

Identification of drug targets and their candidate drugs in multiple sclerosis and bipolar disorder via systems biology approach

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ABSTRACT

Introduction: Multiple sclerosis (MS) is an autoimmune disease characterized by demyelination of the central nervous system. Bipolar Disorder (BD) is a complex psychiatric condition. Patients with MS have a significantly elevated risk of developing BD. The present study aimed to investigate the shared genetic mechanisms between MS-BD using systems biology approaches.

Methods: We constructed a protein-protein interaction (PPI) network of the overlapping MS-BD genes using the STRING database and identified functional modules and hub genes with Cytoscape. Gene ontology and pathway enrichment analyses of the modules and hub genes were performed using g:Profiler. Potential drug targets among these genes were further explored using DGIdb.

Results: A total of 206 genes associated with MS and 201 genes associated with BD were retrieved from the NCBI, of which 55 genes were common to both diseases. PPI network analysis revealed ten functional modules. Ten hub genes—TNF, IL6, IL1B, TLR4, AKT1, BCL2, IFNG, APP, NFKB1, and mTOR—were identified as central players in both conditions. TNF and IL-6 showed upregulated expression in MS-BD and emerged as promising drug targets. The enriched KEGG pathways included tuberculosis, HIF-1 signaling, AGE-RAGE signaling in diabetic complications, and the Toll-like receptor signaling pathway.

Conclusion: Our findings highlight the shared biological processes and gene expression patterns between MS-BD. These results suggest that MS-BD may involve common underlying mechanisms, which could provide opportunities for repurposing existing drugs and developing combined therapeutic strategies. Such insights may ultimately improve prevention and treatment approaches for MS-BD, as well as related comorbidities.

Keywords:

Multiple sclerosis

Bipolar disorder

PPI network

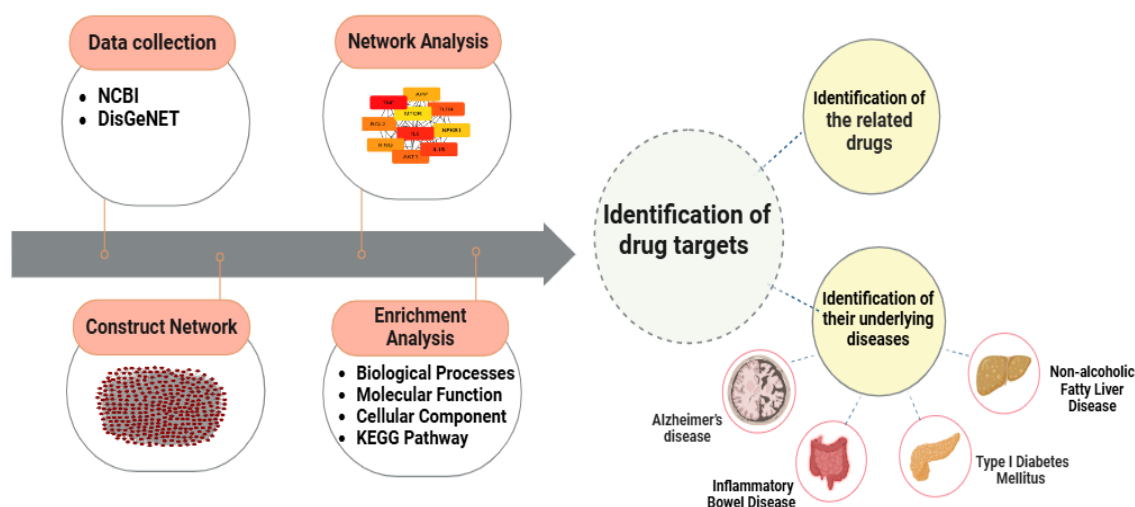
Drug target identification

Systems biology

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Graphical Abstract: This study presents the workflow for constructing a protein-protein interaction (PPI) network, identifying critical shared genes between multiple sclerosis (MS) and bipolar disorder (BD), and performing functional enrichment analysis to discover potential drug targets. Then the related diseases and the FDA-approved drugs were identified and proposed for multiple sclerosis, bipolar disorder, and their underlying diseases.

Introduction

Multiple sclerosis (MS) is an autoimmune disease in which the immune system mistakenly attacks the myelin sheath of the central nervous system (Mora and Chapouly 2023). Therefore, it can damage the nerve fibers. This attack damages the nerve fibers and disrupts signal transmission, leading to a wide range of symptoms including fatigue, visual disturbances, eye pain, muscle weakness, numbness or tingling in the limbs, memory impairment, and bladder dysfunction. Moreover, patients with MS have a higher risk of developing depression and anxiety disorders (Marcus 2022). MS is a multifactorial disease, influenced by both genetic and environmental factors (Goodin et al., 2023). Furthermore, studies show that some of these well-known factors play a role in the progression of MS, such as vitamin D, Epstein-Barr virus (EBV) infection, smoking, exposure to passive smoking, oxidative stress (OS), and obesity (Lutfullin et al., 2023; Vasić et al., 2023; Vong et al., 2023). However, these factors do not fully explain the etiology of MS, and other potential causes remain to be elucidated (Fymat 2023).

The prevalence and incidence of MS have been rising in both developed and developing countries (Vituri et al., 2022). It is estimated that approximately 2.8 million people worldwide are living with MS (Kokas et al., 2023), with an overall prevalence of 35.9 cases per 100,000 individuals. The average age of diagnosis is

32 years (Walton et al., 2020). Furthermore, women are two to three times more likely than men to develop MS (Younger 2023).

Twin studies play a crucial role in disentangling the interplay between genetic and environmental factors that contribute to variability in disease liability. Research suggests that MS develops when environmental factors influence specific genetic susceptibilities (Wautbant et al., 2019). Twin studies have demonstrated high concordance in some monozygotic (MZ) pairs, in which both individuals developed the disease (Kinnunen et al., 1987). Other studies of monozygotic and dizygotic (DZ) twins have further underscored the substantial genetic contribution to MS etiology (Ebers et al., 1986). Overall the genetic component of MS susceptibility is estimated to account for approximately 50% of the risk (Baltcerac and Louapre 2022). In addition, a Swedish study reported that genetic factors contribute significantly to MS susceptibility, with heritability estimates ranging between 35% and 75% (Boles et al., 2023).

Bipolar disorder (BD) is a complex mental health condition influenced by both genetic and environmental factors (Robinson and Bergen 2021). It is associated with numerous adverse outcomes, including elevated suicide risk, sleep disturbances, and impairments in psychological functioning, such as diminished self-esteem (Rantala et al., 2021). The disorder is characterized by alternating episodes of emotional highs (mania or hypomania) and

emotional lows (depression) (McIntyre et al., 2020).

