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RESEARCH ARTICLE

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Shared genetics and causal associations between COVID-19 and multiple sclerosis

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Abstract

Neuroinflammation caused by COVID-19 negatively impacts brain metabolism and function, while pre-existing brain pathology may contribute to individuals' vulnerability to the adverse consequences of COVID-19. We used summary statistics from genome-wide association studies (GWAS) to perform Mendelian randomization (MR) analyses, thus assessing potential associations between multiple sclerosis (MS) and two COVID-19 outcomes (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection and COVID-19 hospitalization). Genome-wide risk genes were compared between the GWAS datasets on hospitalized COVID-19 and MS. Literature-based analysis was conducted to construct molecular pathways connecting MS and COVID-19. We found that genetic liability to MS confers a causal effect on hospitalized COVID-19 (odd ratio [OR]: 1.09, 95% confidence interval: 1.03–1.16) but not on SARS-CoV-2 infection (1.03, 1.00–1.05). Genetic liability to hospitalized COVID-19 confers a causal effect on MS (1.15, 1.02–1.30). Hospitalized COVID-19 and MS share five risk genes within two loci, including TNFAIP8, HSD17B4, CDC37, PDE4A, and KEAP1. Pathway analysis identified a panel of immunity-related genes that may mediate the links between MS and COVID-19. Our study suggests that MS was associated with a 9% increased risk for COVID-19 hospitalization, while hospitalized COVID-19 was associated with a 15% increased risk for MS. Immunity-related pathways may underlie the link between MS on COVID-19.

KEYWORDS

COVID-19, Mendelian randomization, multiple sclerosis

1 | INTRODUCTION

Since the inception of the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a myriad of risk and protective factors have been reported for their association with the susceptibility or severity of COVID-19.[1–8] Meanwhile, a subpopulation of individuals with COVID-19 may suffer from post-COVID-19 syndrome after they recover from acute illness, which is known as long COVID-19.[9–13] Neurological manifestations are common among individuals with COVID-19 infection.[14,15] It is well documented that the coronavirus SARS-CoV-2 invades the central nervous system, impacting the structure, metabolism, and function of the brain.[16] The neurotropic and neuroinvasive properties of COVID-19 pose a remarkable threat to the brain health of affected individuals.

Ancha Baranovaand Hongbao Cao are co-first authors.

Many of the symptoms of "long COVID" are of distinct neurological origins. Pre-existing CNS pathology, especially those affecting the metabolism and integrity of neurons and glia, may make individuals more vulnerable to the consequences of coronavirus invasion and, therefore, may adversely influence COVID-19 outcomes. Multiple sclerosis (MS) is an acquired inflammatory demyelinating disease, possibly triggered by viral infections or reactivation episodes through stimulating immune responses.[17,18] Experimental studies show that coronaviruses may cause demyelination in animal models [19] and, at least in some cases, provoke a relapse of MS in humans.[20]

The Mendelian randomization (MR) framework can be used to infer causative links between genetically determined exposure phenotypes and subsequent disease outcomes; this is done by utilizing genetic variants as instrumental variables. MR analysis has been widely employed in recent studies to explore relationships between related traits.[21–23] It is not known whether the brain pathological changes in MS may aggravate the severity of COVID-19 or MS could be triggered by various COVID-19 outcomes. We sought to explore shared genetic variation and the potential mutual causal associations between MS and two COVID-19 outcomes (SARS-CoV-2 infection and COVID-19 hospitalization). Exploring genetic links between MS and COVID-19 may help to improve the management of MS in the context of coronavirus infection.

2 | METHODS

2.1 | GWAS summary datasets

The study utilized publicly available GWAS summary results. The summary statistics for the outcome of COVID-19 were obtained from the COVID-19 Host Genetics Initiative (HGI) GWAS meta-analysis round 7 (release date: April 8, 2022, without the 23andMe cohort), including SARS-CoV-2 infection (122 616 cases and 2 475 240 controls) and hospitalized COVID-19 (32 519 cases and 2 062 805 controls).[24] The MS GWAS data set included 47 429 cases and 68 374 controls.[25] All participants were of European origin. Ethical approval had been obtained in all the original studies. The SARS-CoV-2 infection data set mainly reflects the overall susceptibility to the virus, whereas hospitalized COVID-19 represents the severity of the disease. We called hospitalized COVID-19 "severe COVID-19."

