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EDITED BY

Clio Mavragani,
National and Kapodistrian University of
Athens, Greece

REVIEWED BY

Hikoaki Fukaura,
Saitama Medical University, Japan
Omid Mirmosayyeb,
University at Buffalo, United States

*CORRESPONDENCE

Hongyu Zhou
zhouhy@scu.edu.cn

[†]These authors have contributed
equally to this work and share
first authorship

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The causal relationship between neuromyelitis optica spectrum disorder and other autoimmune diseases

Xiaofei Wang^{1†}, Ziyang Shi^{1†}, Zhengyang Zhao^{1,2}, Hongxi Chen¹, Yanlin Lang¹, Lingyao Kong¹, Xue Lin¹, Qin Du¹, Jiancheng Wang¹ and Hongyu Zhou^{1*}

¹Department of Neurology, West China Hospital, Sichuan University, Chengdu, China, ²Mental Health Centre and Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, China

Objectives: The coexistence of neuromyelitis optica spectrum disorder (NMOSD) with other autoimmune diseases has been well recognized. However, the causal association between these two conditions has not been fully studied. The etiology and therapies of NMOSD coexisting with autoimmune diseases also need to be elucidated.

Methods: We performed two-sample Mendelian randomization (MR) analysis to examine the causality. Genome-wide association (GWAS) summary data from NMOSD, autoimmune thyroid disease (AITD), systemic lupus erythematosus (SLE), and Sjogren's syndrome (SS) were used to identify genetic instruments. Causal single-nucleotide polymorphisms (SNPs) were annotated and searched for cis-expression quantitative trait loci (cis-eQTL) data. Pathway enrichment analysis was performed to identify the mechanism of NMOSD coexisting with AITD, SLE, and SS. Potential therapeutic chemicals were searched using the Comparative Toxicogenomics Database.

Results: The MR analysis found that AITD, SLE, and SS were causally associated with NMOSD susceptibility, but not vice versa. Gene Ontology (GO) enrichment analysis revealed that MHC class I-related biological processes and the interferon-gamma-mediated signaling pathway may be involved in the pathogenesis of NMOSD coexisting with AITD, SLE, and SS. A total of 30 chemicals were found which could inhibit the biological function of cis-eQTL genes.

Conclusions: Our findings could help better understand the etiology of NMOSD and provide potential therapeutic targets for patients with coexisting conditions.

KEYWORDS

autoimmune diseases, Mendelian randomization, neuromyelitis optica spectrum disorders, genome-wide associated study, causal relation

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disease of the central nervous system (CNS), which may lead to blindness and paralysis (1). Epidemiological studies show that some peripheral autoimmune diseases (ADs) may coexist with NMOSD, including systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), and autoimmune thyroid disease (AITD) (2, 3). This phenomenon makes us curious whether there is a shared pathology between NMOSD and other ADs. There is a certain significance in answering this question for understanding the pathogenesis of autoimmune diseases.

Recently, the Mendelian randomization (MR) method has been widely used to investigate the causal relationships between two diseases using summary statistic data from genome-wide association studies (GWAS). Few studies apply this method to the field of NMOSD. Since the coexistence of NMOSD and ADs can be seen clinically, herein we use MR analysis to investigate the genetic relationships between those two conditions. We found that the activation of MHC class I-related biological processes and the interferon-mediated signaling pathway may be the shared pathology of NMOSD coexisting with other ADs. We also predicted 30 potential therapeutic chemicals for the coexisting condition. Our study provides new insights to the pathogenesis and treatment of NMOSD.

Methods

GWAS summary statistic data

Figure 1 shows the overall design of this study. We investigated the genetic causality between NMOSD and three other ADs that most commonly coexist with NMOSD, including AITD, SLE, and SS. All GWAS summary statistic data were downloaded from the GWAS catalog (4). The most recent traits with European ancestry and the largest sample size were used. The NMOSD trait (GCST005964) includes 215 patients and 1,244 controls. The AITD trait (GCST90014440) includes 859 patients and 324,074 controls. The SLE trait (GCST90014462) includes 624 patients and 324,074 controls. The SS trait (GCST90014460) includes 647 patients and 324,074 controls.

Abbreviations: AD, autoimmune Disease; AITD, autoimmune thyroid disease; cis-eQTL, cis-expression quantitative trait loci; CI, confidence interval; DMF, dimethyl fumarate; GO, Gene Ontology; GWAS, genome-wide association; IV, instrumental variable; IVW, inverse variance weighted; MHC, major histocompatibility complex; MR, Mendelian randomization; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; SNP, single-nucleotide polymorphism.

Genetic instrument selection

The single-nucleotide polymorphism (SNP) used as the exposure instrumental variables (IVs) of AD were selected with a p value less than $5E-8$. Considering the lower sample size of the NMOSD trait, the p value of exposure IVs was set as $1E-6$. Then, the linkage disequilibrium in the selected IVs was clumped with $r^2 < 0.1$ based on the 1000 Genomes Project. The F-statistics of each selected IVs were calculated using mRnd (5) and would be excluded if F-statistics < 10 .

