polymorphism in multiple sclerosis patients. *Hum Immunol.* 1994;40(2):131-134.
doi: 10.1016/0198-8859(94)90057-4
37. Mohammadi N, Adib M, Alsahebhosoul F, Kazemi M, Etemadifar M. An investigation into the association between HLA-G 14 bp insertion/deletion polymorphism and multiple sclerosis susceptibility. *J Neuroimmunol.* 2016;290:115-118.
doi: 10.1016/j.jneuroim.2015.11.019
38. Batchelor JR, Compston A, McDonald WI. The significance

- of the association between HLA and multiple sclerosis. *Br Med Bull.* 1978;34(3):279-284.
doi: 10.1093/oxfordjournals.bmb.a071512
39. Osoegawa K, Creary LE, Montero-Martin G, *et al.* High resolution haplotype analyses of classical *HLA* genes in families with multiple sclerosis highlights the role of HLA-DP alleles in disease susceptibility. *Front Immunol.* 2021;12:644838.
doi: 10.3389/fimmu.2021.644838
 40. Healy BC, Liguori M, Tran D, *et al.* HLA B*44: Protective effects in MS susceptibility and MRI outcome measures. *Neurology.* 2010;75(7):634-640.
doi: 10.1212/WNL.0b013e3181ed9c9c
 41. Chi C, Shao X, Rhead B, *et al.* Admixture mapping reveals evidence of differential multiple sclerosis risk by genetic ancestry. *PLoS Genet.* 2019;15(1):e1007808.
doi: 10.1371/journal.pgen.1007808
 42. Jacobs BM, Taylor T, Awad A, *et al.* Summary-data-based Mendelian randomization prioritizes potential druggable targets for multiple sclerosis. *Brain Commun.* 2020;2(2):fcaa119.
doi: 10.1093/braincomms/fcaa119
 43. Manuel AM, Dai Y, Freeman LA, Jia P, Zhao Z. An integrative study of genetic variants with brain tissue expression identifies viral etiology and potential drug targets of multiple sclerosis. *Mol Cell Neurosci.* 2021;115:103656.
doi: 10.1016/j.mcn.2021.103656
 44. Jia T, Ma Y, Qin F, Han F, Zhang C. Brain proteome-wide association study linking-genes in multiple sclerosis pathogenesis. *Ann Clin Transl Neurol.* 2023;10(1):58-69.
doi: 10.1002/acn3.51699
 45. Linh NTT, Giang NH, Lien NTK, *et al.* Association of PSORS1C3, CARD14 and TLR4 genotypes and haplotypes with psoriasis susceptibility. *Genet Mol Biol.* 2022;45(4):e20220099.
doi: 10.1590/1678-4685-GMB-2022-0099
 46. Yang J, Wei P, Barbi J, *et al.* The deubiquitinase USP44 promotes Treg function during inflammation by preventing FOXP3 degradation. *EMBO Rep.* 2020;21(9):e50308.
doi: 10.15252/embr.202050308
 47. Wang H, Yang B, Cai X, *et al.* Hepatocellular carcinoma risk variant modulates lncRNA HLA-DQB1-AS1 expression via a long-range enhancer-promoter interaction. *Carcinogenesis.* 2021;42(11):1347-1356.
doi: 10.1093/carcin/bgab095
 48. Long J, Liu L, Zhou X, Lu X, Qin L. HLA-DQB1-AS1 promotes cell proliferation, inhibits apoptosis, and binds with ZRANB2 protein in hepatocellular carcinoma. *J Oncol.* 2022;2022:7130634.
doi: 10.1155/2022/7130634
 49. Liu G, Zhang F, Hu Y, *et al.* Multiple sclerosis risk pathways differ in caucasian and Chinese populations. *J Neuroimmunol.* 2017;307:63-68.
doi: 10.1016/j.jneuroim.2017.03.012
 50. Isobe N, Gourraud PA, Harbo HF, *et al.* Genetic risk variants in African Americans with multiple sclerosis. *Neurology.* 2013;81(3):219-227.
doi: 10.1212/WNL.0b013e31829bfe2f
 51. Andlauer TF, Buck D, Antony G, *et al.* Novel multiple sclerosis susceptibility loci implicated in epigenetic regulation. *Sci Adv.* 2016;2(6):e1501678.
doi: 10.1126/sciadv.1501678