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Bioinformatics and system biology approaches to identify pathophysiological impact of COVID-19 to the progression and severity of neurological diseases

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ABSTRACT

The Coronavirus Disease 2019 (COVID-19) still tends to propagate and increase the occurrence of COVID-19 across the globe. The clinical and epidemiological analyses indicate the link between COVID-19 and Neurological Diseases (NDs) that drive the progression and severity of NDs. Elucidating why some patients with COVID-19 influence the progression of NDs and patients with NDs who are diagnosed with COVID-19 are becoming increasingly sick, although others are not is unclear. In this research, we investigated how COVID-19 and ND interact and the impact of COVID-19 on the severity of NDs by performing transcriptomic analyses of COVID-19 and NDs samples by developing the pipeline of bioinformatics and network-based approaches. The transcriptomic study identified the contributing genes which are then filtered with cell signaling pathway, gene ontology, protein-protein interactions, transcription factor, and microRNA analysis. Identifying hub-proteins using protein-protein interactions leads to the identification of a therapeutic strategy. Additionally, the incorporation of comorbidity interactions score enhances the identification beyond simply detecting novel biological mechanisms involved in the pathophysiology of COVID-19 and its NDs comorbidities. By computing the semantic similarity between COVID-19 and each of the ND, we have found gene-based maximum semantic score between COVID-19 and Parkinson's disease, the minimum semantic score between COVID-19 and Multiple sclerosis. Similarly, we have found gene ontology-based maximum semantic score between COVID-19 and Huntington disease, minimum semantic score between COVID-19 and Epilepsy disease. Finally, we validated our findings using gold-standard databases and literature searches to determine which genes and pathways had previously been associated with COVID-19 and NDs.

1. Introduction

Due to severe acute respiratory syndromes coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19) has become the major health issue and the prevalence of COVID-19 is still quickly expanding across the globe [1]. By 21 August 2021, the worldwide World Health Organisation (WHO) has recorded a total of 211,855,573 incidents of laboratory-confirmed COVID-19 infection with 4,433,151 deaths [2]. Because of the rapid development of COVID-19 and the high death rate, it is completely becoming an important research issue to investigate potential risk factors influencing the development of COVID-19 and its comorbidities. COVID-19 may have moderate to extreme effects but SARS-CoV-2 compromised patients usually suffer from fever, dry cough, exhaustion, and lower dysfunctional respiratory systems, including

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elevated rates of pneumonia and acute respiratory distress syndrome (ARDS) [3]. Besides this, a quickly accumulating series of clinical trials, however, reported common COVID-19 symptoms that include neurological indications, including headaches, anosmia, nausea, dysgeusia, respiratory center injury, and brain infarction [4]. Individuals of all ages are still at increased risk for serious illness whether they are suffering from underlying chronic medical problems or neurological comorbidity and immunodeficiency disorders [5]. Thus, comorbidity sufferers are more susceptible to the extreme type of high mortality.

The literature review indicates that patients with neurological comorbidities are more likely than the general people to be affected by COVID-19 to cause substantial morbidity [5]. On the contrary, recent findings have highlighted that COVID-19 has played role in the development of neurological diseases (NDs) [6] which encourages us to explore the associations between COVID-19 and central nervous system (CNS) disorders. Several recent studies show that COVID-19 and CNS disorders, commonly known as Neurological diseases (NDs) such as Alzheimer's disease, Amyotrophic lateral sclerosis, Epilepsy disease, Huntington's disease, Multiple sclerosis, and Parkinson's disease are linked to each other [7].

Alzheimer's disease (AD) is a progressive, irreversible brain disease that affects memory and thinking. AD is the most common type of dementia in older people. The most prominent early sign of AD is memory decline [8]. With the development of the disease, symptoms can include verbal impairment, disorientation (including quick loss) mood swings, lack of confidence, unmanaged self-care, and behavioural difficulties [9]. Epilepsy disease (ED) is a chronic, non-communicable disease of the brain that impacts around 50 million people worldwide. ED is characterized by regular and visible seizures involving part of the body, or whole-body, which are frequently accompanied by unconsciousness and loss of control of the bowels or bladder [10]. The disorder called Amyotrophic lateral sclerosis (ALS) is a progressive illness of the nervous system that affects the brain and spinal cord which causes a loss of muscle control. ALS is also known as Lou Gehrig's disease. ALS begins with tweaking muscles and weakness in the limb or with a slurred speech which influences the muscle's function in walking, chatting, eating, and breathing [11]. Huntington's disease (HD) is a rare disease that causes nerve cell degeneration in the brain. HD has dramatic consequences on the mental capacity of the affected person, influencing speech, visual experience, and psychiatric symptoms. Symptoms of HD can develop at any age but can occur more at the age of 30–40. This disease is called juvenile HD if it happens up to the age of 20 [12]. Multiple sclerosis (MS) is a disorder that can damage the brain and spinal cord and which create a variety of possible symptoms including problems of vision, leg or arm coordination, sensations, and balance. Signs and indicators of MS are somewhat different and depend on the severity of nerve damage. Although certain people with MS discover opportunities to adjust their disability, some undergo extended stretches of rehabilitation without new symptoms [13]. Parkinson's disease (PD) is a chronic disorder induced by the degeneration of nerve cells in the region of the brain called substantia nigra [14]. These nerve cells die or become damaged, thus losing their ability to produce a large chemical called dopamine. Studies have shown that individuals diagnosed with PD have 80% or more dopaminergic cell death in the substantia nigra [15].

Usually, the central nervous system is defended against viral invasion by a very sophisticated brain barrier system. The blood-brain barrier, the blood-cerebrospinal fluid barrier, and the brain cerebrospinal fluid barrier are the three components of the brain barrier. Evidence indicates that SARS-CoV-2 may impact not only the breathing system but also the central nervous system. There is little evidence of the potential mechanisms by which SARS-CoV-2 invaded the central nervous system during COVID-19. (1) Infecting endothelial cells through angiotensin converting enzyme 2 (ACE2), SARS-CoV-2, therefore, penetrates the blood-brain barrier directly. (2) The olfactory nerve allows SARS-CoV-2 to reach the central nervous system through synaptic links. (3) SARS-CoV-2 causes inflammation in the brain, allowing it to penetrate the central nervous system and damage the brain barrier system [16]. COVID-19 may accelerate the progression of neurodegenerative diseases, though the mechanisms remain unclear and may vary among different neurodegenerative diseases, the impact of COVID-19 on ND seems to be significant. Infection with SARS-CoV-2 causes neurodegenerative alterations in cells that include cell death, hyperphosphorylation, and displacement of the tau protein. These changes have been found in AD [17]. COVID-19 may accelerate the progression of neurodegenerative diseases, though the mechanisms remain unclear and may vary among different neurodegenerative diseases, the impact of COVID-19 on ALS patients seems to be significant. Clinically, ALS displays muscle weakness, spasm, respiratory failure, and communication disorders. Recently, results of an internet-based questionnaire including self-perceived anxiety, depression, motor worsening, and changes in clinical care indicate that COVID-19 exert a significant impact on ALS patients. So far, accurate data on SARS-CoV-2 infection in ALS patients are not available. Thereby, based on the impact of COVID-19 on clinical care, diagnosis and related experimental studies of ALS, the indirect impact of COVID-19 on ALS patients seems to be significant [18]. It is found that the neurological symptoms associated with COVID-19 infection in ED are mostly caused by either the entrance of pro-inflammatory cytokines into the brain system or the generation of pro-inflammatory cytokines by microglia and astrocytes. Pro-inflammatory cytokines may damage the blood-brain barrier, raise glutamate and aspartate levels while decreasing GABA levels, decrease ion channel function, and ultimately, excessive cytokines can induce ED [19]. It has been suggested that patients with comorbidities are more likely to have complications. Due to difficulties of swallowing and emptying secretions from the lungs, people with HD may be at a greater risk of COVID-19 infection. Patients with HD who are symptomatic may also be at an increased risk of developing pneumonia as a consequence of being bedridden and undernourished [20,21]. B-cell depleting treatments such as rituximab and ocrelizumab has been shown to be very effective in the treatment of MS. They, however, eliminate a significant proportion (or all) of circulating B cells, damage the humoral arm of the immune system, and raise the chance of infection. As a result, individuals with MS who are treated with B-cell depleting medications may be more susceptible to COVID-19. Indeed, respiratory tract infections are more prevalent in people with MS, and their prevalence rises with age and male sex. Hospitalizations and mortality from influenza are also much greater in persons with MS [22]. The systemic inflammatory response caused by SARS-CoV-2 seems to be adequate to raise concerns about its possible link to neuroinflammation. The neuroinflammation associated with COVID-19 may play a role in the development of neurodegeneration in the future. Taking all of this evidence into consideration, we think that there is a possible link between SARS-CoV-2 and the development of PD. According to a new study, infections with viruses and bacteria may raise the chance of getting PD [23].

Although there is compelling evidence that there are pathological and clinically relevant associations between COVID-19 and a variety of NDs, but the association has not been extensively investigated. As a consequence, the nature of these connections is poorly understood. Due to the complexity of the etiology of COVID-19 and NDs, and the fact that their risk factors overlap considerably, their biological foundation, as well as the molecular processes that underpin this connection are still not fully understood. As a result, the actual effect of the COVID-19 on the progression of neurological comorbidities remains unclear. Additionally, there is still a lack of bioinformatics studies to examine the connection between COVID-19 and NDs. So, the goal of this research was to develop a pipeline based on bioinformatics approaches for identifying possible connections between COVID-19 and NDs. Understanding the nature of these connections may provide significant insights into the molecular mechanisms that underpin these diseases, and eventually lead to the identification of possible targets for therapeutic intervention that could lead to the development of disease-modifying

pharmaceuticals (drugs). We have made use of genomics, omics, molecular, miRNA data, and other public resources to grasp the pathophysiological mechanics involved in the associations that render ND more severe. We explored the functional links between COVID-19 and its ND comorbidities by which they affect each other's development and progression by influencing molecular biomarkers to facilitate the identification of therapeutic targets. Additionally, the incorporation of comorbidity interactions score will enhance the identification beyond simply identifying novel biological mechanisms involved in each disease. Finally, we verified the findings using gold-standard empirically validated databases, including dbGaP, OMIM, and OMIM Expanded, as well as the literature.

2. Materials and methods

We proposed the pipeline incorporating bioinformatics and the network-based approach. Using the R programming language, the proposed integrated pipeline of bioinformatics approach is developed, and it may be found at the following link: https://github.com/HabibUCAS/COVID-93_NDs. In this study, following Bioconductor packages [24]; we used GEOquery for downloading GEO datasets and performing expression set class transformation [25]; limma was used for differentially expressed gene identification from microarray data [26]; gene filter was used for filtering genes [27]; and topGO was used for creating a topology of DAG and finding the significant GO terms [28]. GOSemSim is used to measure the closeness between selected diseases [29]; and Enrichr is used to analyze the pathways that are Enriched [30]. The main steps of the proposed methodologies are described as shown in Fig. 1 and summarized in Algorithm.

2.1. Data collection

Following the comprehensive survey of epidemiological and clinical studies on the development of COVID-19 and its comorbidity, we observed that COVID-19 is related to different neurological disorders, from which we choose for our studies were AD, ALS, ED, HD, MS, and PD. In this study, we have used data from the public repositories [31, 32]. RNA-seq and microarray datasets were collected depending on certain parameters for each disease. When the examined sample settings are too small, control and case samples are missing, datasets with samples repeated, unforeseen formatting and non-human-set data are rejected due to lack of statistical significance. The selected dataset details are shown in Table 1.

2.2. Data preprocessing

Gene expression analysis by microarray and RNA-seq is a responsive tool that can identify differentially expressed genes in human tissues influenced by disorders. The gene expression analysis based on Microarray and RNA-seq datasets is a sensitive method to investigate the global expression of genes and to identify potential molecular pathways triggered by disorders [57]. We investigated such data to identify biomarkers relevant to the progression of COVID-19 and its ND comorbidity. All of these transcriptomic datasets were obtained from comparing the transcriptome profile of diseased tissues against controls. As the data produced are from various sources and types of cells, we have performed preprocessing our data via the transformation of the Z-score to avoid complications [58].

2.3. Gene set enrichment analysis

The Gene Set Enrichment (GSE) test is a technique for interpreting gene expression datasets in order to classify a set of genes with altered expression levels. These genes may be related to the phenotypes of disease [59]. GSE test uses a group of genes that are linked to a certain pathway. It investigates the expression level of genes obtained by DNA microarray and next-generation sequencing of various environments or disease states. The collection of differentially expressed genes (DEGs) is considered as up-regulated and down-regulated with the phenotypical variations [60].

2.4. Pathway enrichment analysis

The molecular pathway involves a series of actions within human cell molecules that trigger a certain product or cell modification. This mechanism, no matter how short, can cause the assembly of new molecules [61]. In addition, a pathway may also activate or disable genes. To obtain understanding of the molecular pathways of COVID-19 that correlate with neurological comorbidity, we used KEGG [62]; WiKi [63]; BioCarta [64] and Reactome [65] pathways databases to classify signaling pathways enriched by DEGs [66].

2.5. Ontology enrichment

Gene ontology (GO) is a conceptual model that includes new knowledge on processes or mechanisms that affect disease in a meaningful way. GO databases are an ongoing effort to provide ever more detailed and up-to-date standardized data on biological systems [67]. There are three fields for GO: cellular function, molecular function, and biological process (BP). We focus our research on the biological process area.

2.6. Semantic similarity computation

Gene Ontology utilizes directed acyclic graphs (DAGs) to determine what a gene product does. Any node in a directed acyclic graph (DAGs) represents one GO term, and two connected GO terms are linked by separate edge types suggesting different relationships. We have used the semantic similarity approach to determine genes and GO proximity of the selected diseases. Semantic similarity is a tool used in ontology to calculate correlation in order to approximate the proximity between terms of the selected diseases [68]. Semantic similarity computation is a graph-based method that uses directed acyclic graphs of terms (genes, GO). The semantics of these terms are determined by their position in the DAG, as well as the semantic contribution factor of all of their ancestor terms.