Two-sample MR analysis

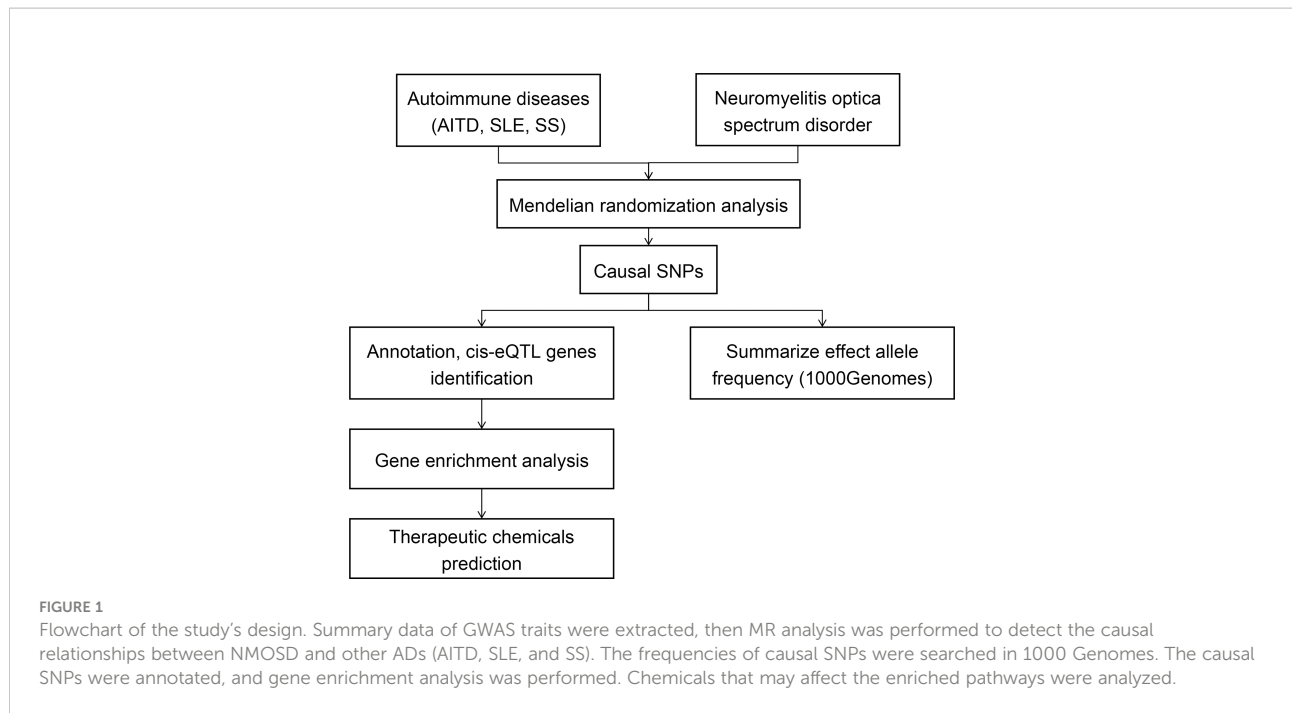
Two-sample MR analyses were performed using five models (MR-Egger, weighted median, inverse variance weighted (IVW), simple mode, and weighted mode) (6, 7). The palindromic SNPs with intermediate allele frequencies were excluded from MR analysis. We performed Cochran's Q test to evaluate heterogeneity and used the p value for the intercept in MR-Egger regression to assess the pleiotropic effect. All analyses were performed using the TwoSampleMR package (version 0.5.6) of R software (version 4.1.2).

Functional evaluation of causal SNPs

We used the 'mr_singlesnp' function in the TwoSampleMR package to extract the basic information of causal SNPs (rsID, location, effect allele). Then, the closest genes of the extracted SNPs were annotated in the dbSNP database (8) and GWAS 4D (9). The frequencies of causal SNPs in different populations were recorded with the reference of the 1000 Genomes Project. To investigate whether causal SNPs affect gene expression, we analyzed cis-eQTL in whole blood from the GTEx Portal (9). cis-eQTL genes with p value $< 0.05/\text{gene number}$ and normalized effect size (NES) > 0 were identified as significant genes and enrolled in enrichment analysis. We used DAVID 6.8 (10) to perform Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis.

Potential therapeutic chemical prediction

To predict potential therapeutic chemicals for NMOSD coexisting with AD, we assessed the Comparative Toxicogenomics Database (CTD) (11). We used GO:id as the query condition and selected chemicals that have clear evidence to inhibit the GO function of cis-eQTL genes. Then, the chemical list was manually reviewed with reference of the PubChem database (12), and information such as



pharmacology, biochemistry properties, FDA UNII, and current clinical applications was recorded. Chemicals were excluded if evidence shows that they may promote the expression of IL-6 or IL-17 (key cytokines in the pathogenic process of NMOSD). Cytoscape software (version 3.9.1) was used to construct the chemical–gene interaction network.

Results

The presence of ADs may facilitate NMOSD pathology

We identified significant causality between NMOSD and other ADs, but the causal effects were stronger on the risk of NMOSD. The IVW analysis showed that the risk of NMOSD was increased on the exposure of AITD odds ratio [(OR): 3.62E13, 95% confidence interval (CI): 2.92E10 to 4.48E16], SLE (OR: 66.55E14, 95% CI: 5.87E08 to 7.31E20), and SS (OR: 2.46E19, 95% CI: 1.41E13, 4.29E25) (Figure 2). Among the above three exposure conditions, SS did not have enough IVs to perform analysis other than IVW. Except for SS, the MR–Egger regression analysis, weighted median estimator, simple mode, and weighted mode of AITD and SLE all provide results of the same direction and magnitude as IVW analysis, which indicates a stable and strong causality in the risk of developing NMOSD. The heterogeneity and pleiotropy were not found (Table 1).

When applying NMOSD as the exposure condition, the IVW analysis showed increased risks of developing AITD (OR: 1.01, 95%

