Gene Expression **2024** vol. 23(2) | 83–97
DOI: 10.14218/GE.2023.00103

Original Article

Elucidating the Role of a Shared lncRNA-miRNA-mRNA Network in Exacerbating Parkinson's Disease Symptoms in the Context of COVID-19 Infection

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Received: June 02, 2023 | **Revised:** November 02, 2023 | **Accepted:** December 15, 2023 | **Published online:** April 09, 2024

Abstract

Background and objectives: Parkinson's disease (PD) is a common neurodegenerative disorder with unclear molecular mechanisms. Noncoding RNAs, such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), have been identified as critical regulators of gene expression. This study aimed to investigate the triple network of lncRNA-miRNA-mRNA, known as competing endogenous RNAs (ceRNAs), and to identify essential lncRNAs that regulate PD-related gene expression through their target miRNAs. The study also identified a common triple network between COVID-19 and PD that may contribute to exacerbating PD symptoms.

Methods: A bioinformatics approach was employed to construct a PD ceRNA network using common PD genes, miRNAs and lncRNAs with the highest interaction with their targets. Also, a PD-COVID-19 triple network was constructed by integrating PD network nodes into the COVID-19 network.

Results: The PD ceRNA network comprised 34 nodes, including 12 lncRNAs, 16 miRNAs with interconnections and six mRNAs, some of which were related to COVID-19. The network showed parallel expression of the *SNCA* and *PARK7* genes as well as the *NEAT1* and *MALAT1* lncRNAs in both PD and COVID-19.

Conclusions: This study provide insights into the molecular mechanisms underlying the worsening of symptoms in PD patients with COVID-19. The PD and COVID-19 ceRNA network indicates that coronavirus could worsen PD symptoms by altering the expression of some genes related to PD. Therefore, COVID-19 could dysregulate the common RNAs involved in PD through lncRNAs, miRNAs.

Keywords: Parkinson's disease; COVID-19; Long noncoding RNA; miRNA; *NEAT1*; *MALAT1*.

Abbreviations: AD, Autosomal Dominant; AR, Autosomal Recessive; ATP13A2, ATPase Cation Transporting 13A2; BST1, Bone Marrow Stromal Cell Antigen 1; CeRNA, competing endogenous RNA; CASC7, cancer susceptibility candidate 7; DDC, DOPA decarboxylase; DRD1, dopamine receptor D1; DRD2, dopamine receptor D2; GAK, cyclin G-associated kinase; GBA, glucocerebrosidase; HLA-DR, Human Leukocyte Antigen-DR isotype; IGF1R, insulin-like growth factor 1 receptor; LINC00938, long intergenic nonprotein coding RNA 938; lncRNAs, long noncoding RNAs; LRRK2, leucine-rich repeat kinase 2; MALAT1, Metastasis associated in lung adenocarcinoma transcript 1; MAOB, monoamine oxidase B; MEG3, maternally expressed 3; MAPT, microtubule-associated protein tau; MIAT, myocardial infarction-associated transcript; mRNA, messenger RNAs; miRNAs, microRNAs; NEAT1, Nuclear Enriched Abundant Transcript 1; PD, Parkinson's disease; PRKN, Parkin RBR E3 ubiquitin protein ligase; PINK1, PTEN-induced kinase 1; PARK7, parkinsonism associated deglycase; RP11-314B1.2, clone-based (vega) gene; SNCA, synuclein alpha; SLC18A2, solute carrier family 18 member 2; TH, Tyrosine Hydroxylase; XIST, X-inactive specific transcript.

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How to cite this article: Yousefi M, Hashemi M-S, Peymani M, Ghaedi K, Irani S, Etemadifar M. Elucidating the Role of a Shared lncRNA-miRNA-mRNA Network in Exacerbating Parkinson's Disease Symptoms in the Context of COVID-19 Infection. *Gene Expr* 2024;23(2):83–97. doi: 10.14218/GE.2023.00103.