A GO term T can formally be described as a graph $DAG_P = (T, C_T, E_T)$, where C_T is the collection of all GO terms in DAG_T as ancestral terms of T along with T in the GO graph itself, and E_T is the subset of associated edges linking the GO terms in DAG_T. The semantic meaning of the GO term T is numerically measured as,

$$\begin{cases} S_T(T) = 1 & t = T \\ S_T(t) = \max\{w_e * S_T(t') | t' \in \text{children of}(t)\} & t \neq T \end{cases} \quad (1)$$

where w_e is the semantic factor for edge e in ($e \in C_T$) and generic term t with its child term t'. Depending on the form of relationship, the semantic contribution is between 0 and 1. The overall semanticized meaning is measured numerically as

$$SV(T) = \sum_{te C_T} S_T(t) \quad (2)$$

if the term M and N have the form $DAG_M = (M, C_T, E_M)$ and $DAG_N = (N, C_T, E_N)$ respectively, then the semantic correspondence between M and N is

$$sim(M,N) = \frac{\sum_{t \in T_M \cap T_N} (S_M(t) + S_N(t))}{SV(M) + SV(N)} \quad (3)$$

If the first set of terms with length k is $M_1 = \{t11, t12, \ldots t1k\}$ and the second set of terms with length n is $N_1 = \{t21, t22, \ldots t2n\}$. Then, we used the best matching average (BMA) for two sets of terms to measure the

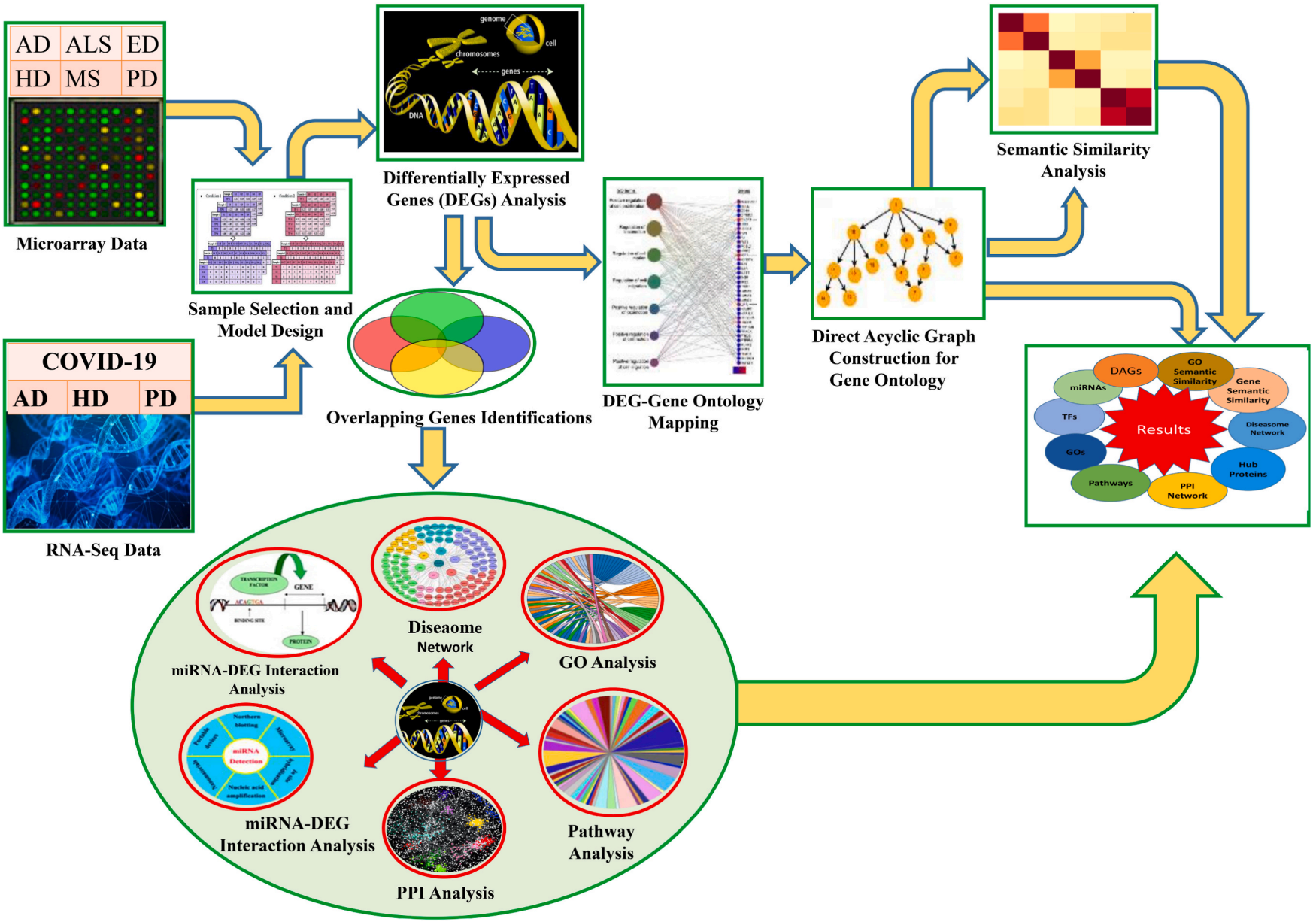


Fig. 1. A flow diagram describing the pipeline of the methodologies utilized in this study.

Table 1
Statistical summary of the datasets utilized in this study.

Dataset	Tissue	Case Samples	Control Samples	DEGs(Pval = 0.05)	DEGs (Pval = 0.05logFC = abs (1))	Raw GSEA	Fisher GSEA
COVID-19 [33]	Peripheral blood mononuclear cells	3	3	4453	2657	3627	446
GSE1297 [34]	Hippocampal CA1 tissue	22	9	2313	238	6094	3998
GSE12685 [35]	Frontal Cortex	6	8	3251	149	6094	3244
GSE28146 [35]	Hippocampal CA1 tissue	22	8	3405	1107	6530	6206
GSE53695 [36]	Human Brain	6	4	701	678	5956	950
GSE53697 [36]	Human Brain	9	8	678	312	5269	794
GSE833 [37]	Spinal cord gray matter	7	4	733	489	4897	4895
GSE4595 [38]	Motor Cortex	11	9	632	431	6544	5855
GSE19332 [39]	Cervical Spinal cord	3	7	4564	2644	6530	6528
GSE52672 [40]	Spinal cord homogenate	10	10	163	80	4643	1464
GSE68605 [41]	motor neurons	8	3	3171	1973	6530	6492
GSE32534 [42]	Pertitumoral neocortex tissue	5	5	2048	451	6530	5174
GSE64810 [43]	Post-mortem Brain	49	20	436	297	5230	748
GSE77558 [44]	iPSCs derived GABA MS-like neurons	6	6	4155	293	6687	4170
GSE79666 [45]	Motor cortex	7	7	1687	607	8568	1884
GSE97100 [46]	iPSC-derived brain microvascular endothelial cells	8	4	2137	757	9434	2204
GSE32915 [47]	White matter brain tissue	12	4	517	202	6560	6497
GSE38010 [48]	Brain Lesion	5	2	1996	1996	8381	1890
GSE52139 [49]	Spinal Cord (periplaque regions)	8	8	2703	1501	6405	6327
GSE7621 [50]	Postmortem human brain	16	9	5949	885	6530	5712
GSE19587 [51]	Post-mortem Brain	6	5	4150	2453	6094	6071
GSE20141 [52]	laser-dissected SNpc neurons	10	8	7094	3614	6530	6530
GSE20333 [53]	Post-mortem human brains	6	6	684	406	5570	5164
GSE28894 [54]	Parkinson's disease brain	55	59	3943	265	6510	4710
GSE42966 [55]	post-mortem substantia nigra	9	6	950	512	6560	6323
GSE68719 [56]	Post-mortem Brain	29	44	664	227	6140	1020

semantic similarity [69] as follows.

$$\mathrm{sim}_{BMA}(M_1, N_1) = \frac{\sum_{i=1}^{k} \max_{1\le j\le n}\{t_{1i}, t_{2j}\} + \sum_{j=1}^{n} \max_{1\le i\le k}\{t_{1i}, t_{2j}\}}{k+n} \ldots \quad (4)$$

The indices are i and j on the terms set M and N respectively.

2.7. Protein-protein interactions (PPIs) analysis and hub protein identification

The common genes between COVID-19 and its several neurological comorbidities have been used for studying the strongest possible associations among them in the form of a PPI network. DEG-encoded proteins and their associations with other proteins are computed by Network Analyst [70] from the STRING database [71] and an overall score > 0.5 (corresponding to highest confidence) is used to establish the preferred threshold for PPI network construction. The topological analysis was conducted using the visualization program Cytoscape [72]; to detect hub proteins using degree matrices from PPI networks. Hub proteins play a significant role in signal transduction during the development of COVID-19 and neurological disorders, and their identification may lead to new therapeutic targets.

2.8. Transcription Factors-MicroRNA interactions analysis

We also carried out an interaction study of DEGs-transcription Factors (TFs) and DEGs-microRNAs (miRNAs) to identify the controlling biomolecules (TFs and miRNAs) that regulate DEGs of interest. We also used the JASPAR database to examine the gene-to-transcription factor (TF) interactions [73]. The identity of microRNA (miRNAs) implicated in the development and progression of COVID-19 and its neurological comorbidities is little known. In this section, we also identified a set of miRNAs that are dysregulated in COVID-19, and are also significantly deregulated in its neurological comorbidities from TarBase database [74] and miRTarBase [75] database that may be used for diagnostic, prognostic, and therapeutic purposes.

Algorithm. An algorithm written in pseudocode

Input: Datasets from microarray and RNA-Seq studies with two conditions: case samples and control samples.
Output: Significant Genes, Diseasome Network, Cell Signalling Pathways, Ontological Pathways, Direct Acyclic Graphs, Gene Semantic Similarity, GO Semantic Similarity, Protein-Protein Interactions (PPIs), Transcription Factors (TFs) and MicroRNAs (miRNAs).

1. Search datasets with some requirements in the public repositories
2. For any number of dataset $i = 1, 2, \ldots, N$:
   (a) Dataset loading
   (b) Build a matrix model
      – Transform a GSE dataset into the corresponding expression class
      – Build a design matrix consisting of case and control
   (c) Filter the Design Matrix using Linear and Bayesian models.
   (d) Determine differential expression of genes
      – Set the P-value and logFC
      – Set False discovery rate (FDR) to find outliers
      – Record significant Differentially Expressed Genes
   (e) Annotation of Gene Ontology
      – Create topGO class with annotation
      – Carry out Fisher's exact test
      – Build and save the DAG tree with GO terms
      – Record Genes-GO terms correspondence
3. Determine Semantic similarity
   – Genes-GO terms correspondence loading
   – Compute semantic similarity:
   for i=1 to k **do**
   for j=1 to n **do**
   $\alpha = \sum_{1=1}^{k} \max_{1 \le j \le n} \{t_{1i}, t_{2j}\}$
   $\beta = \sum_{j=1}^{n} \max_{1 \le i \le k} \{t_{1i}, t_{2j}\}$
   end for
   end for
   return $(\alpha + \beta)/(k + n)$
   – Build and Plot DEGs and GO terms semantic similarity matrix
4. Comparison of DEGs from two different diseases
   – UP-Regulated common gene set
   – DOWN-Regulated common gene set
5. For the significant UP and DOWN regulated DEGs
   – Build gene-disease association network
   – Conduct enrichment analysis for signaling and Ontological pathwyas
   – Conduct PPIs Analysis
   – Conduct DEGs-TFs and DEGs-miRNAs interaction Analysis
   – Record and plot signaling and ontological pathways
   – Build PPIs network and record hub proteins
   – Record and plot TFs and miRNAs
6. Results
   – Differentially Expressed Genes
   – Diseasome Network
   – Cell Signalling and Ontological Pathways
   – Direct Acyclic Graph
   – Gene and GO Semantic Similarity Results
   – PPIs and Hub Proteins
   – TFs and miRNAs

3. Results

3.1. Statistical summary and diseasome network

Genetic links between COVID-19 and neurological disorders are revealed by gene expression profiles in RNA-seq and microarray data. For each dataset, we found the differentially expressed genes (DEGs) with the criterion of providing a p-value of less than 0.05 and an absolute log fold value (logFC) of 1. For all selected studies, the statistical overview and dataset details are shown in Table 1.The p-value is a likelihood measure in Table 1 for choosing differentially expressed genes from a pre-specified degree of significance (cutoff threshold). So, taking a cut-off of 0.05 implies we have a 5% risk of making an incorrect decision. With a cutoff of 0.05, the numbers in the fifth column in Table 1 indicate how many differentially expressed genes there were. Log2 fold change (logFC) is a log-ratio between gene expression levels, which is used for calculating differences in expression levels in two distinct conditions such as control vs case. In the sixth column of Table 1, we documented which genes were differentially expressed at a p-value of less than 0.05 and an absolute log fold value (logFC) of 1. We carried out gene-GO maps using the biological process (BP) gene ontology fields for DEGs. For GO enrichment research, the first step of the GO enrichment analysis is to locate raw GO terms. The number of annotated gene ontology (GO) terms from differentially expressed genes is provided by the seventh column in Table 1. We performed Fisher's exact test after mapping the gene to a functional gene ontology hierarchy to provide statistically significant GO term lists [28].We conducted a classical enrichment test by checking whether genes involved in GO processes were overrepresented in the genes that were differentially expressed. Eight columns in Table 1 represents the number of important GO terms enriched from the Fisher exact test. We have also done a comparison study to determine which of the DEGs are shared between COVID and neurological diseases. Figs. 2 and 3 present the number of shared DEGs between the COVID-19 and NDs. Our methodologies showed 52 DEGs shared between COVID-19 and AD, and 38 of which are upregulated and 14 are downregulated. COVID-19 has 76 DEGs shared with ALS, 55 of which have been upregulated, and 21 genes are downregulated. COVID-19 and ED share eight DEGs, four of which are upregulated and four of which are downregulated.Similarly, the 73 DEGs commons between HD and COVID-19, including 49 upregulated and 24 downregulated genes, were identified. 60 genes were common between MS and COVID-19, and 25 genes were upregulated and 25 genes were downregulated. 91 genes that are common to PD and COVID-19, among these, 72 are upregulated and 19 are downregulated. In order to represent significant linkages between COVID-19 and NDs, upregulated and downregulated disease-gene association networks were constructed using Cytoscape as seen in Figs. 2 and 3 and we note, as compared to other conditions, that COVID-19 has the highest number of shared DEGs with PD. We have provided the abbreviations of all common genes shown in the network as **supplementary file**.