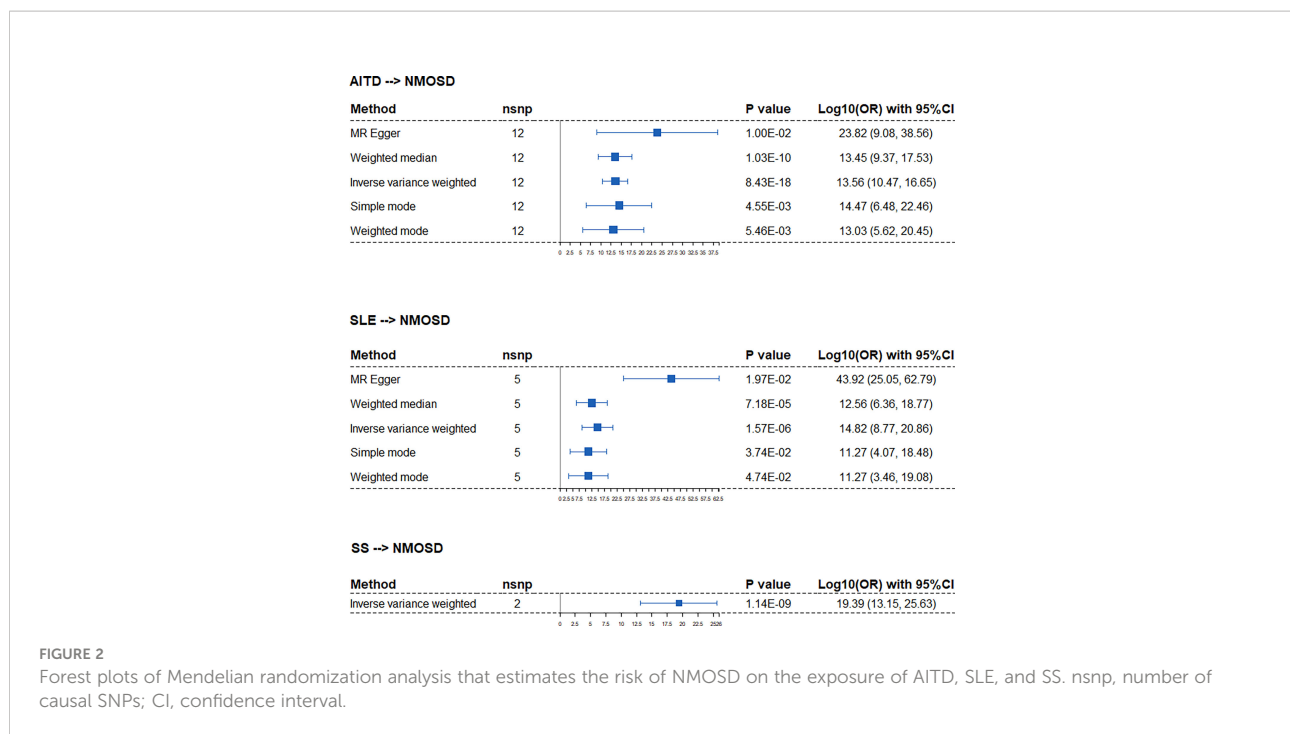
CI: 1.00 to 1.01), SLE (OR: 1.01, 95% CI: 1.01 to 1.02), and SS (OR: 1.01, 95% CI: 1.00 to 1.01) (Figure 3). However, neither the weighted median estimator nor the weighted mode reached a statistical significance with p value $>0.05/5$ (Bonferroni correction). Besides, the MR–Egger regression analysis showed contrasting trends. Taken together, the presence of AITD, SLE, and SS may facilitate NMOSD pathology but not vice versa.

Higher frequencies of causal SNPs in East Asia were found

The below sections focused on the exposure of AITD, SLE, and SS on NMOSD. Obvious differences in the frequencies of causal SNPs between East Asian and Caucasian were found (Table 2), which may explain why the incidence of NMOSD is higher in the East Asia region. However, minimal difference in the frequencies of causal SNPs was noticed between genders (Table 3).

NMOSD coexisting with ADs may be mediated by the antigen processing, interferon, and complement system

When annotating the causal SNPs using the dbSNP database and GWAD 4D (Table 4 and Additional File 1), genes related to class I major histocompatibility complex (MHC) (TAP2, HCP5,



BAG6), MHC-II (HLA-DQB3), and the complement system (C2, CFB) were found to be associated with the pathology of NMOSD that coexists with other ADs. To further clarify the function of the causal SNPs, we first searched cis-eQTL in whole blood (Table 4 and Additional File 1). Then, we performed pathway enrichment using significant cis-eQTL genes with NES >0 (Figure 4). GO enrichment analyses showed that MHC class I-related biological processes, type I interferon signaling pathway, and complement activation were upregulated when NMOSD was followed by the presence of AITD or SLE. On the contrary, MHC class II-related biological processes and the interferon-gamma-mediated signaling pathway are in the leading roles in NMOSD coexisting with SS. KEGG enrichment analyses identified two types of pathway: autoimmune disease-related pathway and virus infection-related pathway (Additional File 2).

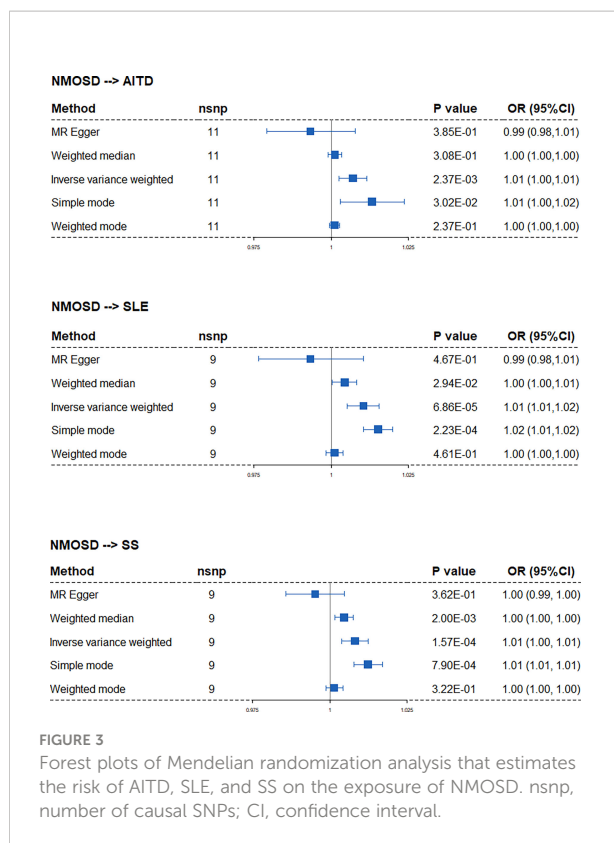
Potential therapeutic chemicals for NMOSD coexisting with other AD

A total of 30 chemicals were found which could inhibit the biological function of cis-eQTL genes (Figure 5). These chemicals include proteasome inhibitors (e.g., carfilzomib, which has been used in treating lymphoma and leukemia), anticarcinogenic agents, traditional immunosuppressive agents [e.g., dimethyl fumarate (DMF), which has been used in treating multiple sclerosis], antiviral agents, Janus kinase (JAK) inhibitor (tofacitinib, has been used in treating SLE, SS, and other connective tissue diseases), natural compounds, anticoagulants, beta-adrenergic receptor antagonist, enzyme inhibitor, histone deacetylase inhibitor, and protein kinase c activator. A detailed list of the information and clinical usage of these chemicals can be found in Additional File 3.