According to diagnostic interview data from the National Comorbidity Survey Replication (NCS-R), the prevalence of bipolar disorder among U.S. adults aged 18 years or older is estimated at 2.8%. In the same survey, the prevalence was nearly identical between women (2.8%) and men (2.9%). Moreover, an estimated 4.4% of U.S. adults are expected to experience BD at some point during their lifetime. Sex-specific models, adjusted for age, sex, left-handedness, and data censoring, revealed a heritability estimate of 60.4% for BD. Despite the significantly higher prevalence in females (62.2% of cases versus 37.8% in males, $p < 0.001$), no significant sex-based differences were observed in BD heritability or sex-specific genetic effects. Overall, heritability estimates for BD range from 60% to 85%, underscoring the substantial contributions of both genetic and environmental factors to its development (Johansson et al., 2019; Kasyanov et al., 2020).

Furthermore, under the assumption of comparable environmental conditions for monozygotic (MZ) and dizygotic (DZ) twins, studies demonstrate higher concordance rates in MZ twins, highlighting the genetic contribution to bipolar disorder (BD). Nevertheless, the imperfect concordance observed even among MZ twins underscores the important role of environmental influences in modulating genetic effects. Overall, research on BD consistently shows stronger concordance in MZ twins than in DZ twins, supporting the substantial genetic basis of the disorder (Kasyanov et al., 2020).

Genetic studies, including genome-wide association studies (GWAS), have provided important insights into the genetic architecture of bipolar disorder (BD). These studies have identified numerous genetic variants associated with the disorder, although each variant individually confers only a small effect size. Furthermore, GWAS have enabled the development of advanced analytical methods for genes and biological pathways, as well as the estimation of genetic correlations between BD and other traits (Fabbri 2021). As previously noted, environmental factors also play a substantial role in triggering BD, including stress, trauma, maternal smoking during pregnancy, and substance abuse (Aldinger and Schulze 2017; Lalli et al., 2021; Menculini et al., 2020; Rantala et al., 2021).

In recent years, debates have emerged regarding the genetic interplay between multiple sclerosis and mental

disorders. Patients with MS are approximately twice as likely to develop mental health conditions compared to the general population (Vesic et al., 2023).

The pooled prevalence of bipolar disorder (BD) in individuals with MS is estimated at 2.95% (95% CI: 2.12–4.09%), with regional variations showing a higher rate in the Americas than in Europe. A more detailed analysis of MS and BD together revealed an 8.4% prevalence of BD in MS patients. Notably, gender-related patterns in the MS population indicated a higher prevalence of BD in females (7.03%) compared to males (5.64%) (Joseph et al., 2021b). Recent studies have further confirmed a link between manic and depressive episodes and systemic inflammation involving immune system dysregulation (Muneer 2016). As previously noted, mania and depression represent the core features of BD, while MS is fundamentally an autoimmune disorder.

Scientists have extensively investigated potential links between multiple sclerosis (MS) and various psychiatric disorders (Liu et al., 2024; Ziaastani et al., 2024). Individuals with MS are at an elevated risk of developing bipolar spectrum disorders. This association underpins the focus of the present study, which aims to identify shared genes and key metabolic pathways between MS and BD (Carta et al., 2014).

Therefore, the present study employs a systems biology approach to investigate the shared genetic and molecular associations between multiple sclerosis (MS) and bipolar disorder (BD). Specifically, this study aims to: (1) identify genes shared between the two diseases and construct a protein–protein interaction (PPI) network; (2) identify hub genes and functional modules within the network; (3) characterize the biological processes and pathways potentially shared by the two disorders; and (4) explore potential drug–gene interactions involving prioritized hub genes. Through these analyses, we aim to provide further insights into the molecular basis of MS–BD comorbidity and identify potential targets for future therapeutic investigation.

Materials and methods

Data collection

We conducted a systematic search in January 2023 using the NCBI Gene database to identify genes associated with multiple sclerosis (MS) and bipolar disorder (BD) (Jin et al., 2024). The search strategy employed the following keywords and synonyms: (“Multiple

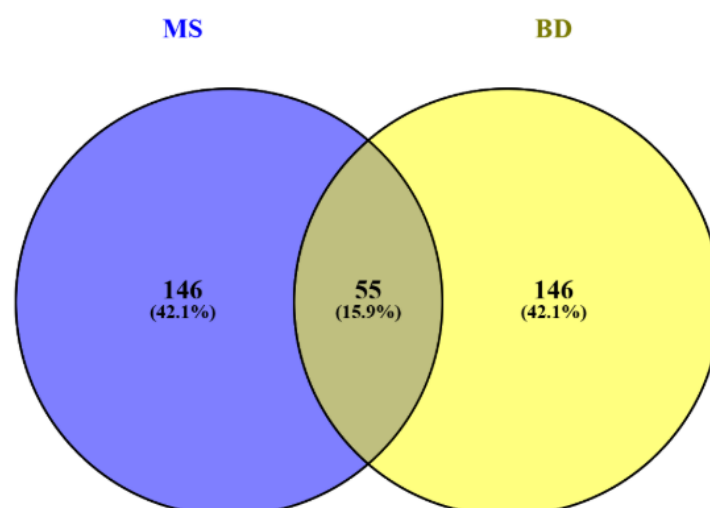


FIGURE 1. The overlapping in MS-BD genes.

Sclerosis” OR “MS” OR “Disseminated Sclerosis”) AND (“Bipolar Disorder” OR “Bipolar Depression” OR “Manic-Depressive Disorder” OR “Manic Depressive Illness”). The search was restricted to “Organism: Homo sapiens.”

After retrieving the initial gene lists from the NCBI Gene database, the lists for multiple sclerosis (MS) and bipolar disorder (BD) were compared. Overlapping genes were identified by intersecting the two lists based on official gene symbols using Venny 2.1 software.

The protein-protein interaction network analysis

A protein-protein interaction (PPI) network was constructed for the shared genes between multiple sclerosis (MS) and bipolar disorder (BD) using the STRING database (version 12) (Szklarczyk et al., 2023). This database integrates protein interactions based on homology, co-expression, gene neighborhood, and experimental evidence. The resulting network was visualized and analyzed using Cytoscape software (version 3.10.1) (Franz et al., 2023). The MCODE plugin was employed to detect functional modules with the following parameters: degree cutoff = 2, node score cutoff = 0.2, k-core = 2, and maximum depth = 100. Additionally, the CytoHubba plugin was applied using the Maximal Clique Centrality (MCC) algorithm to identify the top 10 hub genes in the PPI network. The MCC algorithm prioritizes nodes based on the density of their local cliques and overall connectivity within the network.