Introduction

Dr. James Parkinson first described Parkinson's disease (PD) in 1817 as "shaking palsy".[1] PD is a progressive age-dependent and the most prevalent neurodegenerative disease after Alzheimer's

disease.[2] It is characterized by both motor and nonmotor features. Motor features are caused by degeneration of dopaminergic neurons within the substantia nigra pars compacta, corpus striatum, brain cortex, and cytoplasmic protein components called Lewy bodies[3,4]; nonmotor features are neuronal losses in nondopaminergic areas.[5] It is suggested that nonmotor features may start before the onset of motor features.[6]

Many environmental factors, such as nutrient intake,[7,8] dietary exposure to noxious compounds,[9,10] environmental toxins (like carbon disulfide, cyanide, herbicides, organic solvents and pesticides),[11] and methcathinone, contribute to PD incidence.[12]

Genetic and epigenetic factors can also contribute to PD incidence.[13] Previous investigations have indicated that many noncoding RNAs (ncRNAs) play critical roles in PD-specific physiological and pathological processes.[14,15] NcRNAs include various classes, such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs). In other words, miRNAs and lncRNAs are assumed to be associated with PD.[16,17]

MiRNAs are single-stranded RNA molecules with about 22 nucleotides. They significantly affect biological processes, such as negatively regulating mRNA transcripts, inhibiting the initiation and elongation of target mRNA translation, and degrading or destabilizing mRNAs.[18] LncRNAs have more than 200 nucleotides. The transcription of lncRNAs is performed by RNA polymerase II, which is similar to that of coding RNAs. The 5′ end capping and 3′ end processing, splicing, polyadenylation and exporting to the cytoplasm of lncRNAs are similar to those of coding RNAs. Generally, lncRNAs cannot be translated, but a limited number of them can produce small peptides.[19] LncRNAs interact with proteins, DNAs and other RNAs, enabling them to regulate diverse cellular processes. They can also control gene expression at both the transcriptional and post-transcriptional levels.[20–22]

Besides the fact that miRNAs and lncRNAs have a regulatory role in mRNA expression, they also interact with each other. MiRNAs can control the decay of lncRNAs since many lncRNAs are involved in cell functions. Thus, changes in their abundance directly alter cellular responses in physiological and pathological processes. Also, lncRNAs can influence miRNA levels and functions through the sponge and decay of miRNAs. For miRNA sponges, lncRNAs can act as competing endogenous RNAs similar to miRNA target sequences. Moreover, lncRNAs can compete with miRNAs for binding to target mRNAs. Another way by which lncRNAs can affect miRNAs is by producing miRNAs through lncRNAs.[19]

Recent evidence suggests that viral infections, including COVID-19, may have an impact on the development and progression of neurodegenerative diseases like PD.[23] For instance, Fazzini *et al*. reported that coronavirus antibodies were present in the cerebrospinal fluid of PD patients.[24] SARS-CoV-2, the virus that causes COVID-19, can also enter the nerve cells of the brain or spinal cord through angiotensin-converting enzyme 2 (ACE2) receptors.[25] ACE2 receptors are highly expressed in dopamine neurons.[25] Also, several studies have demonstrated the worsening of motor and nonmotor symptoms and, possibly, higher mortality in PD patients infected with SARS-CoV-2, as compared with those not exposed to SARS-CoV-2.[26–29] Cilia *et al*. also investigated the clinical features of 141 PD patients residing in Lombardy, finding 12 COVID-19 cases (8.5%).[30] So, the changes in clinical features from January 2020 to April 2020 were investigated and then compared with those of 36 PD controls matched for sex, age and disease duration. The findings showed that motor and nonmotor symptoms were significantly intensified in the COVID-19 group. Therefore, we investigated the possible associations of coding and ncRNAs with this worsening of symptoms in PD patients with COVID-19.

To enhance the power and generalizability of PD results, meta-analysis can be employed to obtain and summarize favorable information from existing studies. However, a limited number of meta-studies have been performed on the role of miRNAs and lncRNAs in regulating PD-related gene expression. Therefore, the present study aimed to construct a triple miRNA-mRNA-lncRNA competing endogenous RNA (ceRNA) network related to PD. Additionally, we aimed to identify the specific RNA molecules that show altered expression patterns in PD patients with COVID-19 compared to those without COVID-19 and to investigate the reasons behind the worsening symptoms observed in PD patients with COVID-19. We expected that COVID-19 could dysregulate the common RNAs involved in PD through lncRNAs, miRNAs, and finally, the expression of essential mRNAs. On the other hand, COVID-19 could contribute to altered biological processes like neuroinflammation, an impaired immune response, and oxidative stress, and these processes are known to play crucial roles in PD pathogenesis. By investigating the specific dysregulated RNAs and their involvement in altered biological processes, we aim to provide insights into the molecular mechanisms underlying the worsening of symptoms in PD patients with COVID-19. This knowledge could potentially lead to the identification of novel therapeutic targets and strategies for managing PD and its exacerbation in the context of viral infections like SARS-CoV-2.