TABLE 1 Heterogeneity and pleiotropy tests for the associations of autoimmune diseases with NMOSD.

Exposure	Q-value	P _Q	Intercept	P _{intercept}
AITD	14.014	0.172	-0.275	0.194
SLE	0.686	0.876	-0.804	0.054
SS	0.627	0.429	-	-

AITD, autoimmune thyroid disease; SLE, systemic lupus erythematosus; SS, Sjogren syndrome; NMOSD, neuromyelitis optica spectrum disorder.



Discussion

The coexistence of NMOSD with other autoimmune diseases has been well recognized. The literature review performed by Sareh et al. (2) shows that SLE, SS, and AITD are the most common disorders associated with NMOSD. The International Panel for NMOSD Diagnosis (IPND) suggested in 2015 that the SLE or SS would be a coexistence rather than a

complication, and the presence of these ADs strengthens the confidence of NMOSD diagnosis (13). The coexistence of NMOSD and ADs indicates a shared pathology between these two conditions, possibly due to genetic tendencies toward an abnormal immune system. However, there is no evidence regarding which condition occurs first. While several studies reported that NMOSD occurred following the presence of ADs (14, 15) and even AQP4-IgG is present in the serum years before the first NMOSD attack (16, 17), there is also evidence suggesting that ADs are a consequence of NMOSD (18–21). Our current MR study, for the first time, provides evidence that AITD, SLE, and SS may facilitate NMOSD pathology but not vice versa.

Both environmental (e.g., viral infection) and genetic factors (e.g., polymorphism of MHC region) contribute to the pathogenesis of peripheral ADs. However, it is unclear how the peripheral ADs may facilitate the onset of NMOSD. After peripheral ADs occur, the B and T lymphocytes may become hyperactive and produce high levels of inflammatory cytokines. In the next step, the low-response or bystander T cells specific to AQP4, which has been in the body since maturation, may be activated, and astrocytes may be attacked by AQP4-specific CD8⁺ T cells and the AQP4-IgG antibody (22). (Figure 6). Our study found that IFN signaling pathways were upregulated under the comorbidity condition, which may facilitate the activation of T cells and induce the expression of the MHC-peptide complex on normal cells (22), again aggravating astrocyte damage and demyelination.

It is well recognized that MHC class II-related biological processes have leading roles in the etiopathogenesis of NMOSD. The T-cell receptor (TCR) on CD4⁺ T cells combined with peptides forms a complex with MHC class II molecules and then provides a second signal for B-cell activation. Interestingly, the current study identified that MHC class I-related biological processes may be involved in the pathogenesis of NMOSD

TABLE 2 Frequencies of causal SNPs of NMOSD on the exposure of autoimmune diseases based on regions.

SNP	Effect allele	Effect allele frequency			
		Global	Europe	America	East Asia
AITD → NMOSD					
rs17206350	C	0.581	0.497	0.503	0.677
rs2239701	C	0.487	0.451	0.513	0.537
rs2248372	A	0.315	0.398	0.385	0.215
rs241438	T	0.375	0.359	0.382	0.517
rs2523545	A	0.759	0.651	0.758	0.898
rs2736426	T	0.635	0.551	0.605	0.584
rs2894053	A	0.190	0.283	0.308	0.043
rs3095303	A	0.287	0.324	0.310	0.095
rs3132948	G	0.578	0.464	0.572	0.635

(Continued)

TABLE 2 Continued

SNP	Effect allele	Effect allele frequency			
		Global	Europe	America	East Asia
rs429150	C	0.525	0.511	0.481	0.547
rs805262	T	0.382	0.473	0.416	0.592
rs9268235	T	0.020	0.079	0.019	0.001
SLE → NMOSD					
rs1610615	T	0.360	0.285	0.370	0.408
rs2517485	T	0.362	0.346	0.427	0.186
rs497309	C	0.031	0.074	0.023	0
rs6904670	G	0.421	0.446	0.409	0.328
rs805262	T	0.382	0.473	0.416	0.592
SS → NMOSD					
rs1264347	T	0.042	0.081	0.023	0.024
rs429150	C	0.525	0.511	0.481	0.547

AITD, autoimmune thyroid disease; SLE, systemic lupus erythematosus; SS, Sjogren syndrome; SNP, single-nucleotide polymorphism; NMOSD, neuromyelitis optica spectrum disorder.

TABLE 3 Frequencies of causal SNPs of NMOSD on the exposure of autoimmune diseases based on genders.

SNP	Effect allele	Effect allele frequency							
		Global		Europe		America		East Asia	
		Male	Female	Male	Female	Male	Female	Male	Female
AITD → NMOSD									
rs17206350	C	0.587	0.575	0.513	0.483	0.509	0.497	0.674	0.679
rs2239701	C	0.477	0.496	0.442	0.46	0.471	0.554	0.533	0.54
rs2248372	A	0.319	0.314	0.408	0.388	0.374	0.395	0.189	0.24
rs241438	T	0.369	0.38	0.346	0.371	0.391	0.373	0.496	0.537
rs2523545	A	0.763	0.755	0.629	0.671	0.774	0.743	0.893	0.902
rs2736426	T	0.649	0.622	0.563	0.54	0.609	0.602	0.594	0.575
rs2894053	A	0.194	0.186	0.285	0.281	0.338	0.28	0.049	0.037
rs3095303	A	0.285	0.289	0.31	0.337	0.297	0.322	0.096	0.094
rs3132948	G	0.575	0.582	0.477	0.452	0.574	0.571	0.654	0.617
rs429150	C	0.536	0.514	0.519	0.504	0.479	0.483	0.561	0.533
rs805262	T	0.384	0.38	0.485	0.462	0.424	0.41	0.555	0.627
rs9268235	T	0.019	0.02	0.073	0.084	0.021	0.017	0	0.002
SLE → NMOSD									
rs1610615	T	0.367	0.352	0.281	0.289	0.371	0.37	0.439	0.379
rs2517485	T	0.365	0.359	0.331	0.359	0.418	0.435	0.191	0.181
rs497309	C	0.033	0.029	0.071	0.076	0.026	0.02	0	0
rs6904670	G	0.425	0.418	0.46	0.433	0.397	0.421	0.34	0.317
rs805262	T	0.384	0.38	0.485	0.462	0.424	0.41	0.555	0.627
SS → NMOSD									
rs1264347	T	0.041	0.042	0.081	0.08	0.029	0.017	0.025	0.023
rs429150	C	0.536	0.514	0.519	0.504	0.479	0.483	0.561	0.533

AITD, autoimmune thyroid disease; SLE, systemic lupus erythematosus; SS, Sjogren syndrome; SNP, single-nucleotide polymorphism; NMOSD, neuromyelitis optica spectrum disorder.