2.2 | Genetic correlation analysis

The genetic correlations between MS and the COVID-19 outcomes were calculated using LD score regression.[26,27] The 1000 Genome Project phase 3 was used to estimate the LD structure for European populations. Single-nucleotide polymorphisms (SNPs) were filtered by 1.1 million variants, a subset of 1000 Genomes and HapMap3, with MAF above 0.05.

2.3 | MR analysis

MR demands three main assumptions on an instrumental variable (IV): (1) it is associated with the exposure; (2) it is not associated with confounding factors influencing the relationship between the exposure and the outcome; and (3) it cannot be associated with the outcome directly (but can only indirectly impact the outcome by its effect on the exposure). The analyses were performed using three complementary methods implemented in TwoSampleMR,[28] including inverse variance weighted (IVW), weighted median, and MR-Egger. They have different assumptions about horizontal pleiotropy.[29] We used the IVW model as our primary MR method. The IVW model assumes an intercept of zero and provides a consistent estimate of the causality by a fixed-effect meta-analysis. The weighted median model places more weight on precise IVs; therefore, the estimate remains consistent even if up to 50% of the IVs are invalid or weak. The MR-Egger model assumes that the pleiotropic effects are independent and applies a weighted linear regression of the outcome coefficient on the exposure coefficient.[29] The weighted median and MR-Egger models are less statistically powerful than the IVW model but more robust to horizontal pleiotropy or invalid instruments. The intercept from the MR-Egger regression was utilized to evaluate the average horizontal pleiotropy.[29] The IVs are not all valid when the MR Egger intercept significantly differs from zero. The significant associations between MS and the COVID-19 outcomes were determined by IVW-based FDR < 0.05.

For each exposure phenotype, SNPs with genome-wide significance ($p < 5 \times 10^{-8}$) were selected as IVs and further pruned using a clumping r^2 cutoff of 0.01 within a 10 Mb window, using the 1000 Genomes Project Phase 3 (EUR) as the reference panel. For each MR analysis, we removed SNPs not present in the outcome data set and palindromic SNPs with intermediate allele frequencies. We harmonized each pair of the exposure and outcome datasets by aligning the effect allele for exposure and outcome and obtained variant effects and standard errors of each data set.

2.4 | Shared genomic loci between COVID-19 and MS

To identify overlapping risk genes between COVID-19 and MS, we retrieved genome-wide risk genes for the two traits from the two GWAS datasets. Functional mapping and annotation (FUMA) software was used to map SNPs to genes and identify LD-independent genomic regions.[30] All genes located within the 10 kb vicinity of each variant were mapped. Independent significant SNPs (IndSigSNPs) were extracted when their p value was genome-wide significant ($p \leq 5.0E\text{-}08$) and independent of each other ($r^2 < 0.6$). Lead SNPs were identified as a subset of the independent significant SNPs that were in LD with each other at $r^2 < 0.1$ within a 500 kb window. Genomic risk loci were identified by merging lead SNPs located at a distance of less than 500 kb from each other. Clumping procedures were carried out based on the European 1000 Genomes Project

phase 3 reference panel. Due to extensive LD, the entire major histocompatibility complex locus was merged into one region (chr6: 25–35 Mb).

To identify the tissue specificity of a phenotype, SNP-based tissue enrichment analysis was conducted by FUMA,[30] which utilizes gene-property analyses to test associations between tissue-specific gene expression profiles in general GTEx V8 tissues and GWAS hits.

2.5 | Knowledge-based analysis

To explore the potential connection between MS and COVID-19 at the molecular level, large-scale literature data mining was executed in the Pathway Studio (www.pathwaystudio.com) environment,[31] containing approximately 14 million unique associations from >40 million scientific references. Then, a set of molecular pathways connecting MS and COVID-19 was constructed. First, the downstream targets and upstream regulators of MS and COVID-19 were identified, followed by a manual review of the references and related sentences for quality control of each extracted relationship. The relationships with no polarity or indirectly related to COVID-19 or MS were removed. The remaining relationships were employed to build a map of the molecular pathways connecting MS and COVID-19.