3.2. Identification of significant signalling pathways

We used the DEGs discovered from each neurological disorder and COVID-19 in this enrichment study to discover the cell signaling pathways by utilizing KEGG, Wiki, BioCarta, and Reactome databases. Our identified cellular mechanisms were common to both COVID-19 and each of the neurological disorders that have been chosen.The pathways from these databases have been combined and a total of 72 pathways were found between COVID-19 and AD, among which were top 4 pathways from KEGG, top 4 from Wiki, top 4 from BioCarta, and top 4 from Reactome is enriched and statistically significant. Similarly, a total of 51 pathways were found between COVID-19 and ALS among which were the top 4 pathways from KEGG, top 4 from Wiki, top 4 from BioCarta, and top 4 from Reactome. A total of 27 pathways were found between COVID-19 and ED among which were the top 4 pathways from

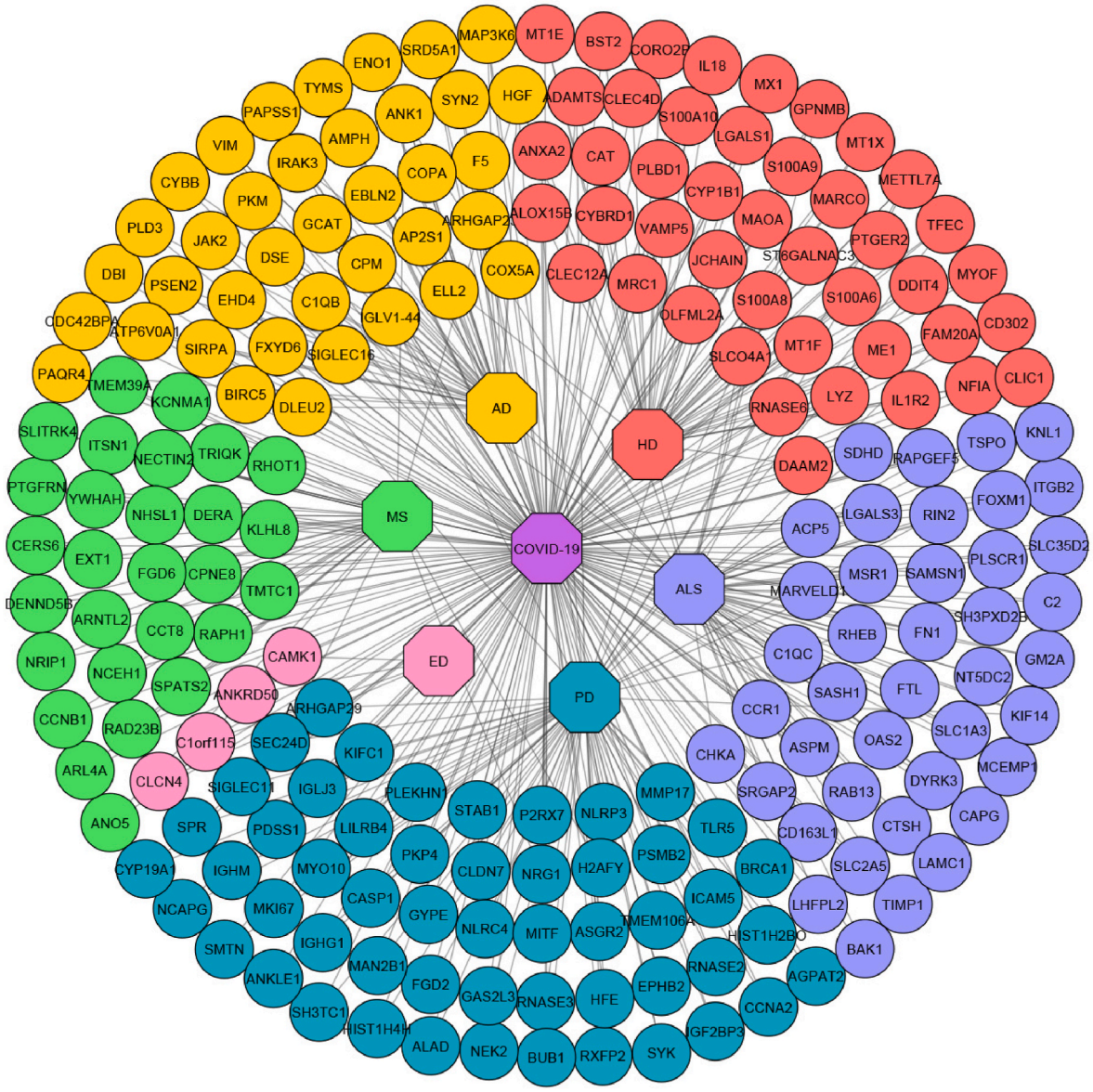


Fig. 2. Genes-Disease Association network (diseasome) of the upregulated genes common between COVID-19 and NDs. Circular node legends are used for genes and hexagonal node legends for diseases.

KEGG, top 4 from Wiki, 2 from BioCarta, and top 4 from Reactome. A total of 45 pathways were found between COVID-19 and HD among which were the top 4 pathways from KEGG, top 4 from Wiki, 2 from BioCarta, and top 4 from Reactome. A total of 32 pathways were found between COVID-19 and MS among which were 2 pathways from KEGG, top 4 from Wiki, top 2 from BioCarta, and top 4 from Reactome. A total of 56 pathways were found between COVID-19 and PD among which were top 4 pathways from KEGG, top 4 from Wiki, top 4 from BioCarta, and top 4 from Reactome are shown in Fig. 4 and the remaining others pathways are shown as a **supplementary file**.

The data obtained from Fig. 4 indicates the Glycolysis/Gluconeogenesis, HIF-1 signaling, Endocytosis, Endocrine and other factor-regulated calcium reabsorption, Natural killer cell-mediated cytotoxicity, Staphylococcus aureus infection, Complement and coagulation cascades, Mineral absorption, Tryptophan metabolism, Histidine metabolism, Arginine and proline metabolism, Cell cycle, Sphingolipid signaling, Osteoclast differentiation, Phospholipase D signaling, NOD-like receptor signaling, and C-type lectin receptor signaling pathway interaction with the number of common genes according to the database of the KEGG pathway.

Meanwhile, Wiki Pathways revealed the Photodynamic therapy-induced HIF-1 survival signaling, Type II interferon signaling (IFNG), Glycolysis and Gluconeogenesis, Complement Activation, TYROBP Causal Network, Mammary gland development, Oxidative Damage, Apoptosis-related network due to altered Notch3 in ovarian cancer, Complement and Coagulation Cascades, MET in type 1 papillary renal cell carcinoma, Association between Physico-Chemical Features and Toxicity Associated Pathways, Prostaglandin Synthesis and Regulation, Oxidative Stress, Zinc homeostasis, Benzo(a) pyrene metabolism, Cell Cycle, Splicing factor NOVA regulated synaptic proteins, Regulation of Microtubule Cytoskeleton and Nuclear Receptors Meta-Pathway interaction with the number of common genes according to the database of the WiKi pathway.

Results from the Biocarta pathway produce the IFN gamma signaling pathway, Metabolism of Anandamide, an Endogenous Cannabinoid, SREBP control of lipid synthesis, Classical Complement Pathway, Stat3 Signaling Pathway, Lectin Induced Complement Pathway, Inhibition of Matrix Metalloproteinases, Alternative Complement Pathway, METS

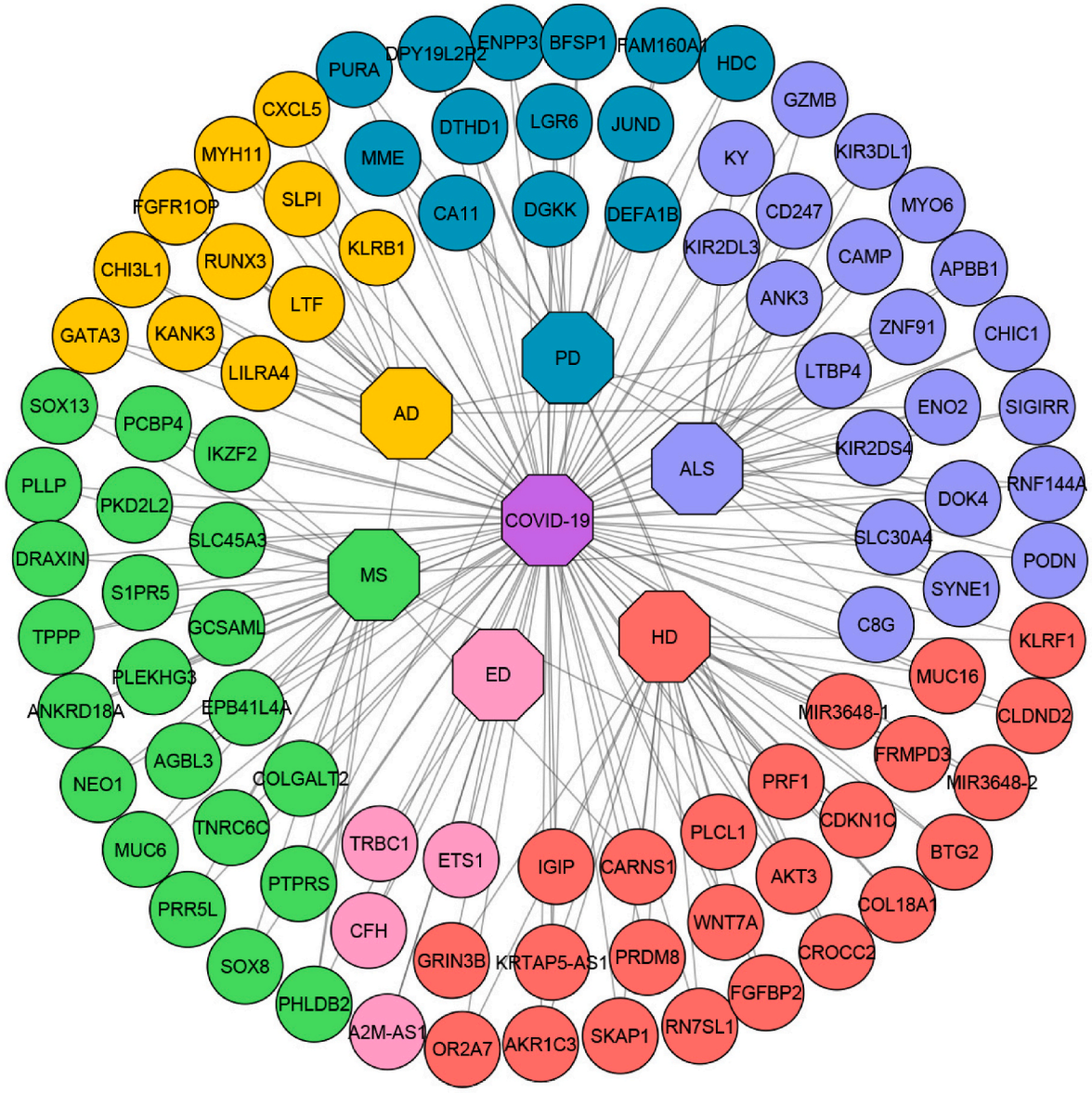


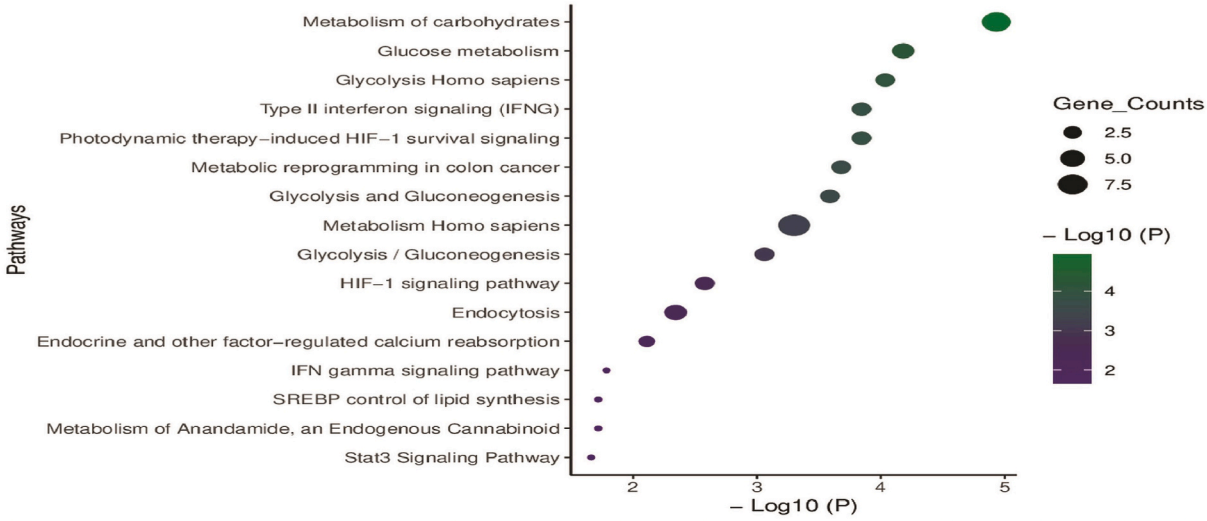
Fig. 3. Genes-Disease Association network (diseasome) of the downregulated genes common between COVID-19 and NDs. Circular node legends are used for genes and hexagonal node legends for diseases.

affect on Macrophage Differentiation, Keratinocyte Differentiation, BTG family proteins, Granzyme A mediated Apoptosis Pathway, and cell cycle regulation, Regulation of cell cycle progression by Plk3, Cell Cycle: G2/M Checkpoint, Neuroregulin receptor degradation protein-1 Controls ErbB3 receptor recycling, FOSB gene expression and drug abuse, D4-GDI Signaling Pathway, cdc25 and chk1 Regulatory Pathway in response to DNA damage, and BRCA1-dependent Ub-ligase activity interaction with the number of common genes according to the database of the Biocarta pathway.