TABLE 4 eQTLs of causal SNPs of NMOSD on the exposure of autoimmune diseases.

SNP	Closest gene	cis-eQTL gene (NES >0)
AITD → NMOSD		
rs17206350	MTCO3P1; HLA-DQB3	AIF1; ATP6V1G2; BAG6
rs2239701	TAP2	C2; C4B; CCHCR1; CYP21A1P
rs2248372	HCP5	CYP21A2; FLOT1
rs241438	TAP2	HCG27; HCG27; HLA-B; HLA-C
rs2523545	DHFRP2; RNU6-283P	HLA-DQA2; HLA-DQA2
rs2736426	VWA7; VARS1	HLA-DQB2; HLA-DQB2
rs2894053	-	HLA-DRB1; HLA-DRB6
rs3095303	-	HLA-DRB9; HLA-S
rs3132948	-	IER3; LINC00243; LY6G5B
rs429150	TNXB	LY6G5C; MICB; MIR6891
rs805262	BAG6; C6orf47; GPANK1	NOTCH4; POU5F1; PRRC2A
rs9268235	TSBP1; TSBP1-AS1	PSMB9; PSMB9; PSORS1C3
SLE → NMOSD		
rs1610615	HLA-F-AS1	STK19B; TAP2
rs2517485	C6orf15	XXbac-BPG248L24.12; ZBTB12
rs497309	C2	
rs6904670	CFB	
rs805262	BAG6; C6orf47; GPANK1	
SS → NMOSD		
rs1264347	LINC00243	AIF1; BAG6; C2; C4B; CCHCR1
rs429150	TNXB	CYP21A2; GABBR1; HCG4P3
		HCP5B; HLA-C; HLA-DRB1
		HLA-F; HLA-H; HLA-U
		LY6G5B; LY6G5C; MICB
		POU5F1; PRRC2A; PSORS1C3
		RPL23AP1; XXbac-BPG248L24.12
		ZFP57

AITD, autoimmune thyroid disease; SLE, systemic lupus erythematosus; SS, Sjogren syndrome; NMOSD, neuromyelitis optica spectrum disorder.

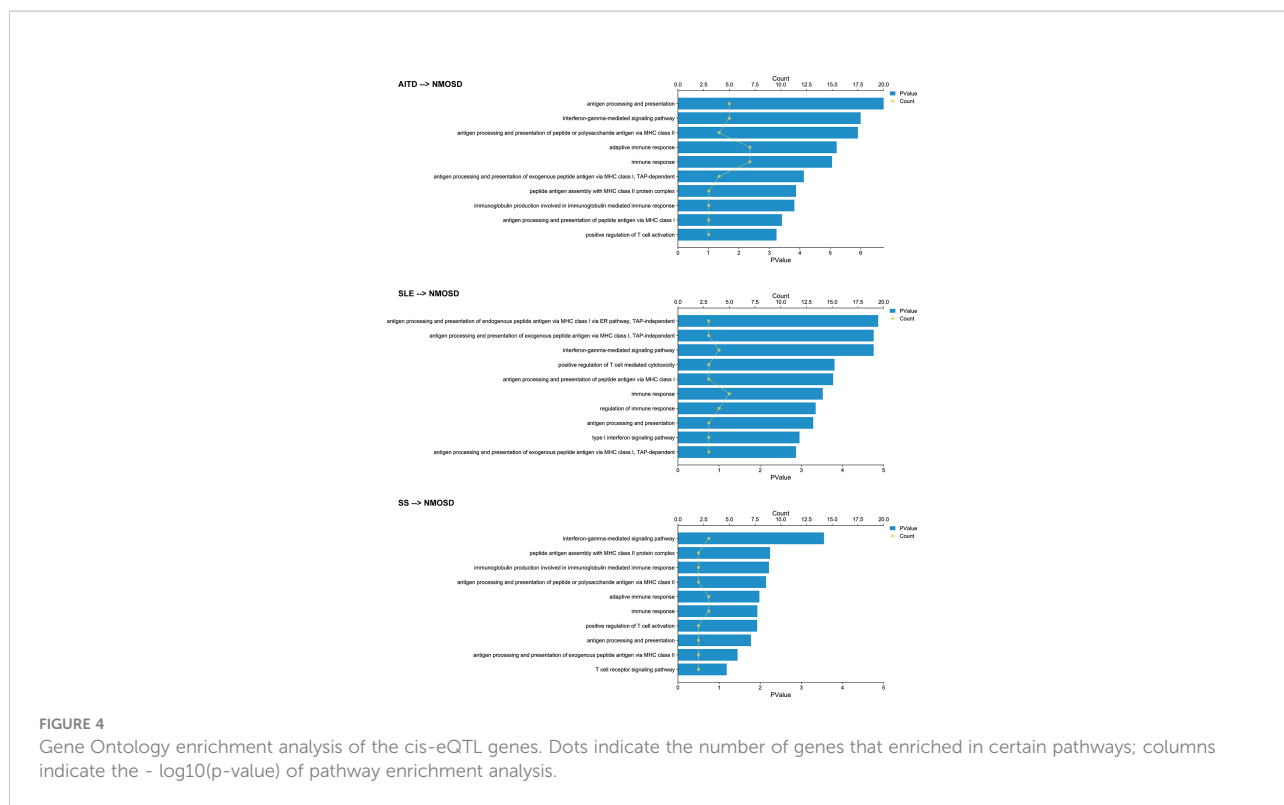
coexisting with other ADs, which suggests an enhanced function of CD8⁺ T cells in those patients. Recent studies of our team have proven that CD8⁺ T cells participate in the pathology of NMOSD as well (23, 24).