Protein-protein interactions (PPIs) among the genes mediating the effect of MS on COVID-19 were derived using STRING v11.[32] KEGG-based pathway enrichment analyses of the genes mediating the effect of MS on COVID-19 were conducted using FUMA.[30]

3 | RESULTS

3.1 | Genetic correlation analysis

Genetic correlation analyses indicated that MS had a nominal positive genetic correlation with hospitalized COVID-19 ($r_g = 0.12 \pm 0.06$, $p = 0.038$, FDR = 0.076). However, MS did not have genetic correlations with SARS-CoV-2 infection ($r_g = 0.06 \pm 0.06$, $p = 0.321$).

3.2 | MR analysis

Since each COVID-19 data set had different sets of SNPs and the SNPs not present in the outcome data set were removed before the MR analysis, different numbers of IVs were yielded for each MR analysis. A total of 82 and 83 IVs were obtained from the MS data set for the MR analysis of MS on SARS-CoV-2 infection and hospitalized COVID-19, respectively. We detected that genetic liability to MS confers a causal effect on hospitalized COVID-19 (odd ratio: 1.09, 95% confidence interval: 1.03–1.16) but not on SARS-CoV-2 infection (1.03, 1.00–1.05, $p = 0.038$, FDR = 0.051) (Table 1 and Figure 1).

In the MR analysis of the causal effects of the COVID-19 outcomes on MS, the numbers of IVs were 21 for SARS-CoV-2 infection and 36 for hospitalized COVID-19. We found that genetic liability to hospitalized COVID-19 conferred a causal effect on MS (1.15, 1.02–1.30, $p = 0.022$, FDR = 0.044) (Table 1 and Figure 1).

The sensitivity analyses showed that the directions of causal effect estimates across the methods were largely the same (Supporting Information: Table 1). Notably, tests of MR-Egger regression did not support directional pleiotropy in this MR analysis (MR-Egger intercept < 0.03, $p > 0.05$).

3.3 | Shared genomic loci between MS and hospitalized COVID-19

In FUMA analysis, a total of 74 and 32 genomic loci were associated with MS and hospitalized COVID-19, respectively (Supporting Information: Tables 2–3). MS and COVID-19 had two overlapping loci, residing in 5q23.1 and 19p13.2 (Table 2 and Figure 2A). These two loci contained 5 protein-coding genes shared between MS and COVID-19, including *TNFAIP8*, *HSD17B4*, *CDC37*, *PDE4A*, and *KEAP1*.

Tissue-specific expression analysis showed that GWAS hits for hospitalized COVID-19 were significantly enriched in the lung (Figure 2B), while GWAS hits for MS were significantly enriched in the spleen, blood, small intestine and lung (Figure 2B).

3.4 | Knowledge-based analysis

Mining of the molecular relationships and subsequent analysis of the reconstructed pathways revealed a total of 30 genes mediating the effect of MS on COVID-19 (Figure 3A and Supplementary Table 4). A set of 24 MS-driven genes that quantitatively change in MS and

TABLE 1 Causal associations between MS and COVID-19

Exposure	Outcome	b (se)	OR [95%CI]	N_IV	Egger_intercept	P_pleiotropy	*p*	FDR
MS	SARS-CoV-2 infection	0.026 (0.012)	1.03 [1.00–1.05]	82	0.003	0.073	0.038	0.051
MS	Hospitalized COVID-19	0.090 (0.031)	1.09 [1.03–1.16]	83	−0.000	0.922	3.45E-03	0.014
SARS-CoV-2 infection	MS	0.165 (0.244)	1.18 [0.73–1.90]	21	0.023	0.387	0.500	0.500
Hospitalized COVID-19	MS	0.143 (0.062)	1.15 [1.02–1.30]	36	0.022	0.083	0.022	0.044

Abbreviations: b, effect size; CI, confidence interval; MS, multiple sclerosis; N_IV, number of instrumental variables; OR, odds ratio; se, standard error.