Methods

Data sources and collection

The method employed in this study is shown in Figure 1. PD-related genes were collected from DisGeNET (*v.7.0*), which is a platform containing one of the largest publicly available collections of genes and variants associated with human diseases. We employed the following keywords in our study: "Parkinson", "AD (Autosomal Dominant) juvenile", "Parkinson disease 2", AR (Autosomal Recessive) juvenile", "late onset Parkinson's disease", and "young onset Parkinson's disease".[31] DisGeNET integrates data from diverse sources such as curated repositories, GWAS catalogs, animal models, and scientific literature.

The common genes of these PD types were identified using a Venn diagram generated by bioinformatics and evolutionary genomics tools, which can show the intersection of the input lists of genes (http://bioinformatics.psb.ugent.be/webtools/Venn/).

MiRNAs involved in PD were identified by a literature review and the MiRTarBase database (*v.8.0*).[32–66] Then, miRNAs having strongly validated interactions with PD-related genes were selected, as observed in the literature or reported in the MiRTarBase database, with strong validation (Reporter assay, Western blot, qPCR). MiRTarBase is a curated database that compiles verified miRNA-target interactions validated through biological experiments. These interactions were gathered from a variety of reliable sources, including articles and CLIP-seq data. This database serves as a valuable resource for studying miRNA-related diseases and has potential applications in disease treatment and drug development.

The verified target lncRNAs of the selected miRNAs were screened using DIANA-LncBase Experimental (*v.2*).[67] LncRNAs in the mentioned database were classified into various biotypes based on their positions in regard to nearby protein-coding loci. In this study, we focused on the lncRNA biotype with a score above 0.6 in

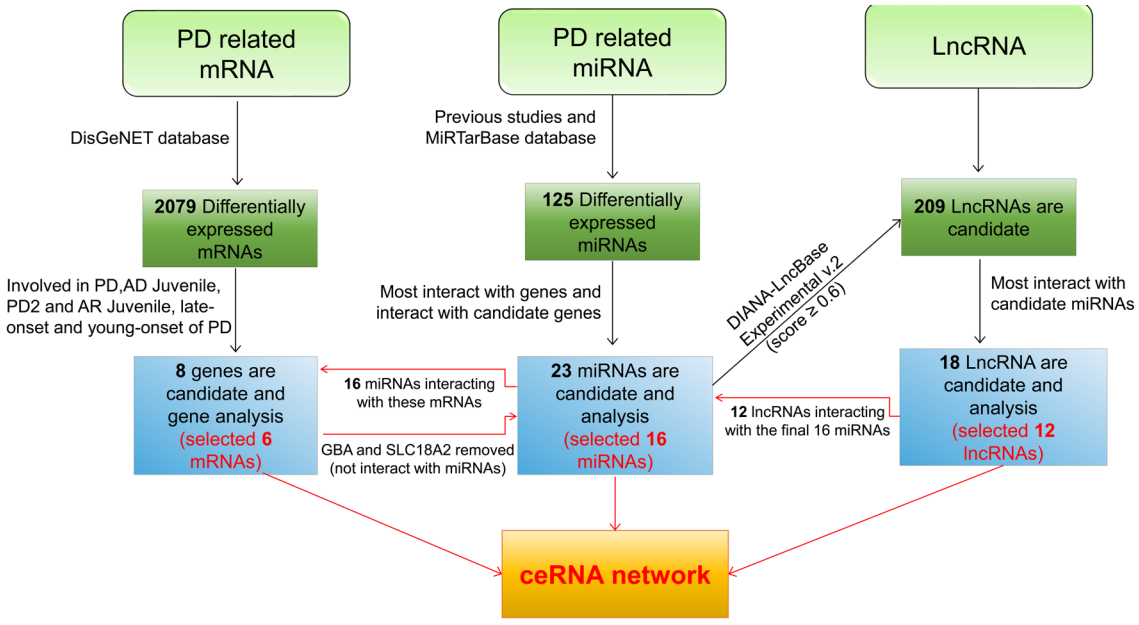

Fig. 1. The workflow of the methods and the results and network construction in the study. PD, Parkinson's disease; lncRNAs, long noncoding RNAs; miRNAs, microRNAs; CeRNA, competing endogenous RNA.