Endogenous antigens (usually produced after virus infection) are presented to CD8⁺ T cells in the form of the peptide–MHC class I molecule complex. The Epstein–Barr virus (EBV) has been recognized as a driver of multiple sclerosis (25, 26), while its role in NMOSD remains unclear. Saeko et al. (27) showed that the CSF anti-EA-IgG titers were also higher in patients with NMOSD than in those with multiple sclerosis. Justin et al. (28) reported a case of NMOSD coexisting with SS whose CSF was positive for EBV. In our study, pathways related to virus infection, such as EBV infection, were also enriched. The above evidence suggests that persistent EBV replication may contribute to the pathogenesis of NMOSD coexisting with ADs.

As for the treatments, whether patients with coexisting conditions should receive the NMOSD recipe or the AD recipe or a different recipe remains unknown. One thing is for sure that tumor necrosis factor- α (TNF- α) monoclonal antibodies (mAbs)

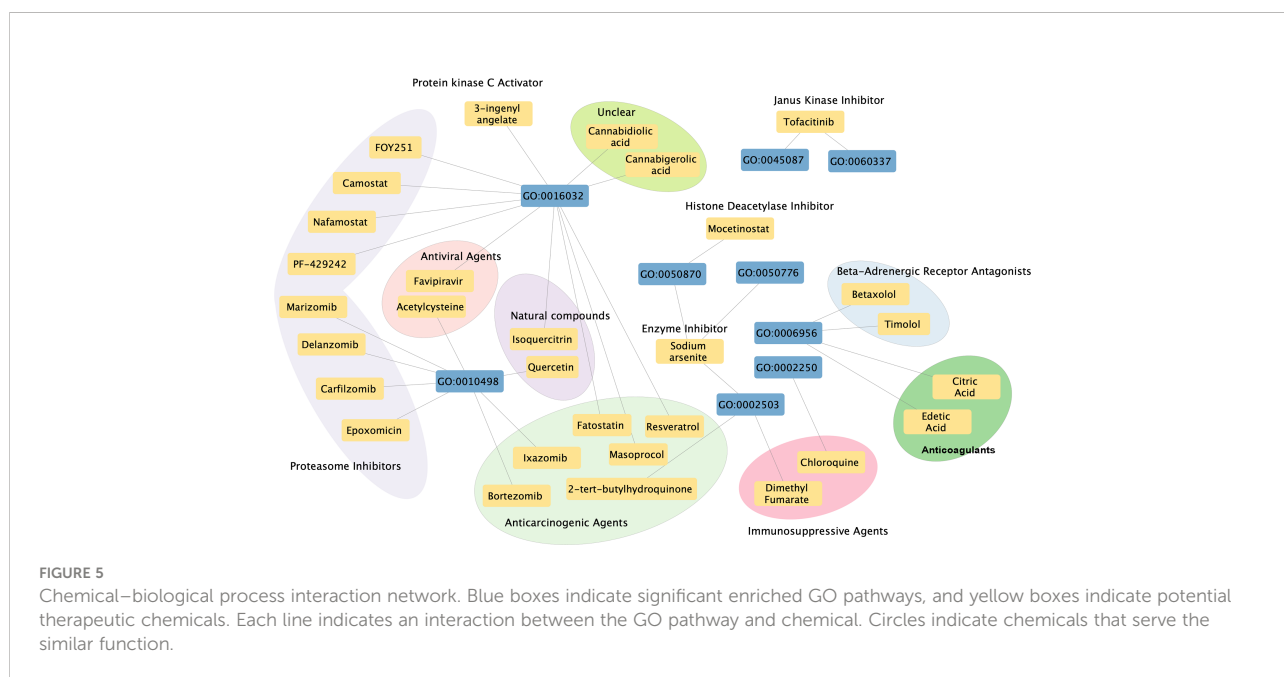
should be avoided because they increase the risk of demyelinating events (29–32). Other than that, rituximab (33) (34), cyclophosphamide (35), and tocilizumab (36) have shown satisfied results. Our current study predicted 30 potential therapeutic chemicals based on the biological processes of cis-eQTL genes, including DMF. DMF is one of the disease-modifying therapies (DMTs) for multiple sclerosis. It is well recognized that DMT will exacerbate the disease severity of NMOSD, but there is a lack of evidence regarding the effects of DMF in treating NMOSD (37). DMF mainly suppresses the function of interferon gamma and reduces the proportion of circulating Th1 (38, 39), and our current study revealed that the interferon-gamma-mediated pathway was involved in NMOSD coexisting with ADs. Therefore, DMF might be a potential therapeutic chemical for NMOSD coexisting with ADs, but the efficacy needs to be verified in *in vivo* and *ex vivo* studies.

Based on the GWAS summary data, our study for the first time demonstrated strong causal effects of AITD, SLE, and SS on the risk of NMOSD. We found that MHC class I-related biological processes may be involved in the pathogenesis of



NMOSD coexisting with other ADs. We also identified 30 chemicals that might have therapeutic effects. However, our study has several limitations. First, the sample size of the NMOSD trait is relatively small, so we adopted a relaxing p value of 1E-6 to screen for more exposure IVs, but this would

compromise the reliability of our MR results. However, we mainly focused on the exposure of AITD, SLE, and SS, which have robust sample sizes for analysis. Second, performing drug prediction by only using causal SNPs would leave out some important therapies, such as IL-6R mAbs and complement