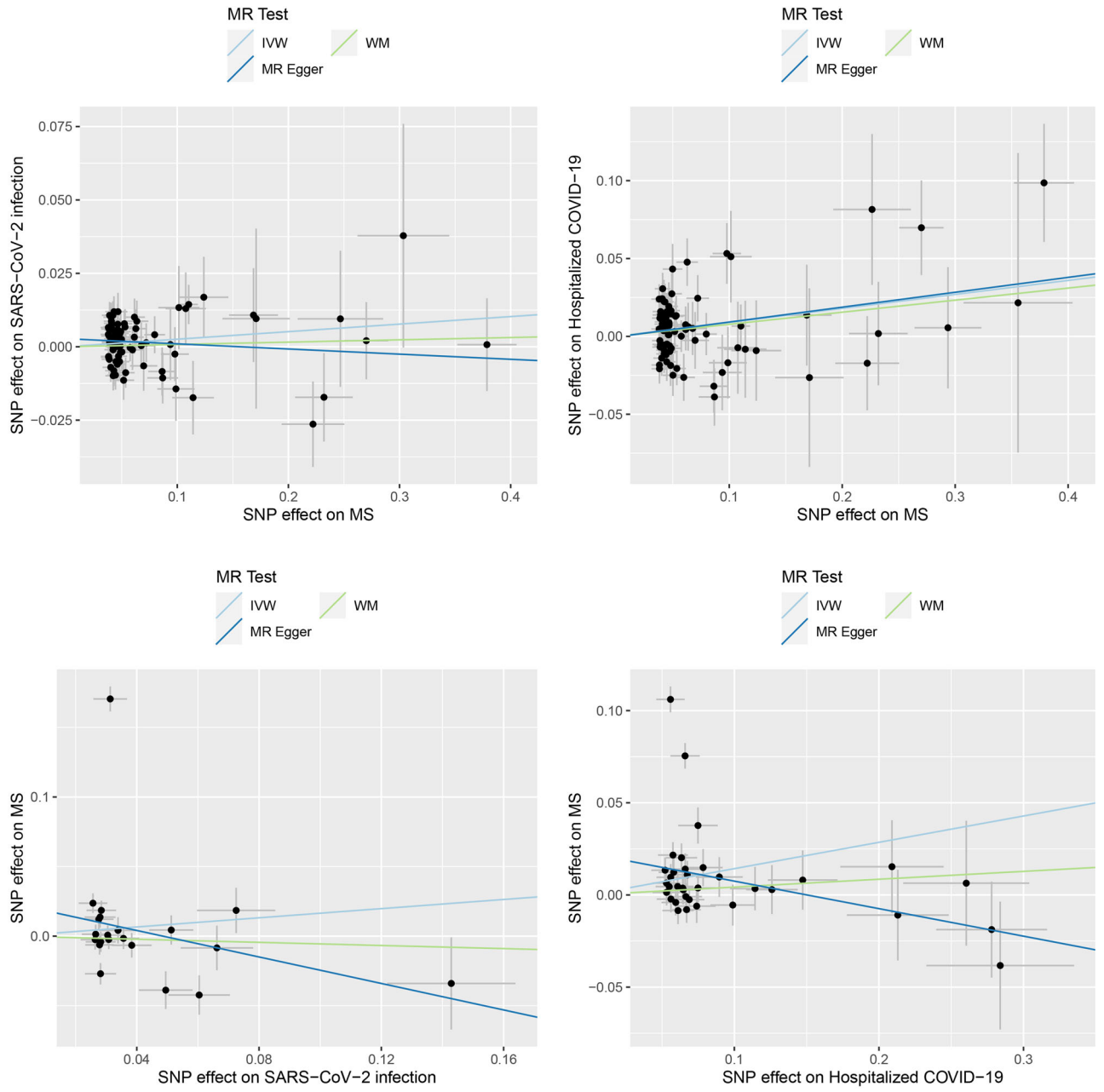

FIGURE 1 Causal associations between COVID-19 outcomes and MS. The upper panel shows the causal effects of MS on COVID-19 outcomes. The lower panel shows the causal effects of COVID-19 outcomes on MS. IVW, inverse variance weighted; MS, multiple sclerosis; WM, weighted median.