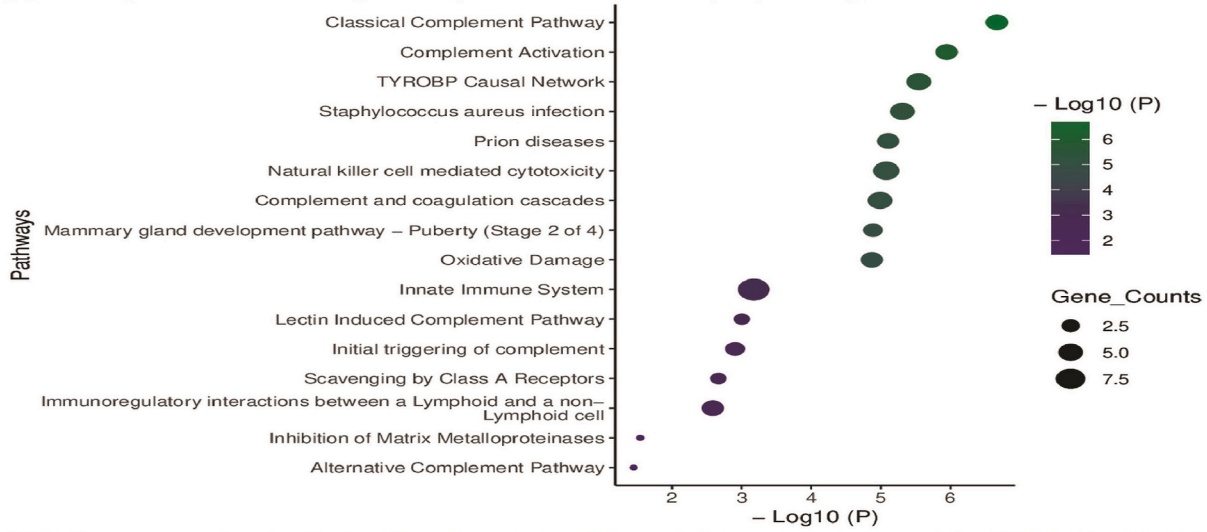
Results from the Reactome pathway include the Metabolism of carbohydrates, Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell, Glucose metabolism, Glycolysis, Metabolism, Translocation of ZAP-70 to Immunological synapse, Innate Immune System, Initial triggering of complement, Scavenging by Class A Receptors, Phosphorylation of CD3 and TCR zeta chains, PD-1 signaling, Regulation of Complement cascade, Response to metal ions, Metallothioneins bind metals, Arachidonic acid metabolism, Dissolution of Fibrin Clot, Chk1/Chk2(Cds1) mediated inactivation of Cyclin B: Cdk1 complex, BMAL1: CLOCK, NPAS2 activates circadian gene expression, TP53 Regulates Transcription of Cell Cycle Genes, GRB7 events in ERBB2 signaling, Inflammasomes, The NLRP3 inflammasome, and NLR signaling pathways interact with the number of common genes according to the database of the Reactome pathway.

3.3. GO enrichment and GO terms tree

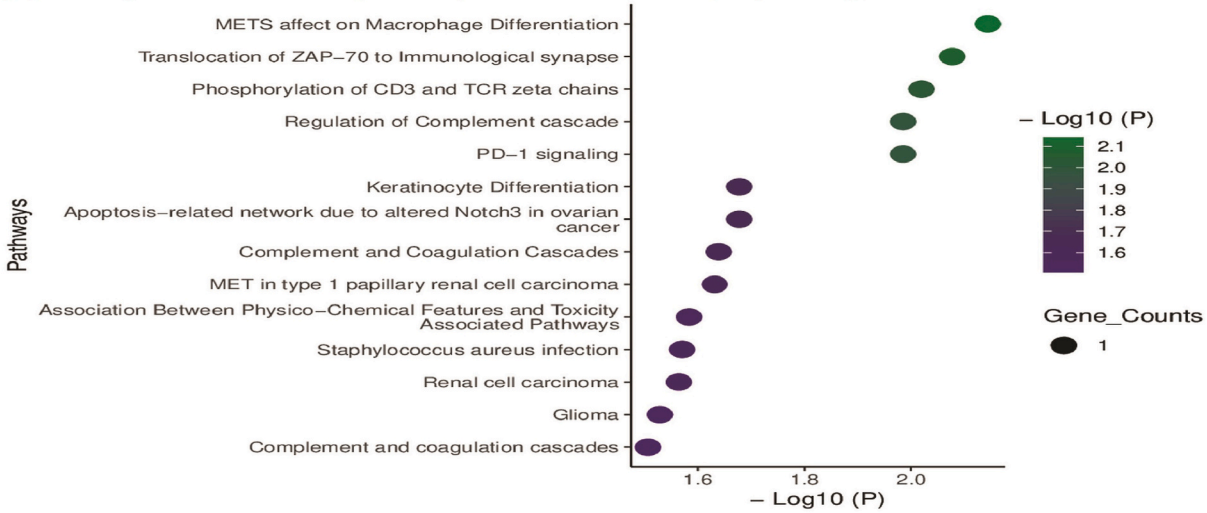
We conducted a GO enrichment analysis for all common DEGs among COVID-19 and NDs to discover common ontological pathways. Through assessing the biological process type of gene ontology, we have identified the pathways of gene ontology. During the study of GO terms, a total of 105 important GO terms were found to be substantially enriched and are summarized in Fig. 5. Fig. 5 demonstrates the most important ontological pathways dependent on the metric of the p-value. Our pipeline reveals the top 19 GO terms between COVID-19 and AD, the top 20 terms between COVID-19 and ALS, 7 terms between COVID-19 and ED, the top 20 terms between COVID-19 and HD, 17 terms between COVID-19 and MS, and the top 20 terms between COVID-19 and PD based on the p-value for the gene ontology group of biological



(a) Pathways associated with significantly common differentially expressed genes of the COVID-19 with AD.

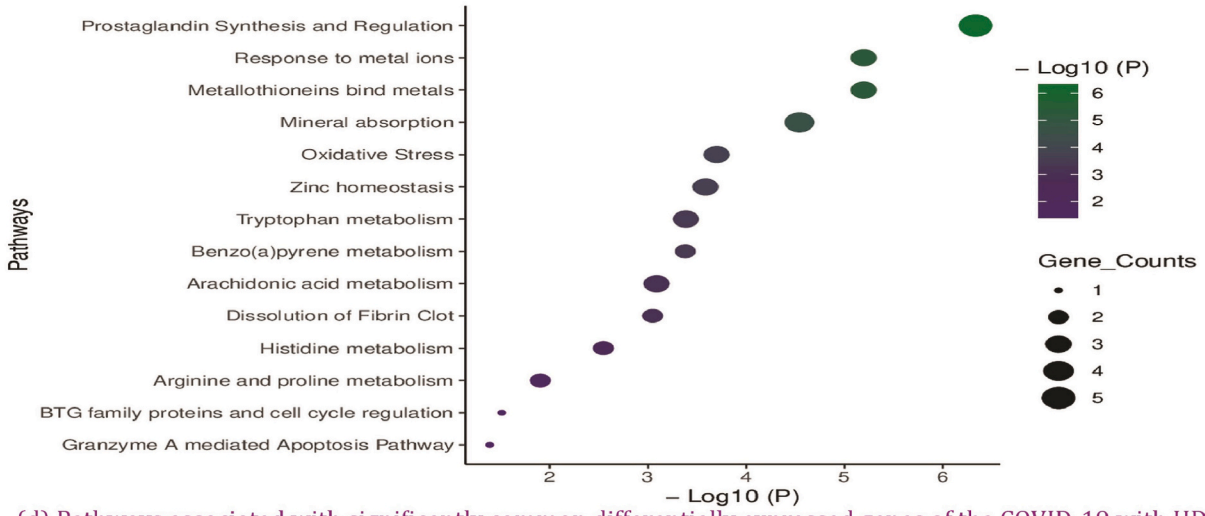


(b) Pathways associated with significantly common differentially expressed genes of the COVID-19 with ALS.

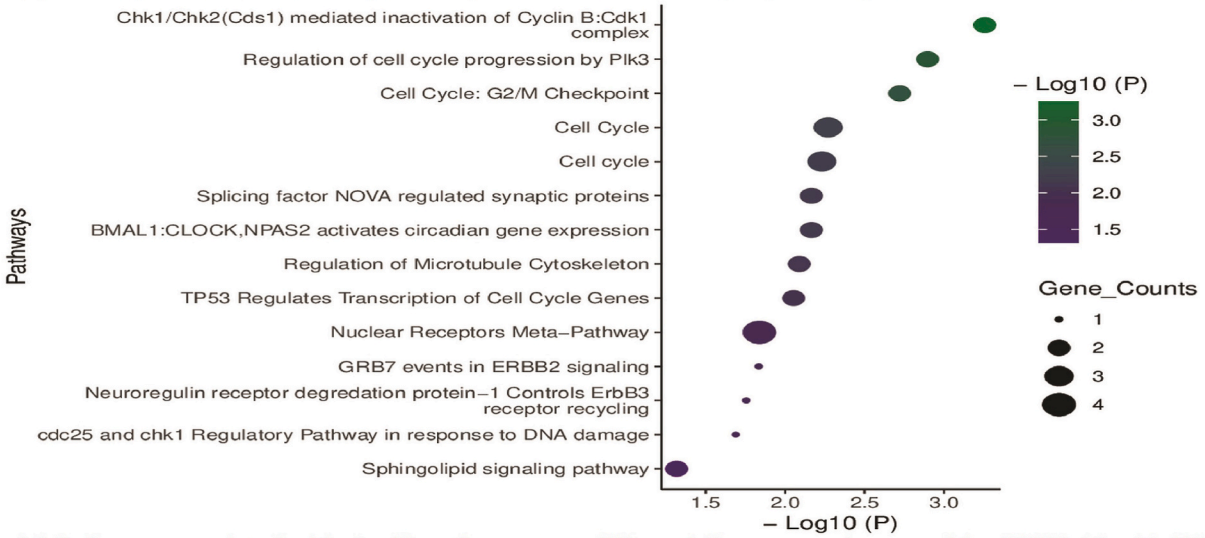


(c) Pathways associated with significantly common differentially expressed genes of the COVID-19 with ED.

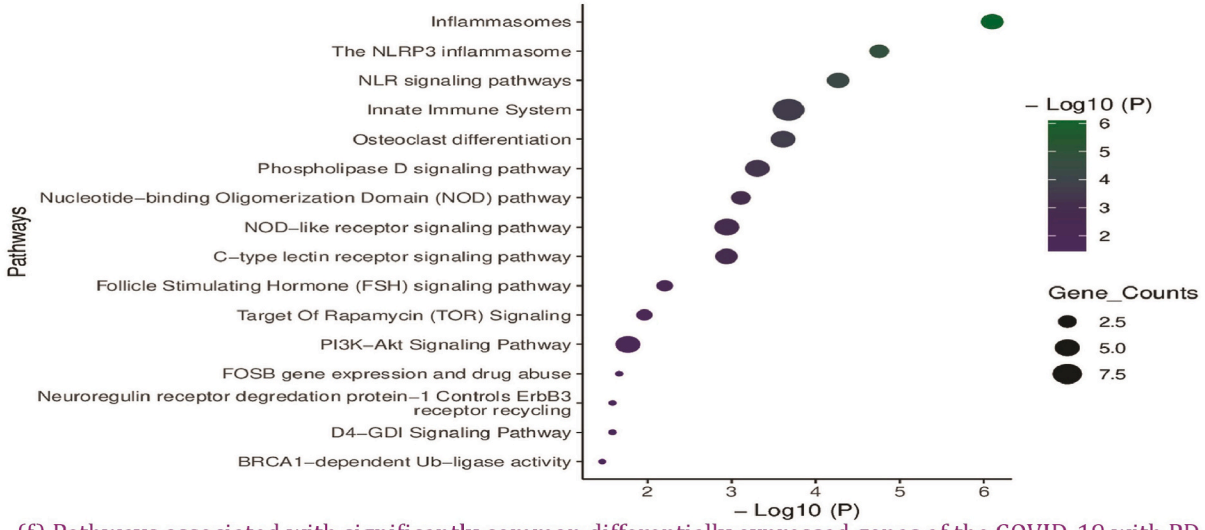
Fig. 4. Top cell signalling pathways between COVID-19 and NDs. Pathways discovered from DEGs were a) pathways linked between COVID-19 and AD b) pathways linked between COVID-19 and ALS c) pathways linked between COVID-19 and ED d) pathways linked between COVID-19 and HD e) pathways linked between COVID-19 and MS and f) pathways linked between COVID-19 and PD.



(d) Pathways associated with significantly common differentially expressed genes of the COVID-19 with HD.



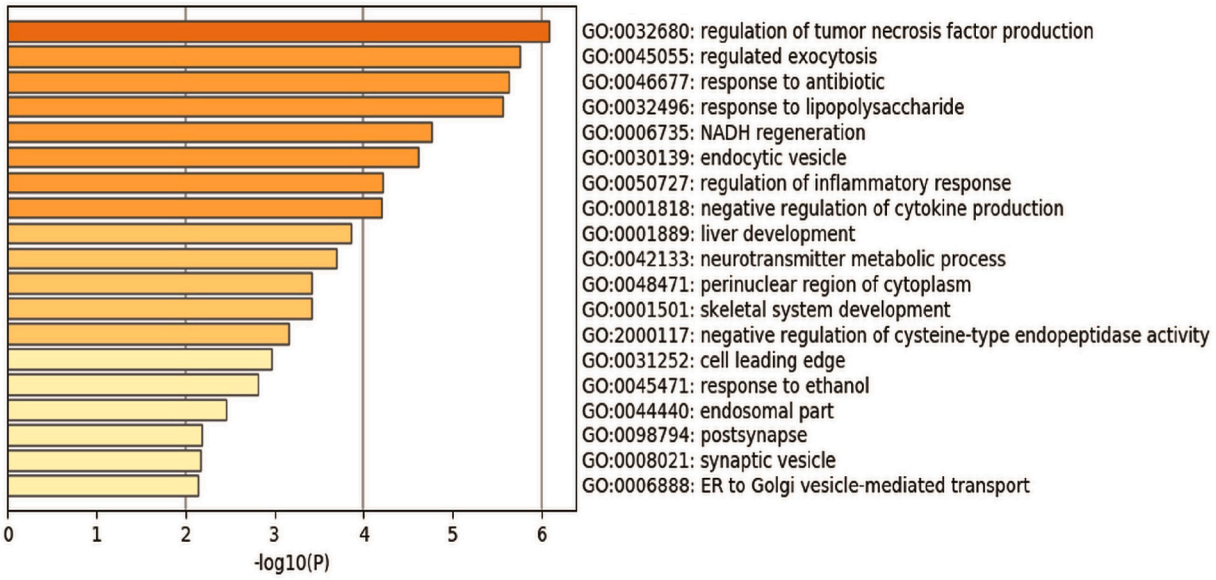
(e) Pathways associated with significantly common differentially expressed genes of the COVID-19 with MS.