Functional enrichment analysis

Functional enrichment analysis was performed using WebGestalt and g:Profiler to annotate the shared genes between MS and BD. These tools were utilized to identify Gene Ontology (GO) terms in three categories: Biological Processes (BP), Molecular Functions (MF), and Cellular Components (CC). Additionally, KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis was conducted to identify significantly enriched metabolic and signaling pathways.

Drug-Hub Gene Interaction Network

Expression patterns of the identified hub genes in MS and BD were assessed through a comprehensive literature review. Due to the unavailability of large, matched transcriptomic datasets containing samples from both diseases, we relied on previously validated gene expression data reported in the literature. FDA-approved drugs targeting the prioritized hub genes were then retrieved from the DrugBank and DGIdb databases. Drug-gene interactions for the hub genes were retrieved from the Drug-Gene Interaction Database (DGIdb v5.0). To ensure clinical relevance and translational potential, only FDA-approved drugs were selected. Queries were performed using the following interaction types as filters: inhibitor, antagonist, antibody, agonist, modulator, and binder.

Result

Analysis of MS-BD Interaction Network

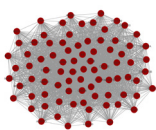
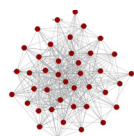
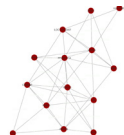
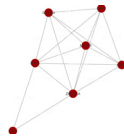
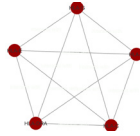
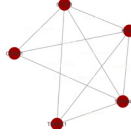
A total of 206 genes associated with MS and 201 genes associated with BD were retrieved from the NCBI Gene database, of which 55 genes were found to be shared between the two diseases (Fig. 1). The complete lists of MS genes, BD genes, and the overlapping genes are provided in Supplementary Tables S1, S2, and S3, respectively. The PPI network was constructed using the

STRING database and consisted of 330 nodes and 8403 edges.

Module Identification and GO Enrichment Analysis

The PPI network was further analyzed using the MCODE plug-in to identify functional modules. Ten modules (M1-M10) were detected, as detailed in Table

TABLE 1: Functional modules identified in the MS-BD PPI network.

Modules	Nodes count	Node's name	Modules figure
M1	84	IFNB1, FAS, CCR2, NFKB1, NCAM1, BCL2, IFNG, CD274, IL17A, SPP1, IL2, MMP2, CCL5, SIRT1, MYD88, CCR5, TNFSF10, LEP, BCL2L1, PPARG, IL7, BDNF, SERPINE1, CXCR5, IL10, MMP9, AP-1, FOXP3, IL18, NGF, TIMP1, MTOR, TNFSF13B, TLR2, FGF2, HMOX1, IDO1, CXCL8, CREB1, PDCD1, ICAM1, CD40, ACE, CD40LG, IL6R, CD4, CTNNB1, NFE2L2, FCGR3A, CXCL12, IGF1, KIT, IL1A, STAT1, EGFR, IL2RA, TLR9, TP53, CD276, AGT, AKT1, ADIPOQ, CTLA4, STAT3, FCGR2A, HAVCR2, TBX21, CXCR4, CRP, TNFRSF1A, HMGB1, ESR1, EDN1, MAPK3, APOE, TNF, CXCL10, CD44, NOS3, TLR3, IL7R, CD86, LGALS3, IL4	
M2	41	IRF8, TNFRSF1B, MAPK14, MET, CD5, CDC42, RHOA, IL1RN, IL1B, MYC, NOD2, EZH2, CCL2, NOTCH1, LCN2, TYK2, PTK2, NLRP3, CDH2, ACE2, FOXO3, VWF, SOD2, VCAM1, HLA-A, TGFB1, KDR, RPS6KB1, ITGB1, RELA, MAPK1, CAV1, NOS2, AGER, SYK, MIF, HSP90AA1, IL6, MUC1, TLR4, GSK3B	
M3	14	NR3C1, CREBBP, SOD1, BRCA1, TERT, FYN, HSPA5, LOC102723407, HLA-DRB1, AR, PIK3R1, XBP1, APOB, PPARGC1A	
M4	7	SLC6A4, ZNF804A, MTHFR, DRD2, DRD4, DAOA, TCF4	
M5	5	HLA-B, HLA-C, HLA-E, HLA-G, HLA-DRA	
M6	5	TENM4, TRANK1, NT5C2, SYNE1, CSMD1	
M7	7	COMT, CACNA1C, CYP2D6, HTR2A, ALDH2, GSTM1, CNR1	

Continuation of Table 1:

Modules	Nodes count	Node's name	Modules figure
M8	3	S100B, NTRK2, SNCA	
M9	3	PRKN, MAPT, HTT	
M10	8	TPH2, HNRNPC, C9orf72, YWHAG, HTR1A, FMR1, SLC6A3, FTO	

TABLE 2: GO analysis of functional modules.

Module	GO ID	Biological Process (BP)	FDR
M1	GO:0006955	Immune Response	< 2.2e-16
M2	GO:0006955	Immune Response	< 2.2e-16
M3	GO:0071459	Cellular Response to Endogenous Stimulus	5.6429e-7
M4	GO:0032225	Regulation of Synaptic Transmission, Dopaminergic	< 0.00023054
M5	GO:0060333	Interferon-Gamma-Mediated Signaling Pathway	0.00048503
M6	GO:2000543	Positive Regulation of Gastrulation	1
M7	GO:0009410	Response to Xenobiotic Stimulus	0.024543
M8	GO:0060291	Long-Term Synaptic Potentiation	0.00089691
M9	GO:0010821	Regulation of Mitochondrion Organization	0.0078087
M10	GO:0042428	Serotonin Metabolic Process	0.031930

1.

Functional enrichment of these modules included Gene Ontology terms (Biological Processes (BP), Molecular Functions (MF), and Cellular Components (CC)), obtained using the Webgestalt and g:Profiler web servers. Results related to the biological process of each module have been provided in Table 2.

Hub Genes Analysis

The top 10 hub genes were identified using the CytoHubba plugin in Cytoscape. These hub genes were Tumor Necrosis Factor (TNF), Interleukin 6 (IL6), In-

terleukin 1 Beta (IL1B), Toll-like Receptor 4 (TLR4), AKT Serine/Threonine Kinase 1 (AKT1), B-cell Lymphoma 2 (BCL2), Interferon Gamma (IFNG), Amyloid Precursor Protein (APP), Nuclear Factor Kappa B Subunit 1 (NFKB1), and Mechanistic Target of Rapamycin Kinase (MTOR). The interaction network constructed from these hub genes comprised 84 edges, with their ranking order presented in Figure 2.