TABLE 2 Shared genomic loci between MS and hospitalized COVID-19

Trait	SNP	CHR	BP	Start:End	A1/A2	*p*	Genes
Hospitalized COVID-19	rs564985937	5	118802956	118734448:118803517	T/C	2.40E-08	TNFAIP8; HSD17B4
MS	rs28762138	5	118815815	118313421:119013643	T/G	1.46E-08	DTWD2; DMXL1; TNFAIP8; HSD17B4
Hospitalized COVID-19	rs34536443	19	10463118	10392638:10662236	C/G	3.83E-20	RAVER1; ICAM1; ICAM5; ICAM4; FDX1L; ICAM3; TYK2; ZGLP1; CDC37; PDE4A; KEAP1;S1PR5; ATG4D
MS	rs28834106	19	10592144	10499002:10616303	T/C	3.79E-11	CDC37; PDE4A; KEAP1

Abbreviations: CHR, chromosome; BP, base pair.

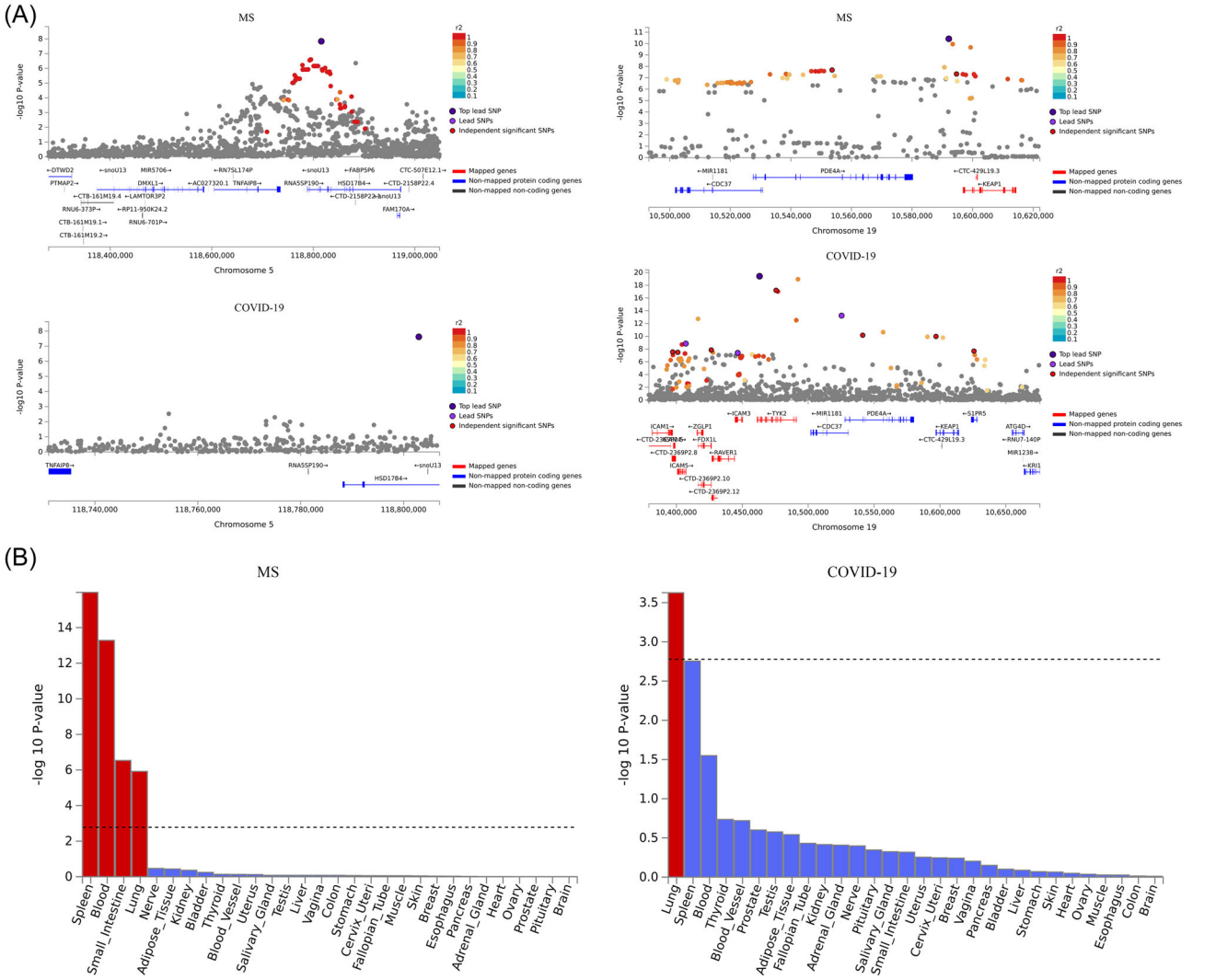

FIGURE 2 Genomic loci and tissue specificity of the two GWAS datasets. (A) Two overlapping loci between MS and hospitalized COVID-19. (B) Tissue-specific expression analysis for MS and hospitalized COVID-19. Significantly enriched tissues are highlighted in red. MS, multiple sclerosis; WM, weighted median.