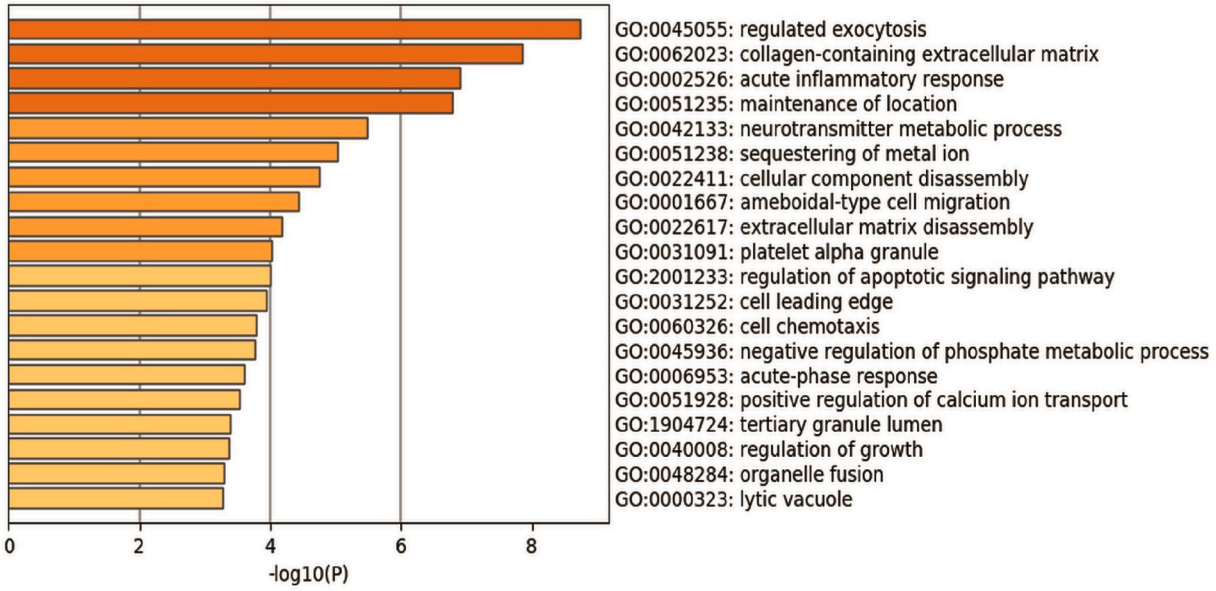
(f) Pathways associated with significantly common differentially expressed genes of the COVID-19 with PD.

Fig. 4. (*continued*).

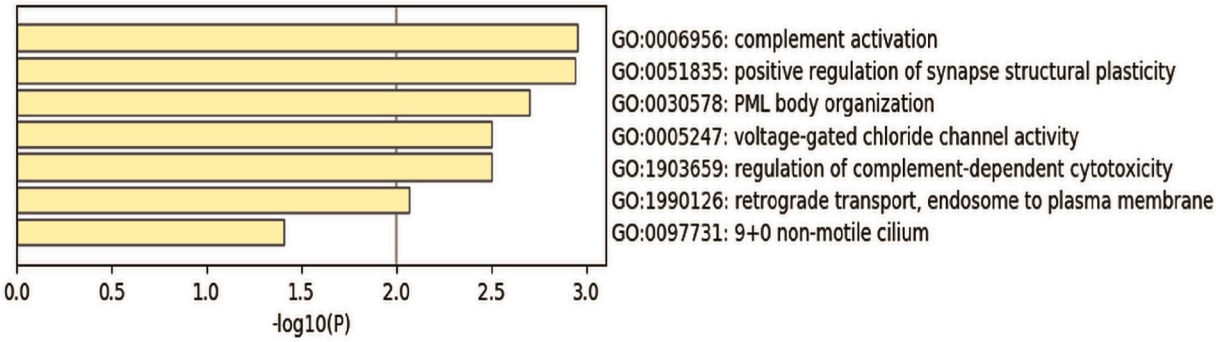
processes shown in Fig. 5. Direct Acyclic Graphs (DAG) are used to define ontologies, in which terms are described as nodes and links as edges. Fig. 6 illustrates how the most important five significant GO terms are spread over the GO graph hierarchy (GO: 0051239: regulation of the multicellular organismal process, GO: 0048584: positive regulation of response to stimulus, GO: 0048731: system development, GO:



(a) Ontology associated with significantly common differentially expressed genes of the COVID-19 with AD.

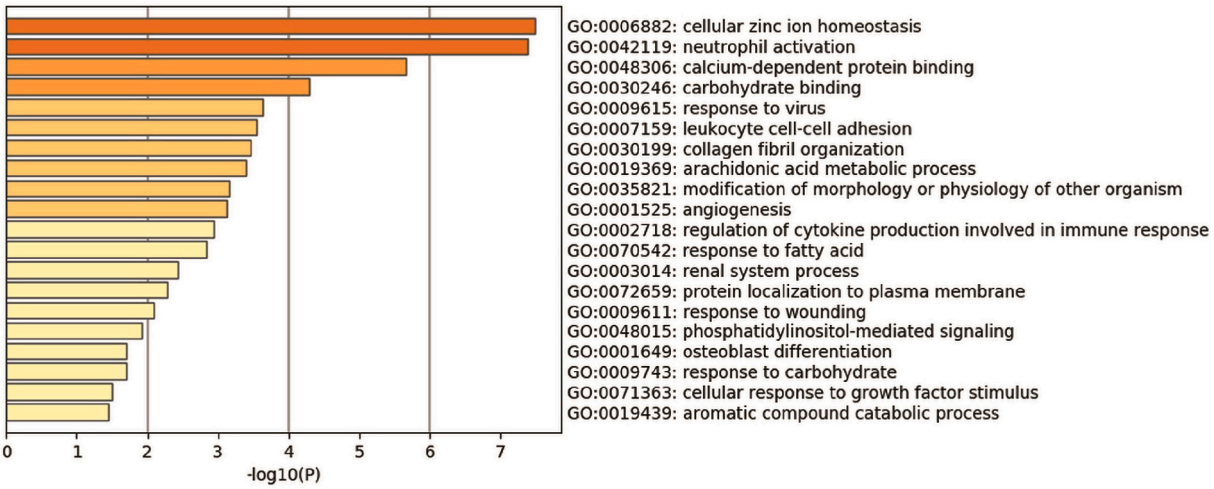


(b) Ontology associated with significantly common differentially expressed genes of the COVID-19 with ALS.

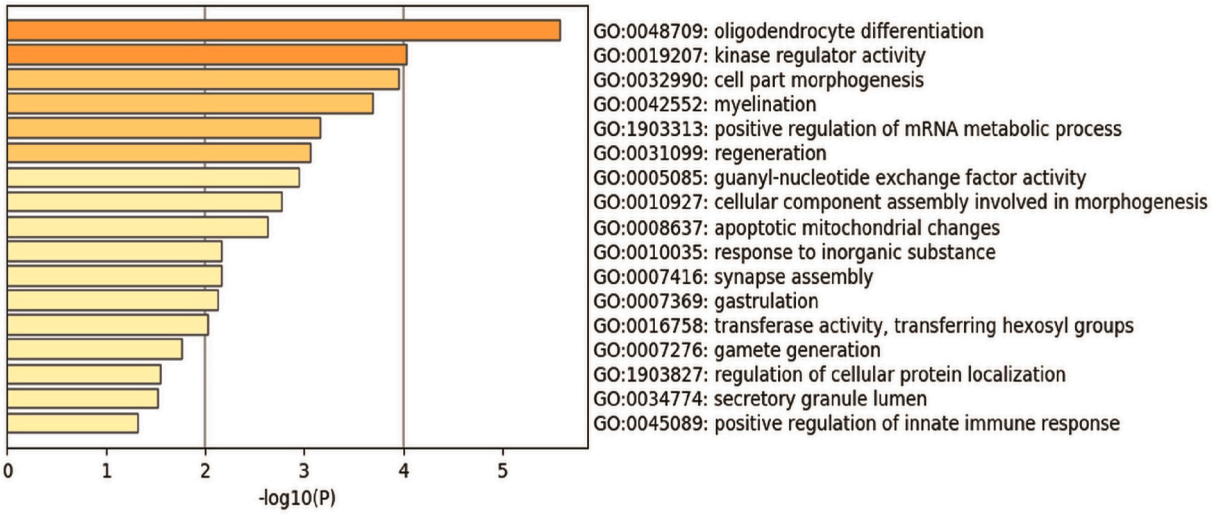


(c) Ontology associated with significantly common differentially expressed genes of the COVID-19 with ED.

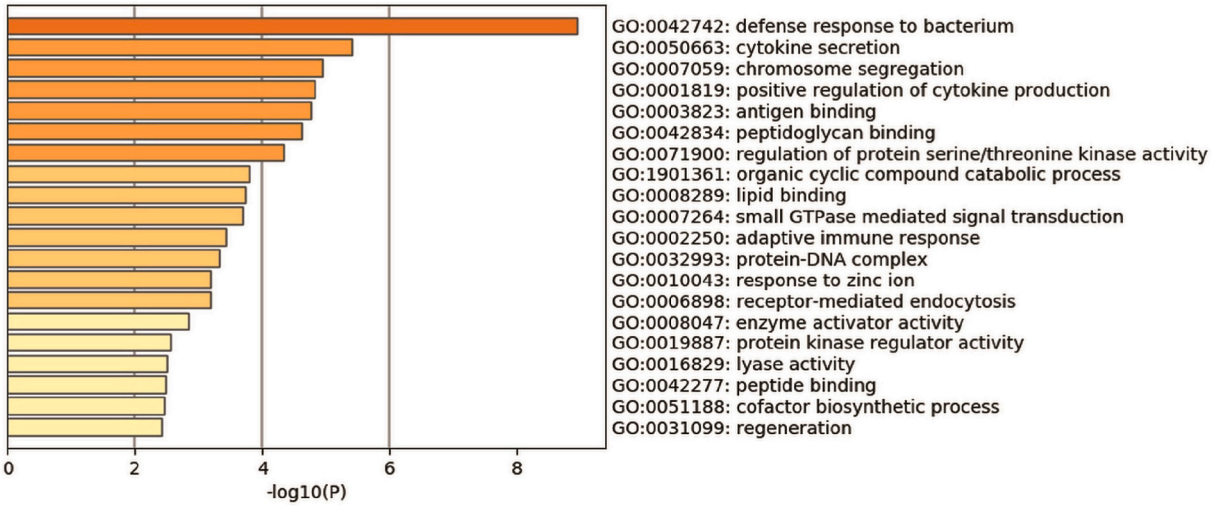
Fig. 5. Top gene ontological pathways between COVID-19 and NDs. Ontological Pathways discovered from DEGs were a) ontologies linked between COVID-19 and AD b) ontologies linked between COVID-19 and ALS c) ontologies linked between COVID-19 and ED d) ontologies linked between COVID-19 and HD e) ontologies linked between COVID-19 and MS and f) ontologies linked between COVID-19 and PD, respectively.



(d) Ontology associated with significantly common differentially expressed genes of the COVID-19 with HD.



(e) Ontology associated with significantly common differentially expressed genes of the COVID-19 with MS.



(f) Ontology associated with significantly common differentially expressed genes of the COVID-19 with PD.

Fig. 5. (*continued*).

01048518: positive regulation of the biological process, GO: 0032501: multicellular organismal process) of the dataset of GSE64810. For GO enrichment study and GO graph structure, we used Fisher's exact test statistics and classical algorithms. Based on p-values, we identified the most significant GO terms (top 5) using a classical enrichment test. The DAG (Directed Acyclic Graph) shows the most important nodes as

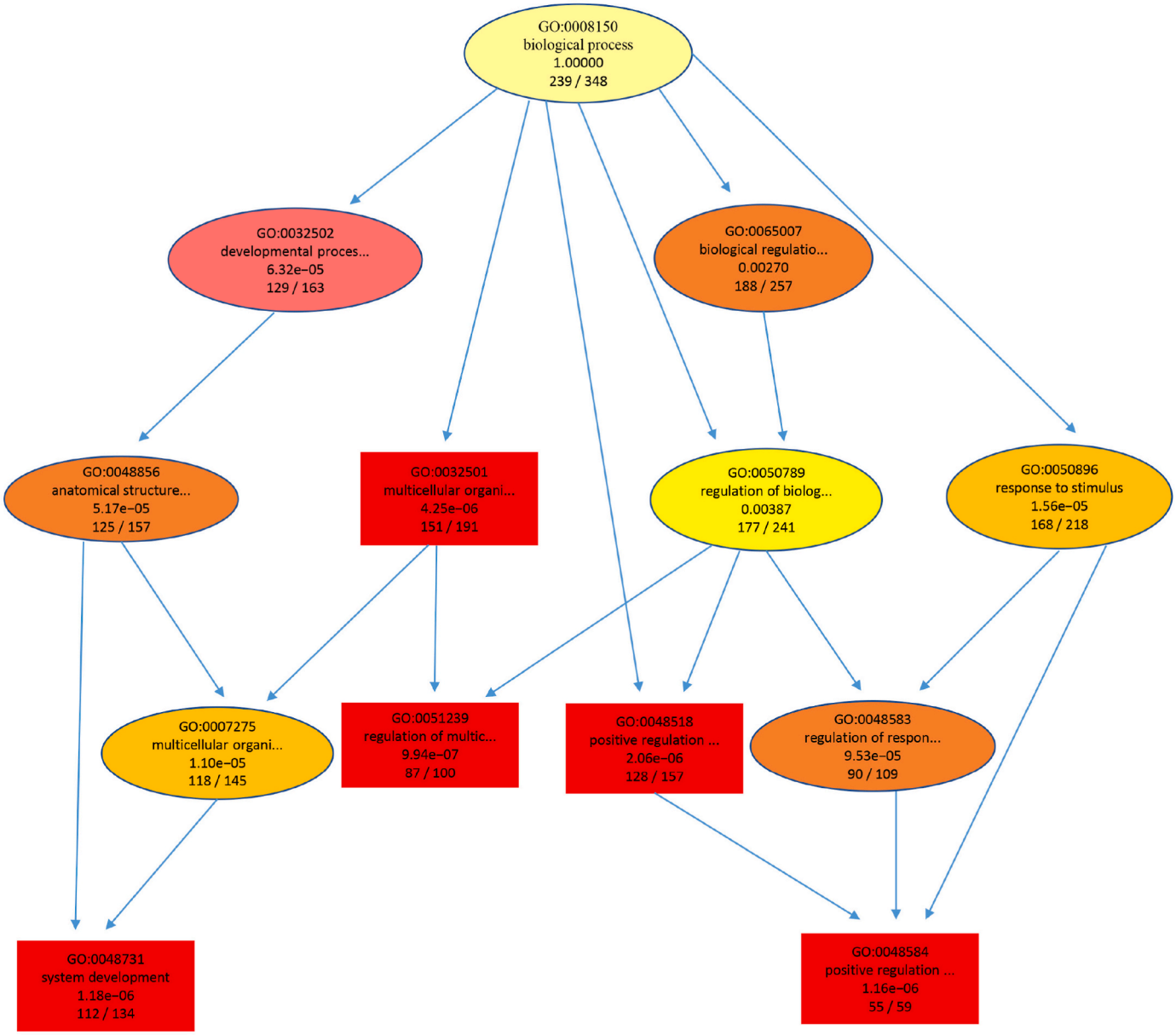


Fig. 6. Direct Acyclic Graphs representing the ontologies for the dataset of GSE64810. The most important terms are represented by red nodes, while the less significant terms are represented by elliptical nodes.

rectangles. For each node in the graph, the first line is GOID, followed by GO term, p-value, and finally, the ratio of the total number of significant genes to the total number of genes annotated for each GO. Black arrows in the DAG demonstrate is-a relationship.