Hub Genes Enrichment

GO enrichment of hub genes was performed using g:profiler (FDR<0.05), as shown in Table 3 and Fig. 3.

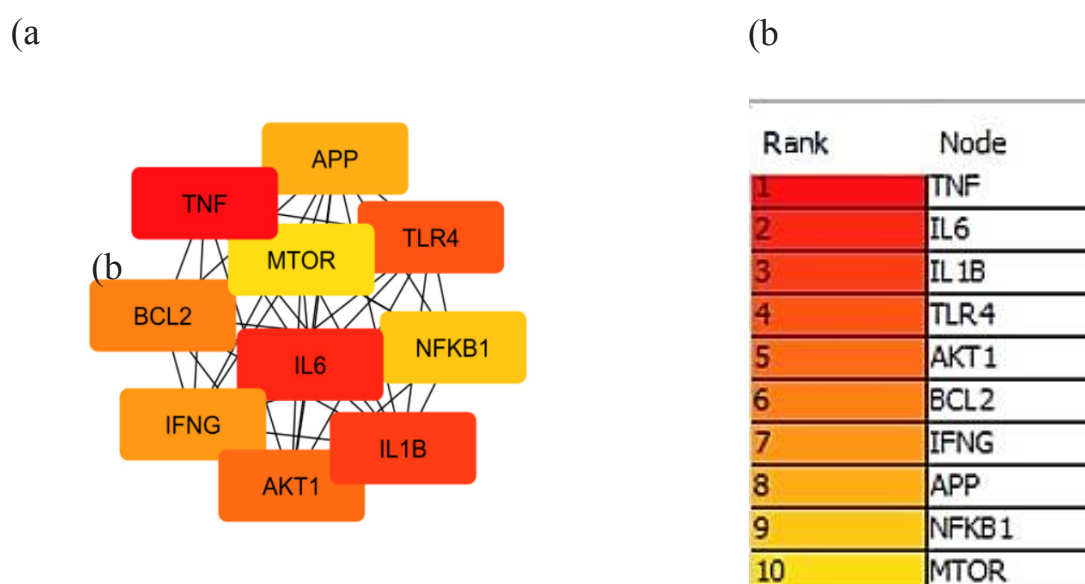


FIGURE 2. MS-BD hub genes interaction network (2a) and their ranking list (2b).

TABLE 3: GO terms of 10 hub genes.

GO ID	GO term	Description	Number of genes	FDR
GO:0010001	BP	glial cell differentiation	8	2.491×10 ⁻¹¹
GO:0002684	BP	positive regulation of immune system processes	10	1.143×10 ⁻¹⁰
GO:0080134	BP	regulation of response to stress	10	1.272×10 ⁻⁹
GO:0006954	BP	inflammatory response	9	2.531×10 ⁻⁹
GO:0002682	BP	regulation of immune system process	10	4.272×10 ⁻⁹
GO:0006952	BP	defense response	10	2.334×10 ⁻⁸
GO:0065009	BP	regulation of molecular function	10	2.441×10 ⁻⁸
GO:0048584	BP	positive regulation of response to stimulus	10	2.555×10 ⁻⁷
GO:0050776	BP	regulation of immune response	8	4.570×10 ⁻⁷
GO:0008219	BP	cell death	10	6.736×10 ⁻⁷

This analysis shows the roles of hub genes in BP and functional pathways.

Drug-Gene Interaction Network

Analysis of hub gene expression revealed significant upregulation of TNF and IL-6 in patients with MS and BD compared to healthy controls (Darrau et al., 2024; Freseigna et al., 2020; Stampanoni Bassi et al., 2020; Xu et al., 2024). These two genes, which are central to modules M1 and M2 in the PPI network (Table 1), were pri-

oritized as potential therapeutic targets due to their critical roles in inflammatory and immune pathways (Table 3). FDA-approved drugs targeting TNF and IL-6 were subsequently identified from the DrugBank and DGIdb databases (Table 4).

These drugs, proposed for potential drug repurposing in MS and BD, require further clinical validation. The triple gene-disease-drug interaction network is shown in Fig.4 .

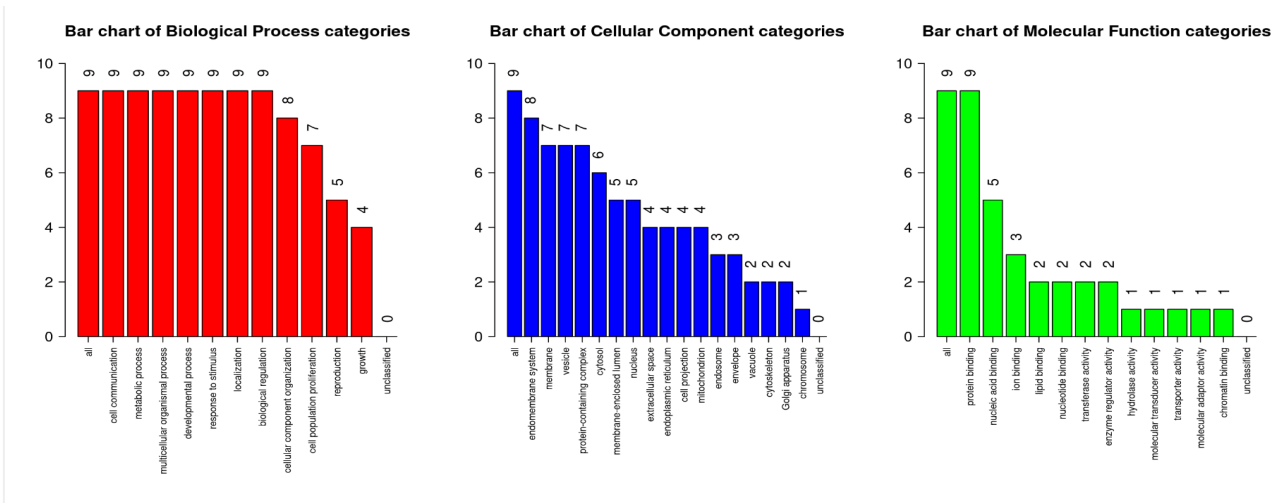


FIGURE 3. GO bar chart related to hub genes via Webgestalt.

TABLE 4: FDA-Approved Drugs Targeting TNF and IL6 Genes.