enhance COVID-19 phenotypes included *ADAMTS13*, *ALB*, *CCL19*, *CMA1*, *CRP*, *CSF2*, *CTLA4*, *CTSB*, *CXCL10*, *IL6*, *ACE*, *CXCL8*, *DPP4*, *F12*, *FN1*, *HRH1*, *IFNB1*, *IL2*, *KLF2*, *NCAM1*, *PADI2*, *SELE*, *TNF*, and *TNFSF12*. On the other hand, 6 MS-driven genetic changes suppress the phenotypes of COVID-19, including *CASP3*, *ERBB2*, *IFNA2*, *MAPK14*, *PLG*, and *TRPV4*.

A total of 29 genes were identified as mediating the effect of COVID-19 on MS (Figure 3C and Supporting Information: Table 5). Among these genes, 22 COVID-19-driven genes can promote the development of MS, including *ADIPOQ*, *CCL2*, *CCL5*, *CSF2*, *CXCL10*, *CXCL8*, *EPO*, *ICAM1*, *IFNG*, *IL17A*, *IL1B*, *IL2*, *IL2RA*, *IL5*, *IL6*, *IL7*, *LEP*, *MPO*, *NLRP3*, *TLR4*, *VCAM1*, *and VEGFA*. Meanwhile, seven COVID-19-related genes can protect against MS, including *CSF3*, *IFNB1*, *IL15*, *TLR3*, *TLR7*, *TNFSF10*, and *VIP*.

Interestingly, five genes overlapped between the 24 MS–COVID-19-promoting genes and 22 COVID-19–MS-promoting genes, including *CSF2*, *CXCL10*, *IL6*, *CXCL8*, and *IL2*.

PPI analysis using the STRING database showed that both the 24 COVID-19-promoting proteins and the 22 MS-promoting proteins formed a tightly interconnected network (Figure 3B,D). KEGG-based pathway enrichment analysis in FUMA showed that both gene sets were enriched in immunity-related molecular pathways, including cytokine receptor interaction, Toll-like receptor signaling, NOD-like receptor signaling, and JAK/STAT signaling pathways (Supporting Information: Figures 1–2).

4 | DISCUSSION

Neurological diseases and COVID-19 have been previously identified as risk factors for each other, with the mechanisms underlying their mutual influences being largely unknown. In this study, we conducted MR analysis to explore the connection between an important neurological condition of autoimmune nature, MS, and COVID-19.