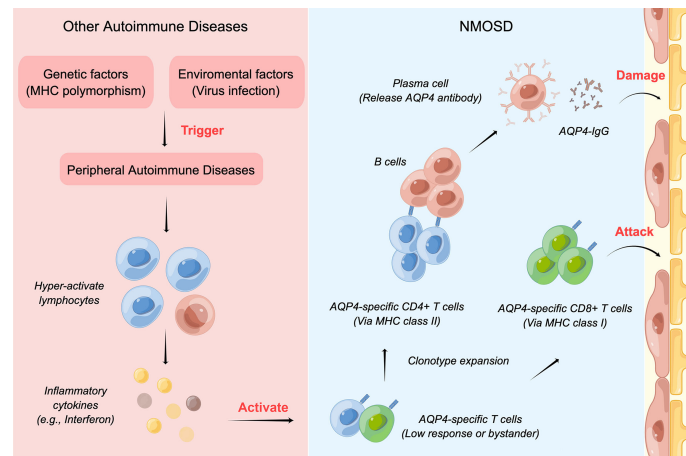


FIGURE 6

The mechanism of NMOSD coexisting with other ADs. Both environmental and genetic factors contribute to the pathogenesis of peripheral ADs. After peripheral ADs occur, lymphocytes may become hyperactive and produce high levels of inflammatory cytokines, which would activate the low-response or bystander T cells specific to AQP4. Then, the astrocytes would be attacked by AQP4-specific CD8+ T cells and the AQP4-IgG antibody.

inhibitors. Third, our results lack validation in the clinical cohort and basic research. Since bioinformatic studies only provide predictions; our results should be interpreted with caution.

In the present study, we provide evidence from genetic levels, but we lack experimental validation. Future studies need to address several questions. First of all, it is unknown whether a common trigger, such as a viral infection, is involved in the pathogenesis of NMOSD and other ADs. Secondly, there is a need to clarify what causes the disruption of the blood–brain barrier during the pathogenesis of systemic autoimmune diseases, since myelitis has also been observed in SLE despite the presence of NMOSDs. Thirdly, it is urgent to determine the best treatment strategy for NMOSD patients coexisting with other ADs, since some biotherapy (e.g., anti-TNF α) may lead to demyelination and increase the disability of NMOSD. Furthermore, prospective cohorts with large sample sizes may be needed to evaluate the sequence of onset of NMOSD and other ADs.

Conclusion

By using GWAS summary data and MR analysis, we identified causal associations of AITD, SLE, and SS with increased risk of NMOSD. We found that MHC class I-related biological processes and interferon-gamma-mediated signaling pathway may be involved in the pathogenesis of NMOSD coexisting with AITD, SLE, and SS. These findings could help

better understand the etiology of NMOSD and provide potential therapeutic targets for patients with coexisting conditions.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding author.

Author contributions

XW wrote the main manuscript text and prepared the tables. ZS and ZZ prepared figures. HC, YL, and LK managed the data. XL, QD, and JW revised the manuscript. HZ provided the conception of this study and supervised this study. All authors reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fimmu.2022.959469/full#supplementary-material>

ADDITIONAL FILE 1

F-statics, annotation, and cis-eQTL results of the causal SNPs.

ADDITIONAL FILE 2

GO and KEGG pathway enrichment results.

ADDITIONAL FILE 3

Prediction of therapeutic chemicals using Comparative Toxicogenomics Database.

References

- Jarius S, Paul F, Weinschenker BG, Levy M, Kim HJ, Wildemann B. Neuromyelitis optica. *Nat Rev Dis Primers* (2020) 6:85. doi: 10.1038/s41572-020-0214-9
- Shahmohammadi S, Doosti R, Shahmohammadi A, Mohammadianinejad SE, Sahraian MA, Azimi AR, et al. Autoimmune diseases associated with neuromyelitis optica spectrum disorders: A literature review. *Mult Scler Relat Disord* (2019) 27:350–63. doi: 10.1016/j.msard.2018.11.008
- Fang C-W, Wang H-P, Chen H-M, Lin J-W, Lin W-S. Epidemiology and comorbidities of adult multiple sclerosis and neuromyelitis optica in Taiwan, 2001–2015. *Mult Scler Relat Disord* (2020) 45:102425. doi: 10.1016/j.msard.2020.102425
- Available at: <https://www.ebi.ac.uk/gwas/>.
- Available at: <https://shiny.cnsgenomics.com/mRnd/>.
- Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-base platform supports systematic causal inference across the human phenome. *Elife* (2018) 7:e34408. doi: 10.7554/eLife.34408
- Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet* (2017) 13:e1007081. doi: 10.1371/journal.pgen.1007081
- Available at: <https://www.ncbi.nlm.nih.gov/snp/>.
- Available at: <https://www.gtexportal.org/home/index.html>.
- david.ncifcrf.gov/.
- Available at: <https://ctdbase.org/>.
- Available at: <https://pubchem.ncbi.nlm.nih.gov>.
- Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* (2015) 85:177–89. doi: 10.1212/WNL.0000000000001729
- Pirro F, Mantero V, Rigamonti A, Scaccabarozzi C, Pozzetti U, Balgera R, et al. A case of longitudinally extensive transverse myelitis in an 80-year-old patient with systemic lupus erythematosus and anti-aquaporin 4 antibodies. *Mult Scler Relat Disord* (2021) 51:102899. doi: 10.1016/j.msard.2021.102899
- Lee H-J, Chang SH, Kang EH, Lee YJ, Song YW, Ha Y-J. A case of primary sjögren's syndrome presenting as mass-like encephalitis, with progression to neuromyelitis optica spectrum disorder. *Arch Rheumatol* (2017) 32:353–7. doi: 10.5606/ArchRheumatol.2017.6201
- Alexopoulos H, Kampylafka EI, Fouka P, Tatouli I, Akrivou S, Politis PK, et al. Anti-aquaporin-4 autoantibodies in systemic lupus erythematosus persist for years and induce astrocytic cytotoxicity but not CNS disease. *J Neuroimmunol* (2015) 289:8–11. doi: 10.1016/j.jneuroim.2015.10.007
- Kovacs KT, Kalluri SR, Boza-Serrano A, Deierborg T, Csepány T, Simo M, et al. Change in autoantibody and cytokine responses during the evolution of neuromyelitis optica in patients with systemic lupus erythematosus: A preliminary study. *Mult Scler* (2016) 22:1192–201. doi: 10.1177/1352458515613165
- Adawi M, Bisharat B, Bowirrat A. Systemic lupus erythematosus (SLE) complicated by neuromyelitis optica (NMO - Devic's disease): Clinic-pathological report and review of the literature. *Clin Med Insights Case Rep* (2014) 7:41–7. doi: 10.4137/CCRep.S15177
- Jacobi C, Stिंगle K, Kretz R, Hartmann M, Storch-Hagenlocher B, Breitbart A, et al. Neuromyelitis optica (Devic's syndrome) as first manifestation of systemic lupus erythematosus. *Lupus* (2006) 15:107–9. doi: 10.1191/0961203306lu2265cr
- Zheng W, Liu X, Hou X, Zhu Y, Zhang T, Liao L. Recurrent optic neuritis in a patient with sjögren syndrome and neuromyelitis optica spectrum disorder: A case report. *Medicine* (2020) 99:e23029. doi: 10.1097/MD.00000000000023029
- Li X, Lu Z, Wang Y. Syringomyelia-like syndrome in neuromyelitis optica spectrum disorder complicated with sjögren's syndrome: A case report. *BMC Neurol* (2018) 18:168. doi: 10.1186/s12883-018-1170-9
- Murphy K, Weaver C. *Janeway's immunobiology 9th edition, 9th ed.* (2016) (New York:Garland Publishing Inc.).
- Cai L, Shi Z, Chen H, Du Q, Zhang Y, Zhao Z, et al. Relationship between the clinical characteristics in patients with neuromyelitis optica spectrum disorders and clinical immune indicators: A retrospective study. *Brain Sci* (2022) 12(3):372. doi: 10.3390/brainsci12030372
- Shi Z, Qiu Y, Zhao Z, Wen D, Chen H, Du Q, et al. CD8+ T cell subpopulations and pro-inflammatory cytokines in neuromyelitis optica spectrum disorder. *Ann Clin Transl Neurol* (2021) 8:43–53. doi: 10.1002/acn3.51241
- Sollid LM. Epstein-Barr Virus as a driver of multiple sclerosis. *Sci Immunol* (2022) 7:eabo7799. doi: 10.1126/sciimmunol.abo7799
- Lanz TV, Brewer RC, Ho PP, Moon JS, Jude KM, Fernandez D, et al. Clonally expanded b cells in multiple sclerosis bind EBV EBNA1 and GlialCAM. *Nature* (2022) 603:321–7. doi: 10.1038/s41586-022-04432-7