Target genes	FDA-approved drugs
IL6	Siltuximab and Tocilizumab
TNF	Infliximab, Adalimumab, Certolizumab pegol, Golimumab, Etanercept, and Pomalidomide

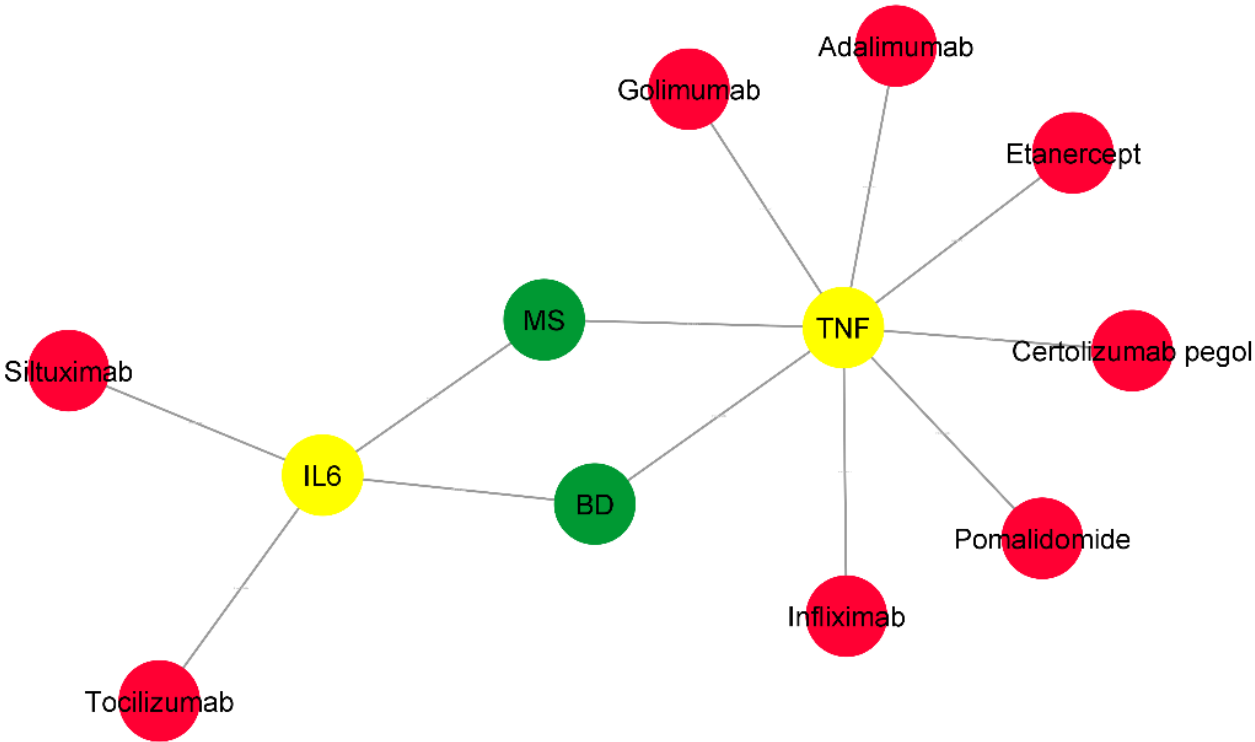


FIGURE 4. The triple network of Gene-Disease-Drug. Yellow points represent target hub genes, green points represent the disease, and pink points represent the candidate drug.

Discussion

The present study demonstrates a substantial molecular overlap between multiple sclerosis (MS) and bipolar disorder (BD). By intersecting 206 MS-associated genes with 201 BD-associated genes retrieved from the NCBI Gene database, we identified 55 shared genes, highlighting significant genetic convergence between the two diseases (Fig. 1; Supplementary Tables S1–S3). The protein-protein interaction (PPI) network constructed using the STRING database contained 330 nodes and 8,403 edges. This highly interconnected network suggests a complex molecular landscape that may contribute to the observed clinical comorbidity between MS and BD (Joseph et al., 2021a; Meier et al., 2020).

Module analysis with the MCODE plugin in Cytoscape uncovered ten functional modules (M1–M10) within the PPI network (Table 1). Notably, the two largest modules (M1 and M2) were strongly enriched for immune response pathways (GO:0006955, FDR < 2.2e-16; Table 2). These modules highlight key inflammatory mediators and further emphasize the pivotal role of immune dysregulation in the shared pathophysiology of MS and BD.

Subsequent hub gene analysis using CytoHubba plugin in Cytoscape prioritized 10 central genes—TNF, IL6, IL1B, TLR4, AKT1, BCL2, IFNG, APP, NFKB1, and mTOR—as key nodes in the network (Fig. 2). These hub genes are predominantly involved in inflammatory cascades, immune regulation, neuronal survival, and apoptosis. This molecular profile provides a plausible explanation for the frequent comorbidity observed between multiple sclerosis (MS) and bipolar disorder (BD). For instance, TNF and IL6, which serve as critical regulators of inflammation and neuronal integrity, are significantly upregulated in patients with both diseases compared to healthy controls (Brietzke and Kapczynski 2008; Gonzalez Caldito 2023; Vadodaria et al., 2021).

Overexpression of these hub genes is likely to sustain a chronic neuroinflammatory environment that exacerbates disease progression and mood instability in both conditions. Similarly, elevated IL1B levels have been implicated in primary progressive multiple sclerosis (MS) and in structural brain changes associated with bipolar disorder (BD), suggesting its potential role as a common driver of neurodegeneration (Li et al., 2021; Strenn et al., 2021). TLR4 appears to exert a context-dependent role, acting as a risk factor in MS while poten-

tially exerting protective effects against certain psychotic features in BD (Aflouk et al., 2024; Asadzadeh Manjili et al., 2020).

Collectively, perturbations in AKT1, BCL2, IFNG, APP, NFKB1, and MTOR converge on several critical pathways, including immune-mediated demyelination, amyloid processing, and metabolic dysregulation (Corrêa-Velloso et al., 2018; Gehrmann et al., 1995; Javed and Reder, 2006; Luczynski et al., 2019; Machado-Vieira et al., 2015; Oktelik et al., 2021). In particular, NFKB1 plays a central role in the NF-κB signaling pathway in MS, whereas MTOR has been implicated as a potential diagnostic and therapeutic marker in both MS and BD (Akbarian et al., 2020; Fazia et al., 2020; Park et al., 2022).

Gene Ontology (GO) enrichment analysis of the hub genes (Table 3, Fig. 3) further supports these findings, revealing highly significant enrichment in biological processes such as glial cell differentiation, positive regulation of immune system processes, inflammatory response, and cell death. In MS, reactive gliosis and glial-mediated inflammation are well-established contributors to demyelination and axonal damage. In BD, emerging evidence indicates that miRNA dysregulation impairs glial support for synaptic plasticity and axon guidance (Bame et al., 2020; Healy et al., 2022). Collectively, these observations suggest that glial dysfunction may represent a critical mechanistic link bridging the neuroinflammatory and neurodegenerative components of both disorders (Rodríguez Murúa et al., 2022; Roman et al., 2021).