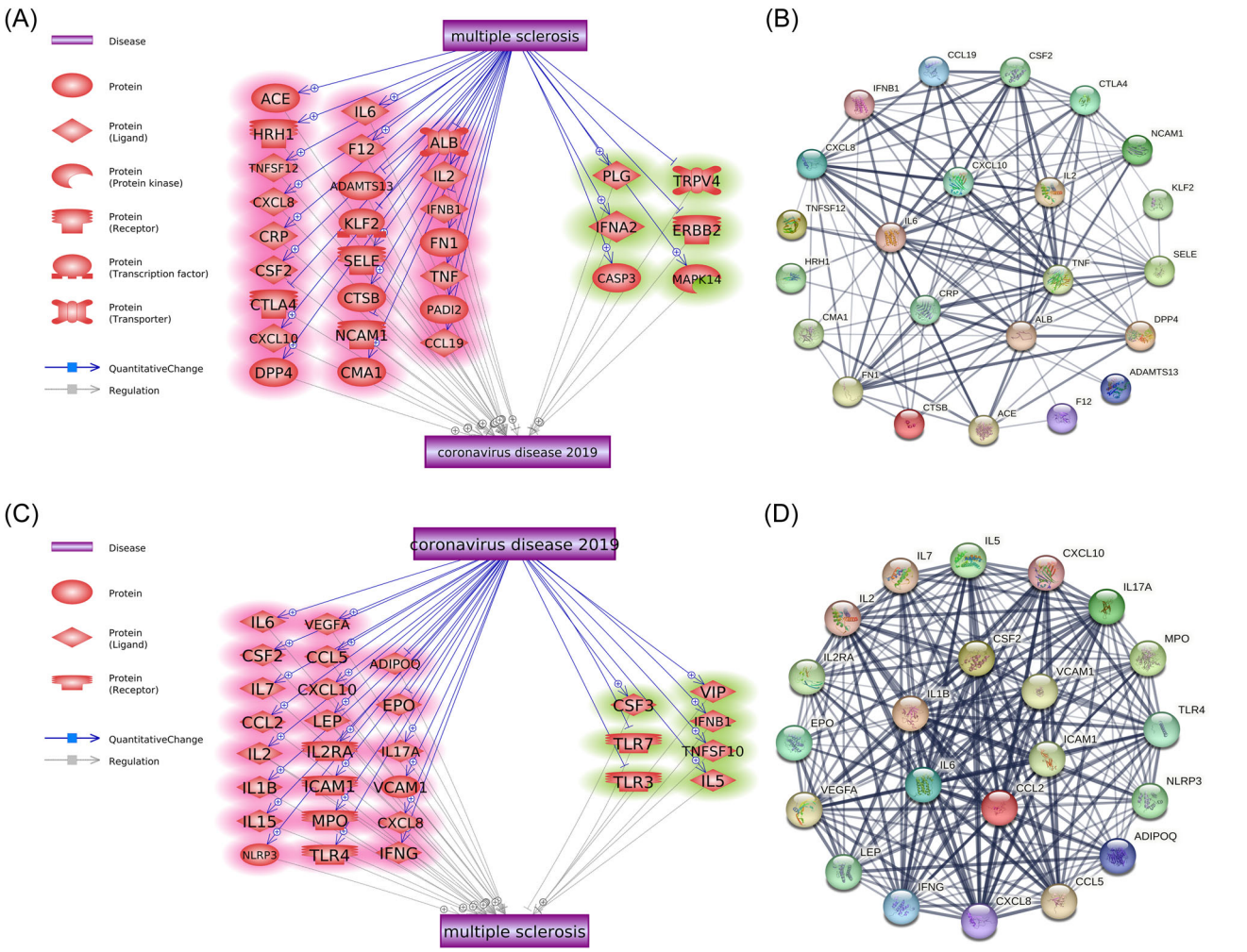

FIGURE 3 Molecular pathways connecting MS and COVID-19. (A) Molecular pathways from MS to COVID-19. Promoting effects are highlighted in red, and inhibitory effects are highlighted in green. Quantitative genetic changes driven by MS exert more promoting than inhibitory effects on COVID-19. (B) Protein–protein interactions among the 24 COVID-19-promoting genes. Line sizes are proportional to the combined scores of the interactions. (C) Molecular pathways from COVID-19 to MS. Quantitative genetic changes driven by COVID-19 exert more promoting than inhibitory effects on MS. (D) Protein–protein interactions among the 22 MS-promoting genes. Line sizes are proportional to the combined scores of the interactions. MS, multiple sclerosis.

Here, we show the causal effect of MS on severe outcomes of COVID-19. MS, especially in its progressive form, is recognized as a significant contributor to adverse COVID-19 outcomes.[33] Garjani et al. found that patients with MS are more likely to experience a prolonged period of acute COVID-19 symptoms and are vulnerable to the effects of the long COVID-19.[34] These results agree with our finding of the positive causal effect of MS on COVID-19 hospitalization. Our results suggest that neural lesions in MS patients contribute to the severity of COVID-19.