the experimental module of DIANA-LncBase Experimental (*v.2*). The LncBase database utilizes a CLIP-Seq-guided algorithm called the microCLIP framework to analyze AGO-CLIP-Seq libraries. This algorithm enables the identification and cataloging of miRNA binding events in lncRNAs. By leveraging CLIP-Seq data, LncBase provides valuable insights into the interactions between miRNAs and lncRNAs, contributing to our understanding of their functional roles and potential implications in various biological processes. Based on the miRcode database (*v.11)*, the seed position and seed type of the selected miRNAs were predicted in the target lncRNAs.[68]

Functional enrichment analysis and construction of ceRNA networks

For the common gene list obtained from the Venn diagram, ontology categories of the related disease and GO biological pathway enrichment analysis were performed according to the Metascape database.[69] Metascape is a web-based portal for gene list annotation and analysis designed for experimental biologists. It offers a comprehensive resource to interpret and explore gene lists from various experiments. Also, the molecular functions of the candidate genes, as well as the biological processes of the candidate miRNAs, were summarized and visualized using REVIGO (adjusted $p < 0.05$).[70] REVIGO is a web server specifically designed to summarize long lists of Gene Ontology (GO) terms. It utilizes a simple clustering algorithm that relies on semantic similarity measures to identify a representative subset of terms. By doing so, REVIGO helps researchers overcome the challenge of dealing with lengthy and complex lists of GO terms, making the information more concise and intelligible. The clustergram of the perturbations of diseases, including PD and COVID-19, was visualized using the Enrichr database based on the altered expression of the candidate lncRNAs and mRNAs.[71] Enrichr provides a diverse collection of gene set libraries for analysis and download. It offers a wide range of gene sets associated with various biological processes, pathways, diseases, and experimental conditions.

Two networks, including mRNA-miRNA and miRNA-lncRNA networks, were used to introduce a PD lncRNA-miRNA-mRNA construct, *i.e.,* an endogenous RNA network. The mRNA-miRNA network was constructed and visualized using Cytoscape software (*v3.7.2*).[72] Cytoscape is an open-source software project that integrates biomolecular interaction networks with high-throughput expression data and other molecular states. It provides a unified conceptual framework for visualizing and analyzing complex biological networks, allowing researchers to gain insights into the relationships and interactions between biomolecules. Then, the network was analyzed, and the miRNAs that interact with two or more mRNAs were selected. Subsequently, a network of the selected miRNAs and lncRNAs described in Section 2.1 was constructed using Cytoscape software. The resulting network was analyzed, and lncRNAs that interact with more than two miRNAs were chosen. Finally, the ceRNA network was constructed and visualized using Cytoscape based on the relationships between the common mRNAs (extracted from the Venn diagram related to PD types), miRNAs and lncRNAs having the most interactions with mRNAs and miRNAs.

The candidate mRNAs (eight genes) and lncRNAs (12 lncRNAs) related to PD were given as input in the Enrichr database. Those related to COVID-19 were specified by the database. So, the ceRNA network nodes simultaneously involved in the PD network and associated with COVID-19 were selected to establish communication between PD and COVID-19. Then, the common genes between PD and COVID-19 were selected. Finally, a ceRNA network was constructed for PD and COVID-19.

Results

Identification of the candidate genes in PD

The DisGeNET database released almost 2079 PD-related genes, of which 360 genes had a score greater than or equal to 0.1 (the DisGeNET score for a gene-disease association reflects its recur-