3.4. Computations of gene and GO semantic similarity

Measures of semantic similarity quantify the degree of similarity or correlation between two disease groups, such as COVID-19 and NDs. A computation of semantic similarity returns a numerical value that represents the closeness between COVID-19 and NDs in context. We carried out semantic similarity measures in two groups: semantic similarity in terms of DEGs and semantic similarity in terms of GO between COVID-19 and NDs. Concerning DEGs, measures of semantic similarity are used to quantify the similarities between genes each with a collection of GO terms annotated. The functional similarity between genes is important and is normally determined by semantic similarities between the GO terms annotated for any gene. With regard to GO, semantic similarity tests are used for the purpose of measuring the similarity between two sets of terms representing two entities.

Fig. 7 depicts the results of semantic similarity in terms of DEGs between pathologies. In terms of semantic value, we notice that COVID-19 is linked to all selected neurological comorbidities. Fig. 8 displays the conceptual similarity matrix of GO terms. Based on our semantic similarity value, it seems that the COVID-19 dataset has a notable correlation with many other neurological databases and well links together with all neurological diseases. We have used so many datasets to reduce biases and to maximize the power of the proposed approach. By computing semantic similarity between COVID-19 and each of the ND, we have observed a maximum semantic score of 0.87 between COVID and AD, 0.87 between COVID-19 and ALS, 0.86 between COVID-19 and ED, 0.86 between COVID-19 and HD, 0.84 between COVID-19 and MS and 0.9 between COVID-19 and PD. Among them, we observed that the semantic score between COVID-19 and PD is maximum and the semantic score between COVID-19 and MS is minimum. Similarly, we have found a gene ontology based maximum semantic score between COVID and HD

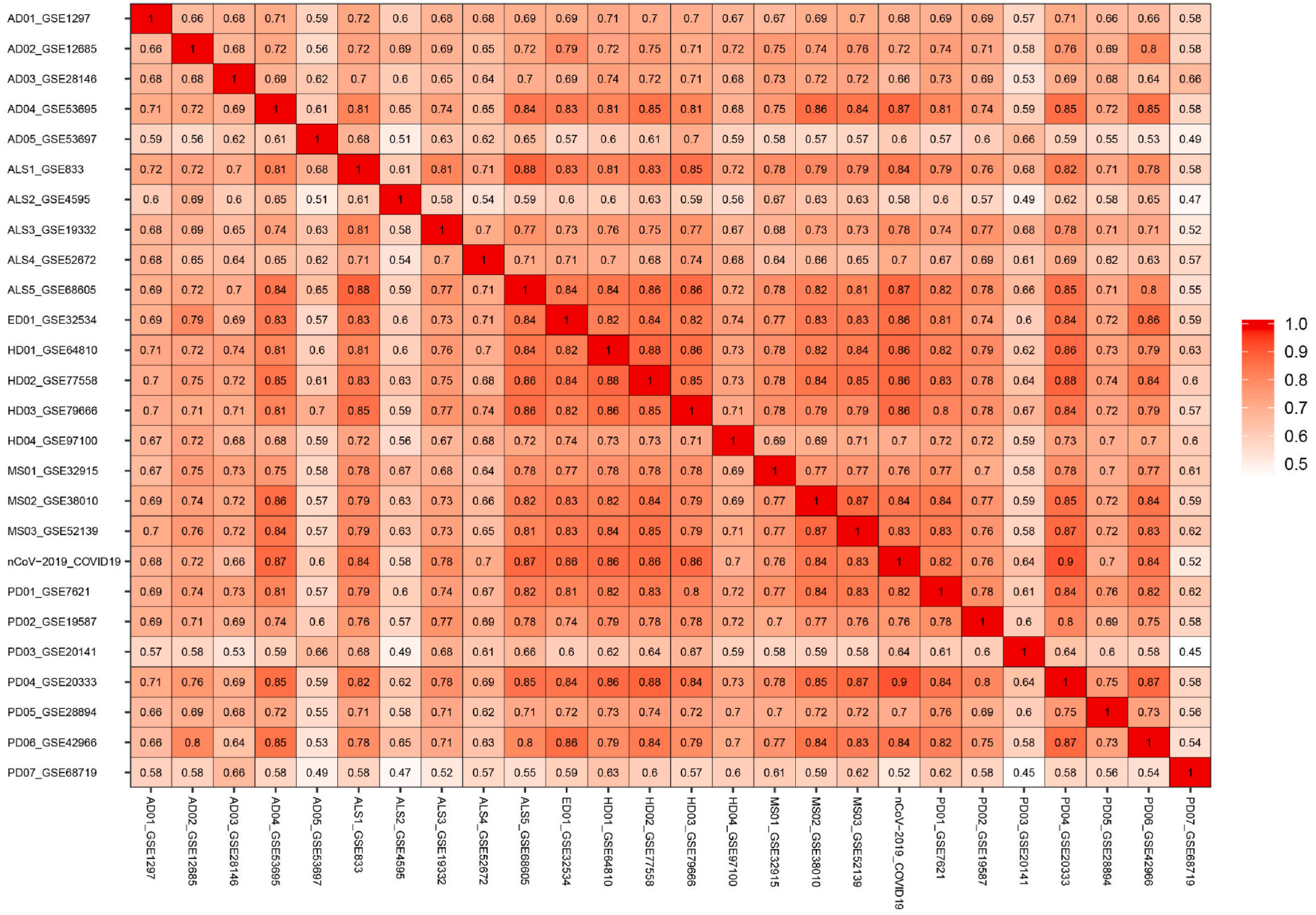


Fig. 7. Results of semantic correlation in terms of DEGs between COVID-19 and NDs. The datasets of the matrix legend were the disease abbreviation, the datset order, and the dataset accession numbers.

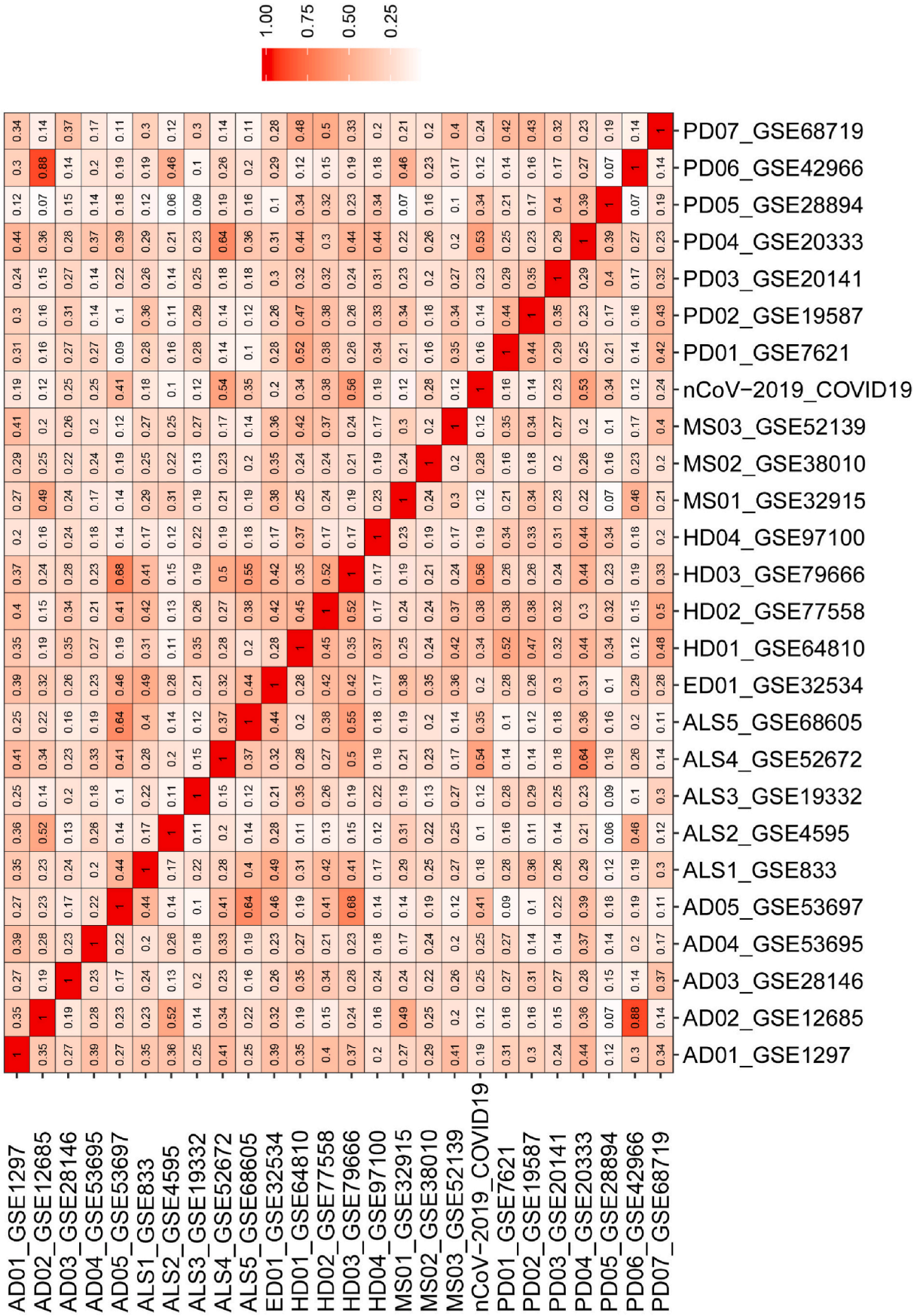


Fig. 8. Results of semantic correlation in terms of GO between COVID-19 and NDs. The datasets of the matrix legend were the disease abbreviation, the datset order, and the dataset accession numbers.

and a minimum semantic score between COVID and ED.

3.5. Study of protein-protein interactions to identify functional networks

We investigated the association between diseases by looking at protein-protein interactions. For this, the common DEGs between COVID-19 and neurological disorders were used to construct the protein-protein interaction (PPI) network in STRING using Network Analyst. Fig. 9 illustrates the participation and interaction of proteins in the PPI network of the signature genes. In the PPI network, proteins are depicted as nodes connected by undirected edges, suggesting the association between two proteins. Moreover, the PPIs network is used for hub protein detection that may help to identify drug molecules for these comorbidities of the disease.

The hub protein of the PPI network is identified using the Cytoscape plugin, as seen in Fig. 9. The hub proteins were sorted according to their degree value 3, showing the number of proteins interactions within the PPI network. Based on the findings of the topological study, we identified the hub proteins (COPB1, AP2S1, COPE, CYBB, JAK2, GATA3, COPA, COX5A, SIRPA, ANK1, HGF) between COVID-19 and AD. Similarly, FN1, ITGB2, C1QB, GZMB, TIMP1, LGALS3, HGF, LAMC1, C1QC, SLC2A5, MCEMP1, CAMP between COVID-19 and ALS. JUN, MAPK1, C3, ETS1, PAX5, CFH between COVID-19 and ED. ANXA2, LYZ, LGALS1, CLEC4D, CLEC12A, IL18, FRMPD3, IL1R2, MARCO between COVID-19 and HD. CDK2, CCT7, CCNB1, CCT8, CCT5, CCT6A, FGD6 between COVID-19 and MS. BRCA1, CCNA2, NCAPG, BUB1, MKI67, KIFC1, NEK2, HIST1H2BO, KIF14, H2AFY, HFE, HIST1H4H between COVID-19 and PD. The abbreviations of all hub proteins are provided as **supplementary file**.

3.6. Identification of controlling biomolecules in the transcriptional and post transcriptional level

Little is understood regarding the identity of transcription factors (TFs) and microRNA (miRNAs or miRs) implicated in the development and progression of NDs owing to comorbidities. In this section, the regulatory biomolecule (i.e. TFs and mi RNAs) controlling DEG of interest at the transcriptional and post-transcriptional levels have been identified by the Network Analyst from the DEGs-Transcription Factors (TFs) and DEGs-MicroRNAs (miRNAs) interaction analysis. To evaluate the DEGs-TFs interaction, we used the JASPAR database. We identified a set of TFs (FOXC1, NFIC, E2F1, YY1, NFKB1) common between COVID-19 and AD. Similarly, JUN, GATA2, CREB1, ANK3, FOXC1, FOXL1 are common between COVID-19 and ALS. HINFP, GATA2, STAT3, FOXC1 are common between COVID-19 and ED. FOXC1, GATA2, YY1, SRF are common between COVID-19 and HD. GATA2, E2F1, FOXC1, FOXL1, TFAP2A are common between COVID-19 and MS. NFYA, FOXC1, FOXL1, GATA2, YY1 are common between COVID-19 and PD using the JASPER database. The abbreviations of all TFs are provided as **supplementary file**. On the other hand, we identified a set of miRNAs such