The NFKB1 gene plays a central role in the NF-κB signaling pathway in MS, while MTOR has been proposed as a potential diagnostic and therapeutic marker in both MS and BD (Akbarian et al., 2020; Fazia et al., 2020; Park et al., 2022).

These findings underscore the critical importance of hub genes in the shared pathophysiology of the two disorders.

From a translational perspective, the gene-disease-drug interaction network provides particularly promising insights. Because TNF and IL6 play important roles and are significantly upregulated in the key modules, several FDA-approved biologics emerge as strong candidates for drug repurposing (Table 4; Fig. 4). These include IL-6 inhibitors (e.g., tocilizumab and siltuximab) and TNF inhibitors (e.g., infliximab, adalimumab, and

etanercept). Repurposing these agents could simultaneously target neuroinflammation and mood dysregulation in patients with comorbid MS and BD. Nevertheless, their efficacy and safety in this specific population require further validation through well-designed clinical trials.

This integrative network analysis provides compelling evidence for shared genetic, immune, and inflammatory mechanisms underlying multiple sclerosis and bipolar disorder. By identifying overlapping genes, functional modules, hub genes, and potential druggable targets, the present study enhances our understanding of the molecular basis of their comorbidity and highlights promising avenues for improved screening, early intervention, and novel therapeutic strategies. Future prospective studies and well-designed clinical trials are warranted to validate these findings and ultimately improve clinical outcomes for patients affected by both conditions.

Conclusion

This study elucidates key shared molecular pathways and hub genes (TNF, IL6, IL1B, TLR4, AKT1, BCL2, IFNG, APP, NFKB1, and MTOR) between multiple sclerosis (MS) and bipolar disorder (BD), highlighting their potential as both biomarkers and therapeutic targets. FDA-approved drugs targeting TNF and IL6, such as infliximab, siltuximab, and tocilizumab, represent promising candidates for drug repurposing in the management of both conditions. Furthermore, the overlap of these genes with other disorders, including Alzheimer's disease and inflammatory bowel disease, suggests broader therapeutic implications across immune-mediated and neurodegenerative conditions. Nevertheless, these findings warrant validation through future prospective studies and clinical trials to confirm the efficacy and safety of the proposed drugs and to develop integrated treatment strategies for patients with MS, BD, and related comorbidities.

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Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Ethics approval

Not applicable.

References

- Aflouk Y, Saoud H, Inoubli O, Yacoub S, Zaafrane F, Gaha L, et al. TLR4 polymorphisms (T399I/D299G) Association with schizophrenia and bipolar disorder in a tunisian population. *Biochemical Genetics* 2024; 62: 2418-2436. <https://doi.org/10.1007/s10528-023-10553-z>
- Akbarian F, Tabatabaiefar M A, Shaygannejad V, Shahpouri M M, Badihian N, Sajjadi R, et al. Upregulation of MTOR, RPS6KB1, and EIF4EBP1 in the whole blood samples of Iranian patients with multiple sclerosis compared to healthy controls. *Metabolic Brain Disease* 2020; 35: 1309-1316. <https://doi.org/10.1007/s11011-020-00590-7>
- Aldinger F, Schulze T G. Environmental factors, life events, and trauma in the course of bipolar disorder. *Psychiatry and Clinical Neurosciences* 2017; 71: 6-17. <https://doi.org/10.1111/pcn.12433>
- Asadzadeh Manjili F, Yousefi-Ahmadipour A, Kazemi Arababadi M. The roles played by TLR4 in the pathogenesis of multiple sclerosis; A systematic review article. *Immunology Letters* 2020; 220: 63-70. <https://doi.org/10.1016/j.imlet.2020.02.004>
- Balcerac A, Louapre C. Genetics and familial distribution of multiple sclerosis: A review. *Revue Neurologique* 2022; 178: 512-520. <https://doi.org/10.1016/j.neurol.2021.11.009>
- Bame M, McInnis M G, O'Shea K S. MicroRNA alterations in induced pluripotent stem cell-derived neurons from bipolar disorder patients: pathways involved in neuronal differentiation, axon guidance, and plasticity. *Stem Cells and Development* 2020; 29: 1145-1159. <https://doi.org/10.1089/scd.2020.0046>
- Boles G S, Hillert J, Ramanujam R, Westerlind H, Olsson T, Kockum I, et al. The familial risk and heritability of multiple sclerosis and its onset phenotypes: A case-control study. *Multiple Sclerosis Journal* 2023; 29: 1209-1215. <https://doi.org/10.1177/13524585231185258>
- Brietzke E, Kapczinski F. TNF- α as a molecular target in bipolar disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2008; 32: 1355-1361. <https://doi.org/10.1016/j.pnpbp.2008.01.006>
- Carta M G, Moro M F, Lorefice L, Trincas G, Cocco E, Giudice E D, et al. The risk of Bipolar Disorders in Multiple Sclerosis. *Journal of Affective Disorders* 2014; 155: 255-260. <https://doi.org/10.1016/j.jad.2013.11.008>
- Corrêa-Velloso J C, Gonçalves M C B, Naaldijk Y, Oliveira-Gi-