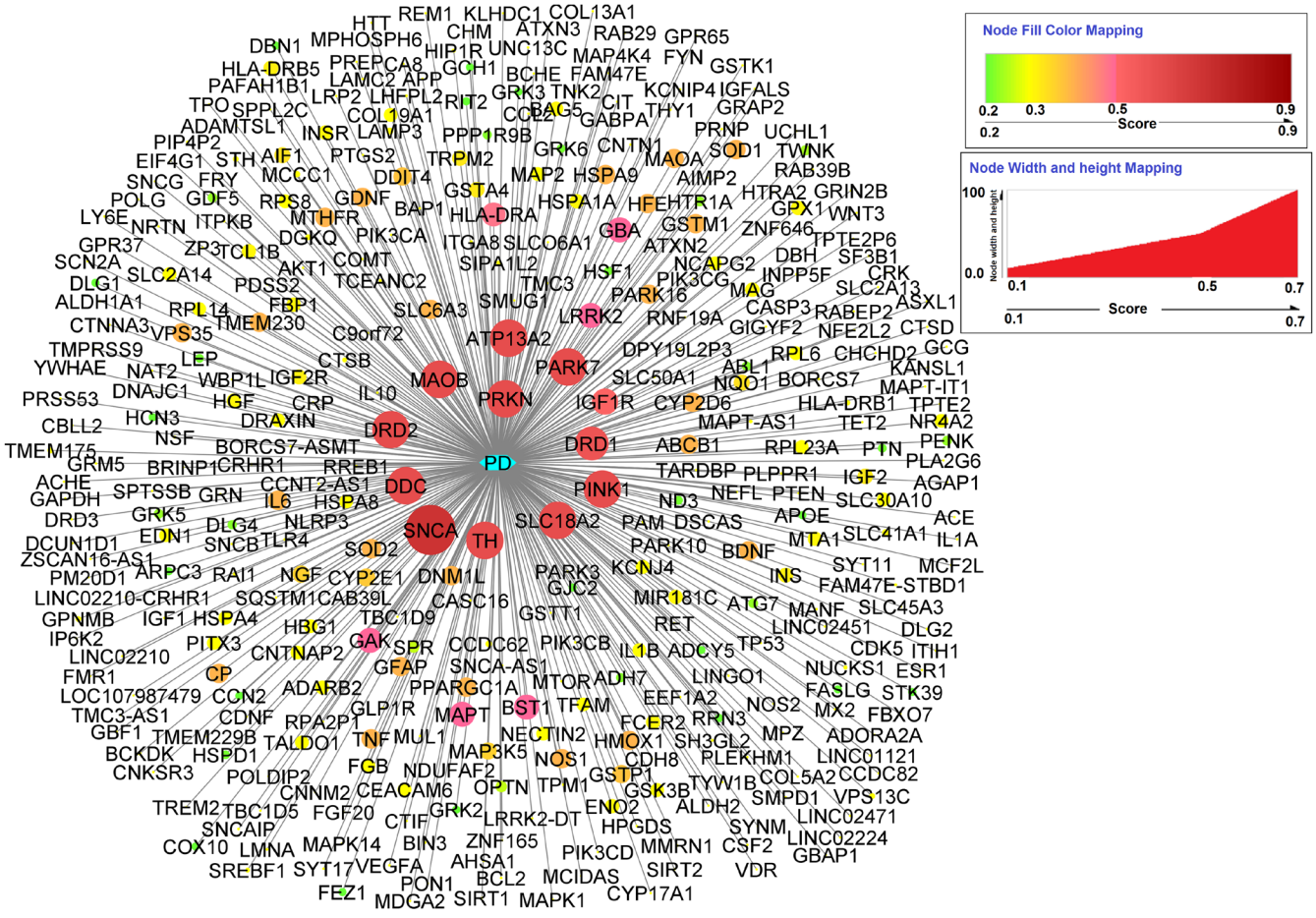

Fig. 2. PD-related genes with scores greater than or equal to 0.1. The node fill color and size of the genes are related to their score. The scores of *SNCA, PARK7, DDC, DRD2, ATP13A2, MAOB, PRKN, PINK1, SLC18A2, TH, DRD1* and *IGF1R* mRNAs range from 0.7 to 0.56, and *LRRK2*, *GAK, GBA, MAPT, BST1* and *HLA-DRA* mRNAs have scores greater than or equal to 0.5. PD, Parkinson's disease.

rence through all databases). The 360 genes identified via Cytoscape are summarized in Figure 2.[31,72] Moreover, genes related to the PD types "Parkinson", "AD juvenile", "Parkinson disease 2, AR juvenile", "late onset Parkinson's disease", and "young onset Parkinson's disease" were collected from the DisGeNET database. Then, eight common genes among them, including *PINK1, LRRK2, PARK7, SNCA, PRKN, ATP13A2, GBA* and SLC18A2 genes, were reported as a Venn diagram, as shown in Figure 3.