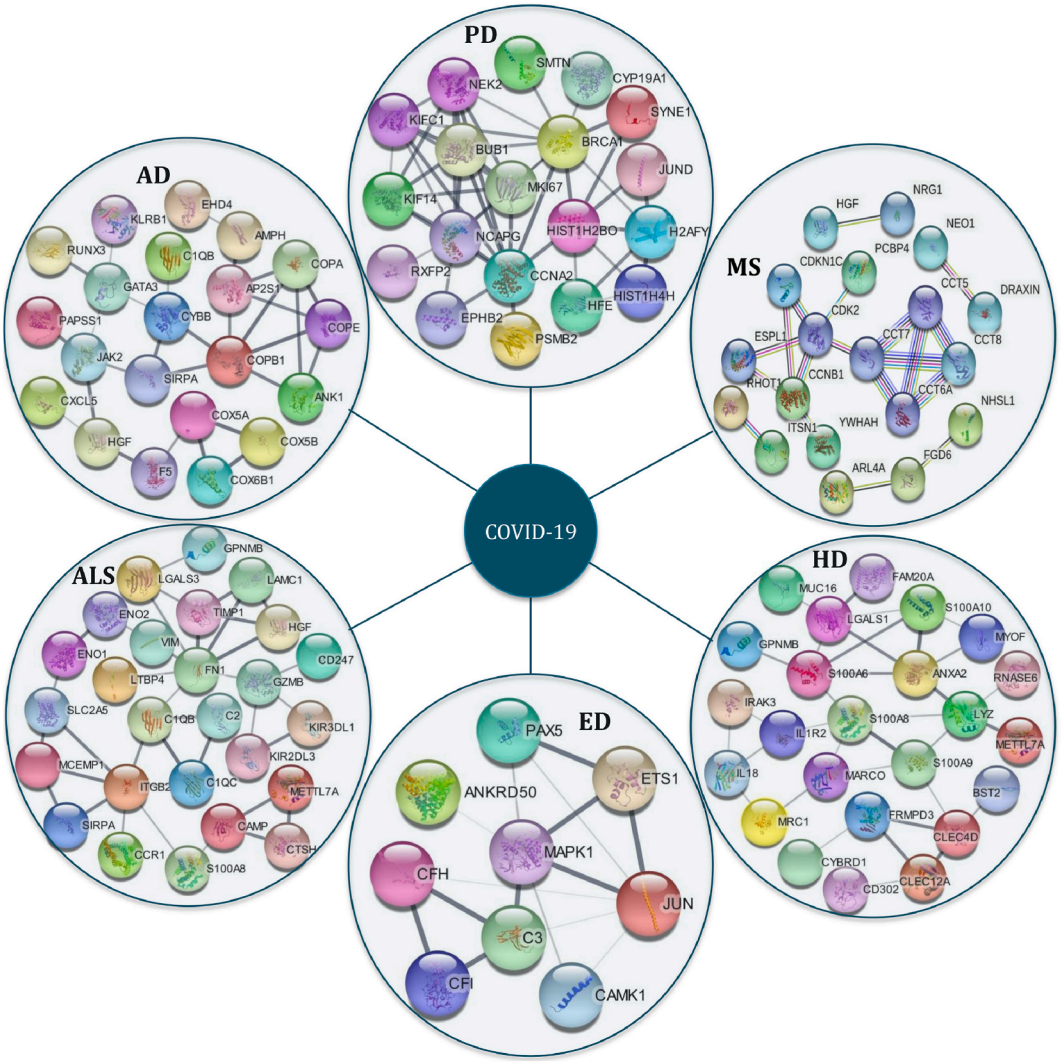


Fig. 9. Network of protein-protein interaction to detect hub proteins built from DEGs common between COVID-19 and NDs.

as hsa-mir-485-5p, hsa-mir-16-5p, hsa-mir-30c-1-3p, hsa-mir-484, hsa-mir-335-3p, hsa-mir-6788-3p, hsa-mir-30c-2-3p common between COVID-19 and AD. Similarly, hsa-mir-485-5p, hsa-mir-3929, hsa-mir-4478, hsa-mir-4419b, hsa-mir-6884-5p, hsa-mir-7977, hsa-mir-26b-5p common between COVID-19 and ALS. hsa-mir-450b-5p common between COVID-19 and ED. hsa-mir-329-3p, hsa-mir-362-3p, hsa-mir-8485 common between COVID-19 and HD. hsa-mir-5011-5p, hsa-mir-1277-5p, hsa-mir-190a-3p, hsa-mir-32-5p, hsa-mir-92a-3p, hsa-mir-8485 common between COVID-19 and MS. hsa-mir-192-5p, hsa-mir-215-5p, hsa-mir-16-5p, hsa-mir-186-5p, hsa-mir-124-3p, hsa-mir-155-5p common between COVID-19 and PD using miRTarBase databases. Figs. 10 and 11 demonstrate the TF-DEG interaction network and miRNA-DEG interaction network to reveal TFs and miRNAs. The amethyst color node represents the TFs and the royal blue color node represents the miRNAs. Node size depends on the degree of the node. The degree of a node implies the number of links it has. Higher-degree nodes are known as important hubs for the network.

3.7. Potential targets verifications

With the use of bioinformatics tools, we have built up a pipeline that will help us to discover biomarkers for which COVID-19 has an impact on the development of neurological diseases. To our knowledge, the impact of COVID-19 on NDs development is not identified by these techniques. There are many more cross-checking tests for the given findings, but they are excessively time-consuming to be clinically useful. A benchmarking study evaluates the results of well-established bioinformatics approaches. The goal of benchmarking studies is to thoroughly compare the findings of various techniques with gold-standard benchmark datasets in order to evaluate the strengths of the results obtained from proposed methods. dbGap, OMIM, and OMIM Expanded are often used to serve as the gold standard database against which we may compare our findings. Our investigations make use of gold-standard datasets to serve as a benchmark and well-defined scoring criteria to evaluate our findings. To evaluate our findings, we fed the dysregulated DEGs (discovered from COVID-19 by our pipeline as a potential candidate.) into the online gene set enrichment analysis tool, Enrichr and retrieved enriched genes and their disease associations from the three gold-standard datasets [30]. We choose only neurological and neurodegenerative diseases for the construction of the disease-gene association network among many diseases with their enriched genes. We identified five of our chosen NDs within the list of NDs gathered from the stated databases after many stages of statistical analysis. Using Cytoscape [72]; Our enriched disease-gene association network is constructed utilizing the list of disorders as in Fig. 12.

Furthermore, we discovered that the genes we identified in Fig. 12 have previously been demonstrated to be related to NDs development in other research. Specifically, Vo Van Giau et al., Longfei Jia et al. and Carlos Cruchaga et al. found APP, PSEN1 and PSEN2 to be associated with AD incidence [76–78]; Callista B. Harper et al., Daniel G.Calame et al. and Callista B Harper et al. found a link between SV2A and EP [79, 80]. Lishou Pan et al. showed ANG to be linked to ALS incidence [81]; M Allen et al., A Spurkland et al., and Lineu Cesar Werneck et al. shown the association of DQA1, DQB1, DRB1, and DPB1 to MS progression [82–84]; Victoria S Burchell et al. identified a link between PINK1 and PD [85]; Tianwen Huang et al. showed PINK1 and FBXO7 to be associated with PD [86]. Our findings are rigorously benchmarked against gold-standard data to build confidence in the results we get via our computational approach. When we look at the literature to see which of our discovered genes have been clinically utilized as biomarkers for GBM development. Therefore, it suggested that COVID-19 may have a strong interaction with NDs.

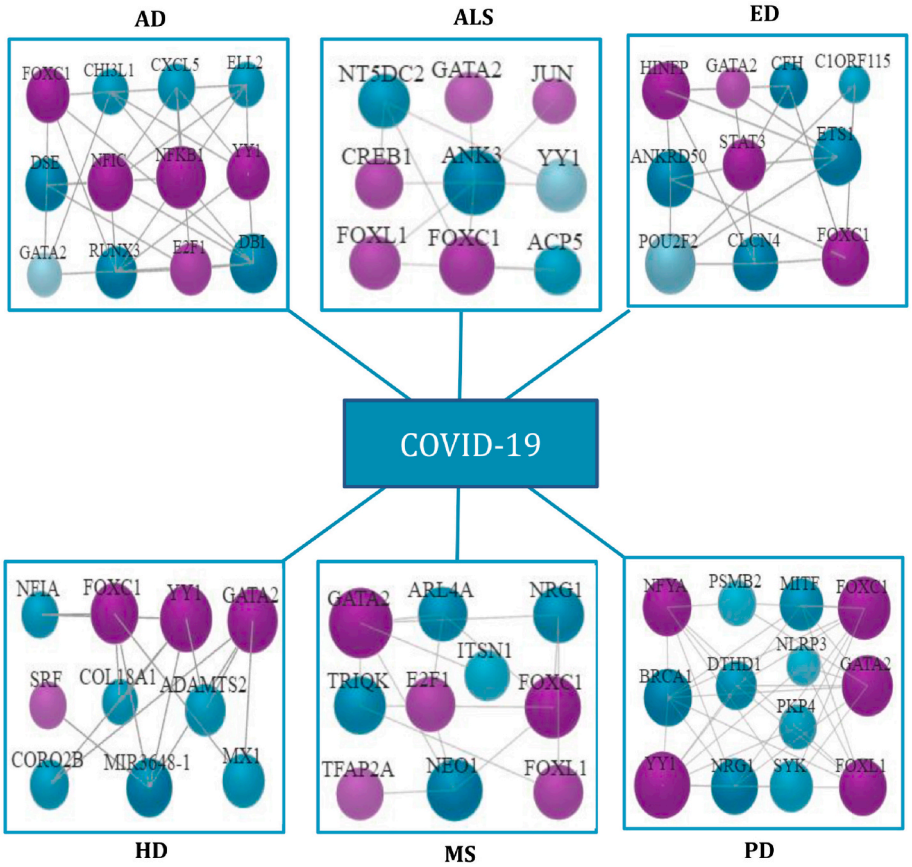


Fig. 10. Results of DEGs-TFs interactions to reveals TFs that regulate DEG of interest common between COVID-19 and NDs at the transcriptional and post-transcriptional levels. The amethyst color node represents the TFs.

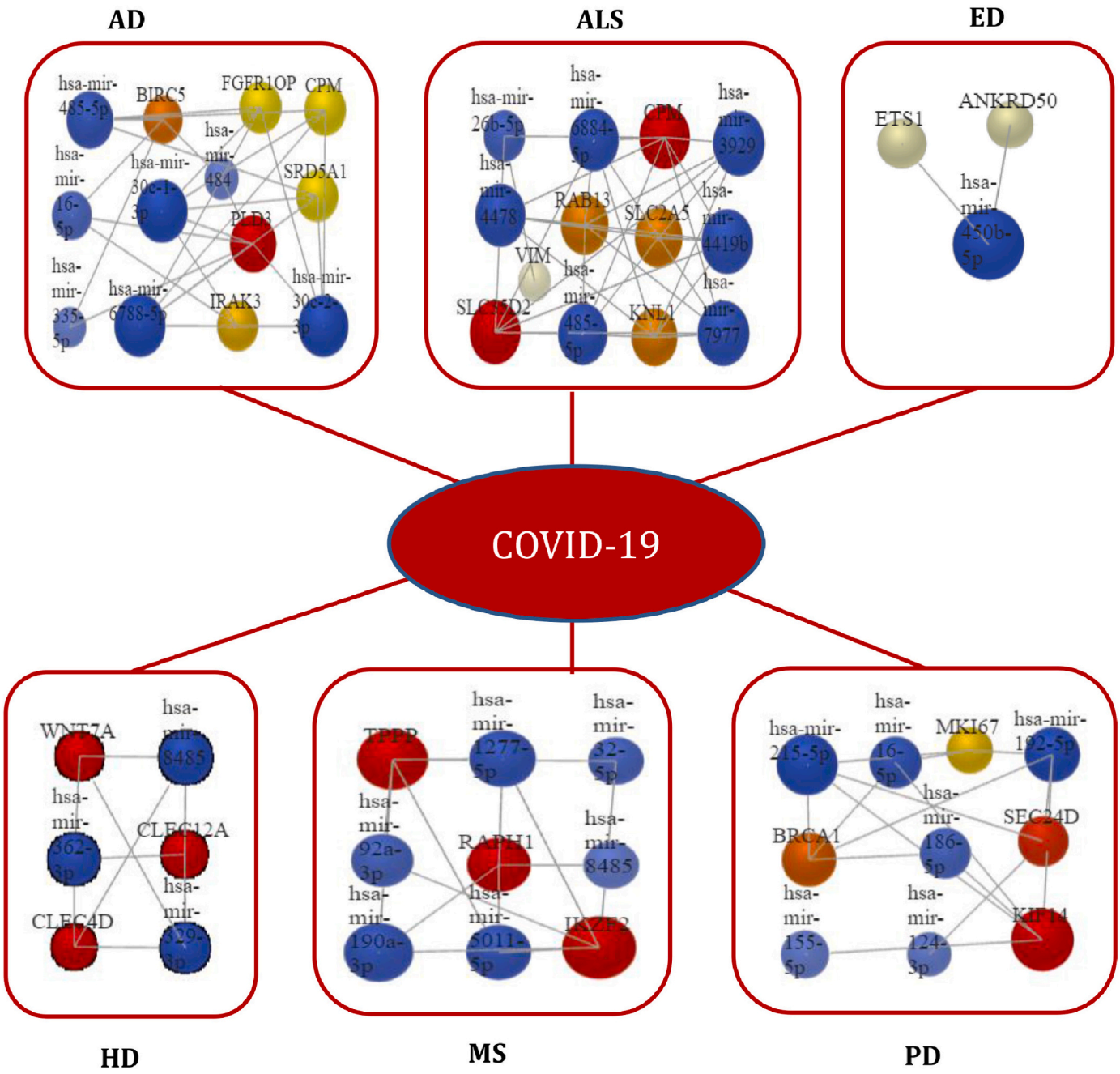


Fig. 11. Results of DEGs-miRNAss interactions to reveal miRNAs that regulate DEG of interest common between COVID-19 and NDs at the transcriptional and post-transcriptional levels. The royal blue color node represents the miRNAs.