- acomelli Á, Pillat M M, Ulrich H. Pathophysiology in the comorbidity of Bipolar Disorder and Alzheimer's Disease: pharmacological and stem cell approaches. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2018; 80: 34-53. <https://doi.org/10.1016/j.pnpbp.2017.04.033>
- Darrau E, Jacquemet E, Pons S, Schlick L, Zouridakis M, Wu C-L, et al. Serum autoantibodies against $\alpha 7$ -nicotinic receptors in subgroups of patients with bipolar disorder or schizophrenia: clinical features and link with peripheral inflammation. *Translational Psychiatry* 2024; 14: 146. <https://doi.org/10.1038/s41398-024-02853-8>
- Ebers G C, Bulman D E, Sadovnick A D, Paty D W, Warren S, Hader W, et al. A population-based study of multiple sclerosis in twins. *New England Journal of Medicine* 1986; 315: 1638-1642. <https://doi.org/10.1056/NEJM198612253152603>
- Fabbri C. The role of genetics in bipolar disorder." *Bipolar disorder: from neuroscience to treatment*. Cham: Springer International Publishing 2021: 41-60. https://doi.org/10.1007/7854_2020_153
- Fazia T, Nova A, Gentilini D, Beecham A, Piras M, Saddi V, et al. Investigating the causal effect of brain expression of CCL2, NFKB1, MAPK14, TNFRSF1A, CXCL10 genes on multiple sclerosis: a two-sample mendelian randomization approach. *Frontiers in Bioengineering and Biotechnology* 2020; 8: 397. <https://doi.org/10.3389/fbioe.2020.00397>
- Franz M, Lopes C T, Fong D, Kucera M, Cheung M, Siper M C, et al. Cytoscape. js 2023 update: a graph theory library for visualization and analysis. *Bioinformatics* 2023; 39: btad031. <https://doi.org/10.1093/bioinformatics/btad031>
- Freseigna D, Bullitta S, Musella A, Rizzo F R, De Vito F, Guadalupi L, et al. Re-examining the role of TNF in MS pathogenesis and therapy. *Cells* 2020; 9: 2290. <https://doi.org/10.3390/cells9102290>
- Fymat A L. Multiple sclerosis: II. Diagnosis and symptoms management. *Journal of Neurology and Psychology Research* 2023; 4: 1-21.
- Gehrmann J, Banati R B, Cuzner M L, Kreutzberg G W, Newcombe J. Amyloid precursor protein (APP) expression in multiple sclerosis lesions. *Glia* 1995; 15: 141-151. <https://doi.org/10.1002/glia.440150206>
- Gonzalez Caldito N. Role of tumor necrosis factor-alpha in the central nervous system: a focus on autoimmune disorders. *Frontiers in Immunology* 2023; 14: 1213448. <https://doi.org/10.3389/fimmu.2023.1213448>
- Goodin D S, Khankhanian P, Gourraud P-A, Vince N. Multiple sclerosis: Exploring the limits and implications of genetic and environmental susceptibility. *PLOS One* 2023; 18: e0285599. <https://doi.org/10.1371/journal.pone.0285599>
- Healy L M, Stratton J A, Kuhlmann T, Antel J. The role of glial cells in multiple sclerosis disease progression. *Nature Reviews Neurology* 2022; 18: 237-248. <https://doi.org/10.1038/s41582-022-00624-x>
- Javed A, Reder A T. Therapeutic role of beta-interferons in multiple sclerosis. *Pharmacology & Therapeutics* 2006; 110: 35-56. <https://doi.org/10.1016/j.pharmthera.2005.08.011>
- Jin Q, Yang Y, Chen Q, Lu Z. GeneGPT: augmenting large language models with domain tools for improved access to biomedical information. *Bioinformatics* 2024; 40: btac075. <https://doi.org/10.1093/bioinformatics/btac075>
- Johansson V, Kuja-Halkola R, Cannon T D, Hultman C M, Hedman A M. A population-based heritability estimate of bipolar disorder - In a Swedish twin sample. *Psychiatry Research* 2019; 278: 180-187. <https://doi.org/10.1016/j.psychres.2019.06.010>
- Joseph B, Nandakumar A L, Ahmed A T, Gopal N, Murad M H, Frye M A, et al. Prevalence of bipolar disorder in multiple sclerosis: a systematic review and meta-analysis. *BMJ Mental Health* 2021a; 24: 88-94. <https://doi.org/10.1136/ebmental-2020-300207>
- Joseph B, Nandakumar A L, Ahmed A T, Gopal N, Murad M H, Frye M A, et al. Prevalence of bipolar disorder in multiple sclerosis: a systematic review and meta-analysis. *Evidence-Based Mental Health* 2021b; 24: 88-94. <https://doi.org/10.1136/ebmental-2020-300207>
- Kasyanov E D, Merkulova T V, Kibitov A O, Mazo G E. Genetics of bipolar spectrum disorders: focus on family studies using whole exome sequencing. *Russian Journal of Genetics* 2020; 56: 786-801. <https://doi.org/10.1134/S1022795420070054>
- Kinnunen E, Koskenvuo M, Kaprio J, Aho K. Multiple sclerosis in a nationwide series of twins. *Neurology* 1987; 37: 1627-1627. <https://doi.org/10.1212/WNL.37.10.1627>
- Kokas Z, Járdánházy A, Sandi D, Biernacki T, Friciska-Nagy Z, Füvesi J, et al. Real-world operation of multiple sclerosis centres in Central-Eastern European countries covering 107 million inhabitants. *Multiple Sclerosis and Related Disorders* 2023; 69: 104406. <https://doi.org/10.1016/j.msard.2022.104406>
- Lalli M, Brouillette K, Kapczynski F, de Azevedo Cardoso T. Substance use as a risk factor for bipolar disorder: A systematic review. *Journal of Psychiatric Research* 2021; 144: 285-295. <https://doi.org/10.1016/j.jpsychires.2021.10.012>
- Li Z, Liu Y, Jia A, Cui Y, Feng J. Cerebrospinal fluid cells