27. Masuda S, Mori M, Arai K, Uzawa A, Muto M, Uchida T, et al. Epstein-Barr Virus persistence and reactivation in neuromyelitis optica. *J Neurol Neurosurg Psychiatry* (2015) 86:1137–42. doi: 10.1136/jnnp-2014-308095
28. Levinson JB, Alvarez MR, Koci K, Feoktistov A, McFarlane IM. Epstein - Barr virus infection in a patient with neuromyelitis optica spectrum disorder and sjögren's syndrome: A case report and review of literature. *Clin Case Rep Rev* (2018) 4(5):1–5. doi: 10.15761/CCRR.1000411
29. Hsieh Y-H, Chung C-H, Sun C-A, Chen P-H, Chen Y-H, Liang C-M, et al. Association between optic neuritis and inflammatory bowel disease: A population-based study. *J Clin Med* (2021) 10(4):688. doi: 10.3390/jcm10040688
30. Bosch X, Saiz A, Ramos-Casals M. Monoclonal antibody therapy-associated neurological disorders. *Nat Rev Neurol* (2011) 7:165–72. doi: 10.1038/nrneurol.2011.1
31. Kalén E, Piehl F, Andersson M. Demyelinating events following anti-tumor necrosis factor alpha therapy: Rare but challenging to treat. *Eur J Neurol* (2022) 29(5):2047–2055. doi: 10.1111/ene.15318
32. Kumar N, Abboud H. Iatrogenic CNS demyelination in the era of modern biologics. *Mult Scler J* (2019) 25:1079–85. doi: 10.1177/1352458519828601
33. Shidahara K, Hayashi K, Sada KE, Hiramatsu S, Morishita M, Watanabe H, et al. Refractory neuromyelitis optica spectrum disorder in systemic lupus erythematosus successfully treated with rituximab. *Lupus* (2018) 27:1374–7. doi: 10.1177/0961203318760994
34. Torgashina AV, Vasilyev VI. The efficacy of rituximab in the therapy of neuromyelitis optica in a patient with sjogren's syndrome: Case-report and literature review. *Ter Arkh* (2018) 90:76–80. doi: 10.26442/terarkh201890576-80
35. Polgár A, Rózsa C, Müller V, Matolcsi J, Poór G, Kiss EV. Devic's syndrome and SLE: challenges in diagnosis and therapeutic possibilities based on two overlapping cases. *Autoimmun Rev* (2011) 10:171–4. doi: 10.1016/j.autrev.2010.09.021
36. Komai T, Shoda H, Yamaguchi K, Sakurai K, Shibuya M, Kubo K, et al. Neuromyelitis optica spectrum disorder complicated with sjogren syndrome successfully treated with tocilizumab: A case report. *Mod Rheumatol* (2016) 26:294–6. doi: 10.3109/14397595.2013.861333
37. Pitarokouli K, Gold R. Dimethyl fumarate for patients with neuromyelitis optica spectrum disorder. *Mult Scler J* (2018) 24:364–5. doi: 10.1177/1352458517717090
38. Safavi F, Thome R, Li Z, Zhang GX, Rostami A. Dimethyl fumarate suppresses granulocyte macrophage colony-stimulating factor-producing Th1 cells in CNS neuroinflammation. *Neurology(R) neuroimmunol Neuroinflamm* (2020) 7(4):e729. doi: 10.1212/NXI.0000000000000729
39. Wu Q, Wang Q, Mao G, Dowling CA, Lundy SK, Mao-Draayer Y. Dimethyl fumarate selectively reduces memory T cells and shifts the balance between Th1/Th17 and Th2 in multiple sclerosis patients. *J Immunol* (2017) 198:3069–80. doi: 10.4049/jimmunol.1601532