4. Discussion

In this work, we have developed an empirical pipeline of the bioinformatics and network-based approaches for comorbidity studies and demonstrated its usefulness for mining knowledge from public databases. We explored the genetics of COVID-19 to the progression of neurological disorders, where intra- and interconnections between genes, proteins, and pathways may provide useful knowledge regarding their functions in the development of those diseases. We identified which genes were differentially expressed in each dataset and to find shared genes, we matched COVID-19's DEGs to one of the six other neurological diseases of concern. We find the greatest number of common genes between COVID-19 and PD, in comparison, we noticed the least number of common genes between COVID-19 and ED, as seen in Figs. 2 and 3. We identified important cell signaling mechanisms and biological gene ontological pathways using gene set enrichment analysis in order to investigate the relationship of COVID-19 with neurological diseases. Fig. 4 shows the findings from the pathway databases of KEGG, WiKi, Biocarta, and Reactome. Among the identified pathways we observed that some pathways have been shown previously to be associated with COVID-19 and NDs. The glycolysis/gluconeogenesis and hypoxia-inducible factor-1 (HIF-1) signaling pathways are shown to be associated with COVID-19 and ND [87,88]. Endocytosis is used by SARS-CoV-2 to enter the host cell and induce COVID-19 [89] and the alteration in the endocytic pathway is thought to play a key role in the pathogenesis of NDs [90]. Type II interferons (IFNs) have been linked to higher COVID-19 severity [91] and the development of ND [92]. It is proposed that astrocyte SREBPs are involved in neuronal function in the

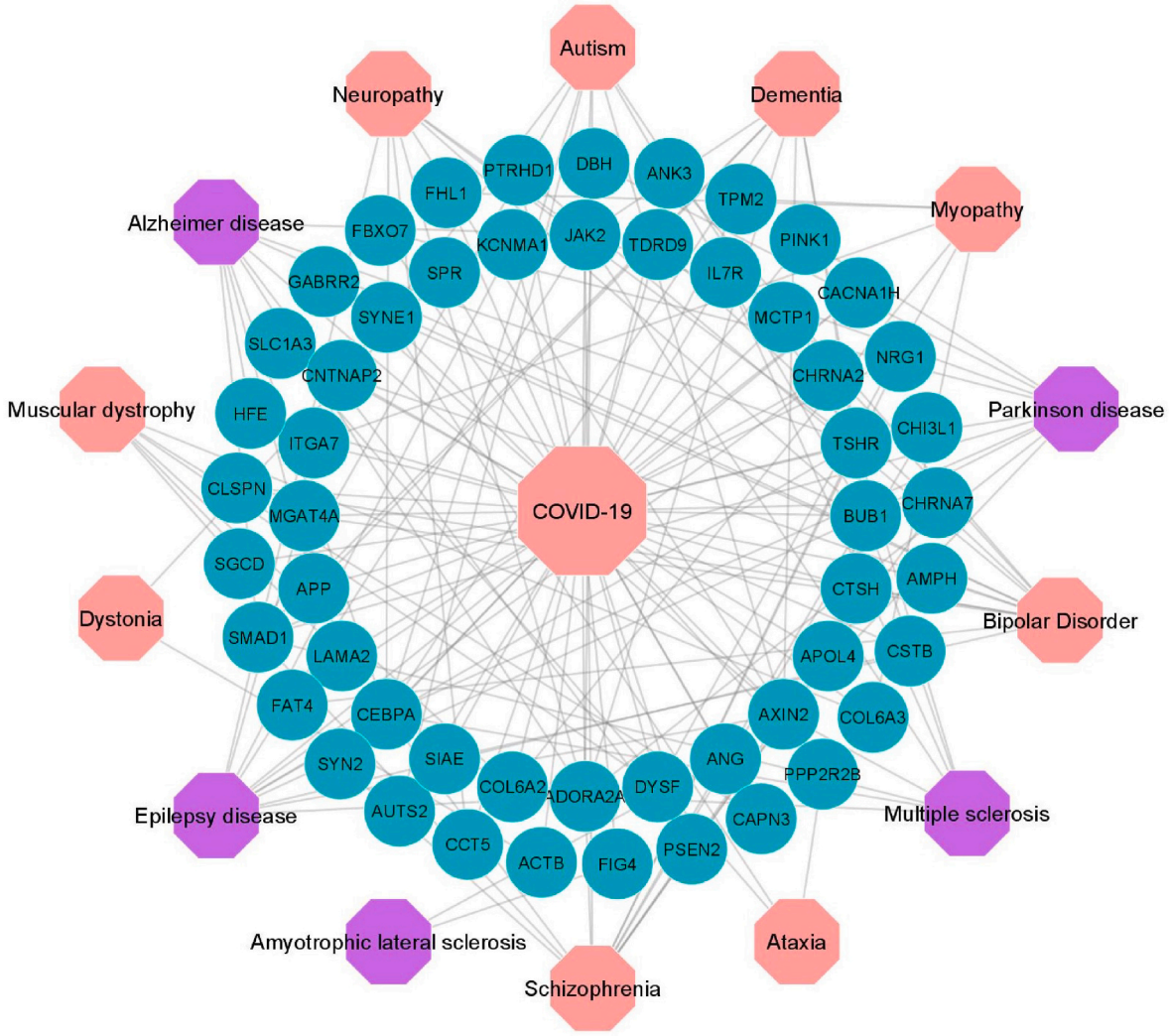


Fig. 12. Gene-disease association network demonstrating the validity of our research. Various NDs are represented by red-colored octagon-shaped nodes. The five NDs we chose are represented by violet-colored octagon-shaped nodes, nodes with round-shaped teal-colored indicate genes that are differently expressed for COVID-19.

central nervous system [93]. The STAT3 pathway plays a novel role in neural progenitor cell differentiation. During brain inflammation, inhibiting STAT3 inhibits astrogliogenesis and promotes neurogenesis [94] and the mechanisms of STAT3 contribute to COVID-19 pathogenesis [95]. Impaired glucose metabolism is linked with severe COVID-19 infection [96] and altered glucose metabolism regulation in the brain is connected with neurodegenerative diseases [97]. Bacteremia caused by Staphylococcus aureus is linked with a significant death rate in individuals hospitalized with COVID-19 [98] and has been linked to increased neurodegeneration [99]. NK cell-mediated cytotoxicity has also been involved in different brain diseases [100] and associated with SARS-CoV-2 viral RNA shedding and mortality in COVID-19 patients [101]. The pathology of COVID-19 and neurodegenerative diseases is affected by oxidative stress [102,103]. The development of lung damage in COVID 19 is linked to the activation of conventional and alternative complementary pathways [104]. Inhibition of matrix metalloproteinases has a role in the development of COVID-19 [105] and the neuroinflammatory response in many neurological disorders [106]. Variability in innate immune system components is a major factor to the COVID-19 caused by SARS-CoV-2 [107]. The innate immune system is a critical mechanism that activates microglia, causes neuroinflammation, and contributes to clinical issues including neurodegenerative disorders [108]. Apoptosis may have a role in neuronal cell death in certain diseases and cell death is a factor in many neurological diseases [109] and COVID-19 severity is linked to apoptosis-induced T-cell lymphopenia [110]. A growing number of recent studies show the significance of the PD-1/PD-L pathway in CNS diseases [111] and the role of PD-1/PD-L1 in COVID-19 [112]. The complement activation plays the role to contribute COVID-19 severity [113]. Essential mineral deficiencies or excesses (e.g., iron, zinc, copper, and magnesium) may impair brain development and neurophysiology, resulting in neurodegenerative disorders [114] and it has been implicated in the pathophysiology of COVID-19 [115]. Tryptophan is metabolized mainly via the kynurenine pathway, which has significant effects on central nervous system neurons and causes neurodegenerative diseases [116]. The tryptophan has a function in the immune response to SARS-CoV-2 and possible connection to the clinical severity of the COVID-19 [117]. Zinc inadequacy has demonstrated that it affects and increases neurogenesis, leading to learning and memory loss. Impaired zinc homeostasis is also indicated as a neurodegenerative disease risk factor [118]. Zinc deficiency may exacerbate immune system dysregulation and increases vulnerability to infections caused by COVID-19 [119]. Dysregulation of the cell cycle has been linked to the development of neurodegenerative diseases [120]. The alteration in normal cell cycle regulatory systems caused by SARS-CoV-2 may damage cell physiology and may eventually lead to COVID-19 diseases [121]. Alterations in arachidonic acid (AA)

metabolism has been linked to neurological and neurodegenerative diseases [122] and a potential association between the AA pathway and COVID-19 pathophysiology [123]. Sphingolipids are a diverse and complicated family of lipids found in the central nervous system (CNS). Alterations in sphingolipid metabolism affect the central nervous system [124] and are associated with COVID-19 [125]. The neuronal cytoskeleton serves a vital role in sustaining neuronal functioning. Dysregulation of neuronal architecture is associated with both injury and diseases of the central nervous system [126] and regulation of cytoskeleton is associated with COVID-19 [127]. The PI3K/AKT signaling pathway is involved in various aspects of COVID-19 [128]. The regulatory mechanisms of the PI3K/AKT/mTOR signaling pathway are associated with the development of neurodegenerative diseases [129]. Severe COVID-19 instances are characterized by a severe inflammatory response which may lead to organ failure and patient mortality in the long run [130]. Recent inflammasome discoveries have disclosed new molecular pathways that contribute to a wide variety of neurological diseases [131]. The NLRP3 inflammasome is known as a critical component in the development of neuroinflammation which is identified as a causal factor in a variety of neurological disorders [132] and the NLRP3 inflammasome is involved in the pathogenesis of COVID-19 [133].

For the identification of Gene Ontology (GO) terms, the identified differentially expressed genes have been used. As per the p-value, GO terms were chosen. The GO terms with the relation between COVID-19 and each ND in the biological process category of gene ontology are shown in Fig. 5. For each chosen pathology, Direct Acyclic Graphs (DAG) were built for semantic similarities, and Fig. 6 displays the DAG for the dataset of GSE64810. The high level of genomic similarity can be caused by the analogous pathogens and clinical presentation of the disease. Our findings of semantic similarities suggest that COVID-19 is highly linked to selected neurological disorders. The association between protein-protein interactions, TF-DEG, and DEG-miRNA interactions has also been discovered. The subsequent study of the PPI network offers a deeper understanding of the fundamental underlying processes that drive progression. That is why we integrated the findings of a statistical investigation into the pattern of protein interaction to create a PPI network across the DEGs we have defined. Topological analyses were used to find hub proteins (i.e., hubs) that engage in several pathways. From the study of the PPI network, we found 11 proteins between COVID-19 and AD. Similarly, 12 proteins between COVID-19 and ALS. 6 proteins between COVID-19 and ED. 9 proteins between COVID-19 and HD. 7 proteins between COVID-19 and MS. 12 proteins between COVID-19 and PD as shown in Fig. 9. These proteins are concerned with the comorbidity of COVID-19 and NDs that could be regarded as candidates for prospective drug targets. TFs regulate transcription rates while miRNAs are important players in RNA silencing and post-transcriptional modulation of gene expression. In various complicated diseases, these regulatory biomolecules serve as possible biomarkers. Both are thus essential for understanding the development of these diseases. Keeping this part in memory, the behaviors of TF-DEG and miRNAs-DEG interactions that are studied for the control of common differentially expressed genes are visualized in the coregulatory TF-miRNA network in Figs. 10 and 11. In this regard, this analysis unveiled the connection between common DEGs and their respective TFs and regulatory miRNAs. During the development of particular diseases, TFs and miRNAs typically attack host proteins to modify their expression. The analysis shows 29 TFs and 29 miRNAs as shown in Figs. 10 and 11.

Identification of the interconnection at the molecular level within a collection of pathologies will enrich our understanding of the mechanism of the disease process which would potentially contribute to more precise diagnoses and more efficacious therapies. Beyond simply identifying new biological processes, the usage of semantic correlations in terms of genes and GO terms to measure disease comorbidity score improves identification and characterization of these disease comorbidity. For the disease comorbidity analysis, the number of previous methods was developed by analyzing datasets from a particular omics experiment or from a clinical trial such as comoR [134]; POGO [135]; comorbidity4j [136]; comorbidity [137] and CytoCom [138]. The R module comoR analyses relative risk and phi-correlation for identifying associated genes and comorbidity prediction pathways where the author just looks at gene expression and molecular information [134]. Moni et al. developed a 'POGO" R software method to assess disease comorbidity using omics, pathology, and ontological data [135] but the genetic influences on diseases were not taken into account in this study. Ronzano et al. developed the Comorbidity4j software framework to identify a number of comorbidity indexes using clinical data in Ref. [136]. Gutièrrez-Sacristán et al. introduced a comorbidity approach that conducts disease comorbidity analysis incorporating clinical evidence and information dependent on genotype-phenotype, but the hereditary impact on diseases was not taken into consideration by this method [137]. Moni et al. developed CytoCom for the Cytoscape app to represent the network for disease comorbidity [138]. Compared to other recent approaches, the number of prior reported methods concentrated on identifying the relationships between diseases by taking into account particular omics or clinical datasets. In comparison, we have adopted an integrated methodology utilizing enormous amounts of publicly accessible datasets of gene expression which is a highly efficient way of identifying molecular mechanisms related to the interaction of comorbidity. The usage of too many datasets maximizes this approach's strength by reducing data set biases and maximizing knowledge about other prior research. It is currently unknown whether there are any previous comorbidity studies using Gene Set enrichment and semantic comparisons to identify the comorbidity interactions between COVID-19 and ND but we identified the interactions at the molecular level using Gene Set Enrichment and semantic similarity-based approaches which outperforms the previous approaches. Our approach ensures the ability to reuse accessible data and to identify DEGs, GO terms, molecular mechanisms, PPIs, hub proteins, TFs, and miRNAs that induce disease. The results reported in this study were enhanced by the use of diverse datasets, help us to fill a wide gap of biological knowledge in COVID-19 and the understanding of the interactions between the COVID-19 and its neurological comorbidities. Thus, this approach may be useful in discovering new knowledge from already released datasets. Since COVID-19 and its neurological comorbidities are not recommended for specific antiviral treatment. This bioinformatics and network-based analysis by using genomics, omics, miRNA, and molecular data will offer an insight into the COVID-19 and its ND comorbidity which will help to diagnose disease risk, drug treatment, and dosage selection, and eventually, it will reflect the advancement of personalized medicine. Furthermore, physicians and medical professionals may use this method to learn more about the basic disease mechanisms that underpin the pathology and etiology of disease comorbidity and our results may assist in the development of more reliable and efficient treatments in the form of individualized and personalized pharmacotherapy. Therefore, it's of crucial importance to further grasp the pathophysiological pathways and unanswered questions involved in the association between COVID-19 and its NDs, which make COVID-19 and ND more serious using the pipeline of bioinformatics and network-based approaches.

5. Conclusion

We explored how the methodologies explained in this manuscript can be used to examine the transcriptome of COVID-19 and NDs for the identification of comorbidity interactions. In this research, we identified DEGs, cell signaling pathways and gene ontology mechanisms that connect the comorbidities between COVID-19 and NDs and we explored how SARS-CoV-2 infection may impact neurological disease progression and how COVID-19 patients are seriously impaired by the existence of neurological diseases. We have conducted transcriptional and post-transcriptional studies to detect DEG-TF interactions, DEG-miRNA interactions, and protein-protein interactions. This study provides

molecular insights into the possible biomarkers and regulatory elements that may contribute to the development of potential novel drugs to combat the serious COVID-19 and the progression of neurological diseases. The comorbidity study provided here offers mechanistic insight into the disorder and related prognostic characteristics for COVID-19 and neurological disorders. Thus, our approach will drive the decision-making forward for personalized medicine. This study has its drawbacks, in spite of our best efforts. The sample size for certain disease studies may be insufficient to capture all of the critical disease-associated genes required to identify the common DEGs. So, further research may be required to fully assess the biological relevance of the putative target candidates discovered in this work.

Author contributions

Md Habibur Rahman, Silong Peng conceived and designed the study; Md Habibur Rahman performed the computational analyses and wrote the draft manuscript; Humayan Kabir Rana prepared the tables and figures and helped writing the manuscript. Silong Peng, Md. Golam Kibria, Md. Zahidul Islam and S. M. Hasan Mahmud were involved in the preparation of the important intellectual content and critical revision; Mohammad Ali Moni supervised the study. All authors approved the final version for submission.

Declaration of competing interest

The authors have declared that no Conflict of Interest exists.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2021.104859.

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