On the other hand, genetic liability to MS may not increase the risk for SARS-CoV-2 infection as such. It seems that the differences in vulnerability to SARS-CoV-2 infection may be due to some prevention disparity between healthy individuals and those suffering from MS, possibly related to vaccine hesitancy in the MS cohort,[35] rather than to underlining genetics. On the other hand, the severity of the resultant disease may differ in these two groups. This observation is well aligned with the current understanding of the earliest stages of COVID-19 and with commonly observed age- and disease-dependent differential risks for the development of cytokine storms.[36]

It is surprising to note that GWAS hits for MS were enriched in the spleen, blood, small intestine, and lung, instead of the brain, which supports the pivotal role of the inflammatory process in the development of MS. Lung, blood, and spleen are three tissues considered as most relevant to COVID-19. The enriched tissues provide another layer of evidence for the MS-COVID-19 connection.

Comparison of GWAS hits of COVID-19 and MS revealed two loci harboring five overlapping protein-coding genes, which possibly contribute to the shared pathophysiology of these two diseases. The list of pleiotropic risk factors underpinning the association between MS and COVID-19 severity includes *CDC37*, *PDE4A* and *KEAP1* on chromosome 19p13.2, as well as *TNFAIP8* and *HSD17B4* on chromosome 5q23.1.

The most interesting candidate is *KEAP1*, which encodes Kelch-like ECH-associated protein 1, which, along with nuclear factor erythroid 2-related factor 2 (*NRF2*), constitutes a central redox-sensitive pathway that controls antioxidant, inflammatory, and immune system responses, facilitating GSH activity.[37] GSH depletion plays a prominent role in both MS [38] and COVID-19.[39] Another interesting candidate in the KEAP1 neighborhood is PDE4A, a phosphodiesterase implicated in the degradation of cAMP in most, if not all, immune and inflammatory cells, including the cells in the lungs.[40] PDE4 inhibitors are approved for the treatment of chronic obstructive pulmonary disorder and atopic diseases while gaining attention for various neurological applications, including MS and COVID-19.[41]

On chromosome 5q23.1, *HSD17B4* encodes a bifunctional enzyme that is involved in the peroxisomal beta-oxidation pathway for both straight-chain and 2-methyl-branched-chain fatty acids. Mutations in this locus lead to a distinct neurological condition due to the inherent defect of beta-oxidation.[42] While no specific studies of *HSD17B4* have been reported in MS or COVID-19 thus far, peroxisome pathways are disturbed in each of these two disorders.[43,44]

A total of 24 protein-coding genes were implicated by the analysis of molecular relationships within the reconstructed pathways mediating the synergistic link between MS and COVID-19. A majority of these genes participate in various branches of cytokine signaling and danger sensing/pattern recognition, including Toll-like receptors, T-cell receptors, and the Jak/Stat machinery. Notably, many of the molecules highlighted by our analysis were widely discussed either as targets of COVID-19 therapy (CCL19, CXCL10, IL6, CXCL8, DPP4, IL2, and TNF) [45–47] or as biomarkers of COVID-19 severity (CRP, ALB, and F12).[48,49] Our results strengthen the proposed viewpoint that MS-related processes may hasten COVID-19 progression by overactivating innate immunity and the resultant "cytokine storm."

The main strength of the study is that MR analysis is less affected by causality pitfalls, which are common in traditionally designed observational studies due to confounding factors and reverse causation. The largest available GWAS summary datasets were utilized for tracing the causative association between COVID-19 and MS. All the participants in the GWAS datasets were of European ancestry, reducing the potential population heterogeneity. Our study has several limitations. In particular, we assessed only genetic liability for both diseases with no regard to the effects of the environment, which are critical for both MS and COVID-19. We acknowledge that MR analyses may be biased due to pleiotropy, especially in nonhomogenous datasets. Therefore, we have tested the MR assumptions using various models.

5 | CONCLUSIONS

In summary, our study supports that MS may augment the severity of COVID-19, while hospitalized COVID-19 may causally increase the risk for MS. Immunity-related, inflammation-driven pathways may underlie the link between MS and COVID-19.

AUTHOR CONTRIBUTIONS

Fuquan Zhang conceived the project and supervised the study. Fuquan Zhang and Ancha Baranova analyzed the data. Ancha Baranova, Fuquan Zhang, and Hongbao Cao wrote the manuscript. Shaolei Teng and Kuan-Pin Su revised the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in The Covid19 Host Genetics Initiative (https://www.covid19hg.org/results/r7/) and The International Multiple Sclerosis Genetics Consortium (https://imsgc.net/).

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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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