- immune landscape in multiple sclerosis. *Journal of Translational Medicine* 2021; 19: 1-16. <https://doi.org/10.1186/s12967-021-02804-7>
- Liu S, Chen H, He X-D, Yang X-O. Glucometabolic-related genes as diagnostic biomarkers and therapeutic targets for Alzheimer's Disease and type 2 Diabetes Mellitus: a bioinformatics analysis. *Neurology Research International* 2024; 2024: 5200222. <https://doi.org/10.1155/2024/5200222>
- Luczynski P, Laule C, Hsiung G-Y R, Moore G R W, Tremlett H. Coexistence of Multiple Sclerosis and Alzheimer's disease: A review. *Multiple Sclerosis and Related Disorders* 2019; 27: 232-238. <https://doi.org/10.1016/j.msard.2018.10.109>
- Lutfullin I, Eveslage M, Bittner S, Antony G, Flaskamp M, Luessi F, et al. Association of obesity with disease outcome in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* 2023; 94: 57-61. <https://doi.org/10.1136/jnnp-2022-329685>
- Machado-Vieira R, Zanetti M V, Teixeira A L, Uno M, Valiengo L L, Soeiro-de-Souza M G, et al. Decreased AKT1/mTOR pathway mRNA expression in short-term bipolar disorder. *European Neuropsychopharmacology* 2015; 25: 468-473. <https://doi.org/10.1016/j.euroneuro.2015.02.002>
- Marcus R. What is Multiple Sclerosis? *Journal of the American Medical Association* 2022; 328: 2078-2078. <https://doi.org/10.1001/jama.2022.14236>
- McIntyre R S, Berk M, Brietzke E, Goldstein B I, López-Jaramillo C, Kessing L V, et al. Bipolar disorders. *The Lancet* 2020; 396: 1841-1856. [https://doi.org/10.1016/S0140-6736\(20\)31544-0](https://doi.org/10.1016/S0140-6736(20)31544-0)
- Meier U-C, Ramagopalan S V, Goldacre M J, Goldacre R. Risk of Schizophrenia and Bipolar Disorder in Patients With Multiple Sclerosis: Record-Linkage Studies. *Frontiers in Psychiatry* 2020; 11. <https://doi.org/10.3389/fpsyg.2020.00662>
- Menculini G, Balducci P M, Attademo L, Bernardini F, Moretti P, Tortorella A. Environmental risk factors for bipolar disorders and high-risk states in adolescence: a systematic review. *Medicina* 2020; 56: 689. <https://doi.org/10.3390/medicina56120689>
- Mora P, Chapouly C. Astrogliosis in multiple sclerosis and neuro-inflammation: what role for the notch pathway? *Frontiers in Immunology* 2023; 14: 1254586. <https://doi.org/10.3389/fimmu.2023.1254586>
- Muneer A. Bipolar disorder: role of inflammation and the development of disease biomarkers. *Psychiatry Investig* 2016; 13: 18-33. <https://doi.org/10.4306/pi.2016.13.1.18>
- Oktelik F B, Yilmaz V, Turkoglu R, Akbayir E, Tuzun E, Deniz G, et al. Expression of Akt1 and p-Akt1 in peripheral T cell subsets of multiple sclerosis patients. *Acta Neurologica Belgica* 2021; 121: 1777-1782. <https://doi.org/10.1007/s13760-020-01518-9>
- Park S W, Seo M K, Webster M J, Lee J G, Kim S. Differential expression of gene co-expression networks related to the mTOR signaling pathway in bipolar disorder. *Translational Psychiatry* 2022; 12: 184. <https://doi.org/10.1038/s41398-022-01944-8>
- Rantala M J, Luoto S, Borráz-León J I, Krams I. Bipolar disorder: An evolutionary psychoneuroimmunological approach. *Neuroscience & Biobehavioral Reviews* 2021; 122: 28-37. <https://doi.org/10.1016/j.neubiorev.2020.12.031>
- Robinson N, Bergen S E. Environmental risk factors for schizophrenia and bipolar disorder and their relationship to genetic risk: current knowledge and future directions. *Frontiers in Genetics* 2021; 12. <https://doi.org/10.3389/fgene.2021.686666>
- Rodríguez Murúa S, Farez M F, Quintana F J. The immune response in multiple sclerosis. *Annual Review of Pathology: Mechanisms of Disease* 2022; 17: 121-139. <https://doi.org/10.1146/annurev-pathol-052920-040318>
- Roman K M, Jenkins A K, Lewis D A, Volk D W. Involvement of the nuclear factor- κ B transcriptional complex in prefrontal cortex immune activation in bipolar disorder. *Translational Psychiatry* 2021; 11: 40. <https://doi.org/10.1038/s41398-020-01092-x>
- Stampanoni Bassi M, Iezzi E, Drulovic J, Pekmezovic T, Gilio L, Furlan R, et al. IL-6 in the Cerebrospinal Fluid Signals Disease Activity in Multiple Sclerosis. *Frontiers in Cellular Neuroscience* 2020; 14. <https://doi.org/10.3389/fncel.2020.00120>
- Strenn N, Pålsson E, Liberg B, Landén M, Ekman A. Influence of genetic variations in IL1B on brain region volumes in bipolar patients and controls. *Psychiatry Research* 2021; 296: 113606. <https://doi.org/10.1016/j.psychres.2020.113606>
- Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Research* 2023; 51: D638-D646. <https://doi.org/10.1093/nar/gkac1000>
- Vadodaria K C, Mendes A P, Mei A, Racha V, Erikson G, Shokhirev M N, et al. Altered neuronal support and inflammatory response in bipolar disorder patient-derived astrocytes. *Stem Cell Reports* 2021; 16: 825-835. <https://doi.org/10.1016/j.stemcr.2021.05.005>

- [org/10.1016/j.stemcr.2021.02.004](https://doi.org/10.1016/j.stemcr.2021.02.004)
- Vasić M, Topić A, Marković B, Milinković N, Dinčić E. Oxidative stress-related risk of the multiple sclerosis development. *Journal of Medical Biochemistry* 2023; 42: 1. <https://doi.org/10.5937/jomb0-37546>
- Vesic K, Gavrilovic A, Mijailović N R, Borovcanin M M. Neuroimmune, clinical and treatment challenges in multiple sclerosis-related psychoses. *World Journal of Psychiatry* 2023; 13: 161-170. <https://doi.org/10.5498/wjp.v13.i4.161>
- Vitturi B K, Rahmani A, Dini G, Montecucco A, Debarbieri N, Sbragia E, et al. Occupational outcomes of people with multiple sclerosis: a scoping review. *BMJ Open* 2022; 12: e058948. <https://doi.org/10.1136/bmjopen-2021-058948>
- Vong V, Simpson-Yap S, Phaiju S, Davenport R A, Neate S L, Pisano M I, et al. The association between tobacco smoking and depression and anxiety in people with multiple sclerosis: A systematic review. *Multiple Sclerosis and Related Disorders* 2023; 70: 104501. <https://doi.org/10.1016/j.msard.2023.104501>
- Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie R A, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS. *Multiple Sclerosis Journal* 2020; 26: 1816-1821. <https://doi.org/10.1177/1352458520970841>
- Waubant E, Lucas R, Mowry E, Graves J, Olsson T, Alfredsson L, et al. Environmental and genetic risk factors for MS: an integrated review. *Annals of Clinical and Translational Neurology* 2019; 6: 1905-1922. <https://doi.org/10.1002/acn3.50862>
- Xu F, Su Y, Wang X, Zhang T, Xie T, Wang Y. Olink proteomics analysis uncovers inflammatory proteins in patients with different states of bipolar disorder. *International Immunopharmacology* 2024; 131: 111816. <https://doi.org/10.1016/j.intimp.2024.111816>
- Younger D S. Chapter 6 - Multiple sclerosis: Motor dysfunction. In: Younger DS, editor. *Handbook of Clinical Neurology*. Vol 196: Elsevier, 2023: 119-147. <https://doi.org/10.1016/B978-0-323-98817-9.00016-8>
- Ziaastani Z, Kalantari-Khandani B, Niazi M-J, Kazemi-pour A. Identification of critical genes and metabolic pathways in rheumatoid arthritis and osteoporosis toward drug repurposing. *Computers in Biology and Medicine* 2024; 180: 108912. <https://doi.org/10.1016/j.compbiomed.2024.108912>