Interaction between mRNAs and miRNAs

The construction of the mRNA-miRNA network was derived from the correlation among the 2079 mRNAs (obtained from the DisGeNET database) and 125 miRNAs (obtained from the literature and the MiRTarBase database), as validated by strong methods. As shown in Figure 4, 32 mRNAs out of 2079 mRNAs were the targets of the abovementioned 125 miRNAs, described as a network; there was overlap between six candidate genes (described in Section 3.1, the glucocerebrosidase and SLC18A2 genes did not interact with the mentioned miRNAs, and these genes were removed in the next step) and 32 mRNAs. Among the miRNAs listed, we identified 61 miRNAs that interact with two or more mRNAs; among them, 23 miRNAs interacted with the abovementioned six genes using the Cytoscape software (Supplementary Excel 1).

Interaction between miRNAs and lncRNAs

Based on the experimental results of DIANA tool, we obtained 209 lncRNAs interacting with 23 candidate miRNAs. The miRNA-lncRNA network was constructed using Cytoscape software (Fig. 5).[72] Among the mentioned lncRNAs, we identified 18 lncRNAs that interact with more than two miRNAs (Supplementary Excel 2). The last step for the construction of a PD ceRNA network was to gather all selected mRNAs, miRNAs and lncRNAs together. We identified six mRNAs (described in Section 3.2). On the other hand, 16 out of the 23 candidate miRNAs that interact with these six mRNAs and target the abovementioned lncRNAs were selected; also, 12 out of the 18 lncRNAs that interact with the final selected miRNAs and mRNAs were selected.

GO analysis and PD

Gene Ontology enrichment analysis of Metascape demonstrated that 87.50% of the candidate genes were negatively related to neuron death, 75% of them were involved in the regulation of cellular catabolic processes, and 62.50% of them were negatively related to the neuronal apoptotic process (Fig. 6a).[73] The DisGeNET graph bar showed the number of selected genes involved in a different type of PD and other diseases (Fig. 6b). Significantly enriched GO terms (adjusted $p < 0.05$) were summarized and visualized using

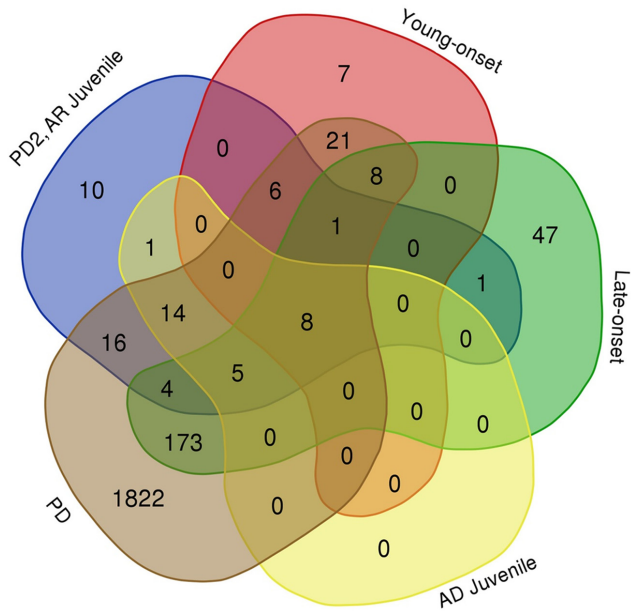

Fig. 3. Venn diagram of the genes related to PD, AD juveniles, PD2 and AR juveniles, and late-onset and young-onset PD. The *PINK1*, *LRRK2*, *PARK7*, *SNCA*, *PRKN*, *ATP13A2*, *GBA* and *SLC18A2* genes are common to all of them. AD, Autosomal Dominant; PD, Parkinson's disease; AR, Autosomal Recessive.

REVIGO. The "molecular functions of the selected genes" were the binding category and catalytic activity (Fig. 6c).[70]

The GO biological processes of the candidate miRNAs were summarized and visualized using REVIGO. The biological process of the mentioned miRNAs had a regulatory role in gene expression, the cell cycle, the apoptosis signaling pathway, angiogenesis, protein serine/threonine kinase activity, nitric oxide biosynthesis, interleukin-1 alpha, and interferon-beta production (Fig. 6d).[70]

Enrichr (Crowd) analysis of the candidate lncRNAs showed that the differential expression of these lncRNAs was related to various diseases. The GSE7621 microarray with the GPL570 platform (Affymetrix Human Genome U133 Plus 2.0 Array) was then used to obtain gene expression data from the substantia nigra in the postmortem human brain of 940 samples. This dataset reported an association between high and low expression of the candidate lncRNAs and various diseases. As shown in Fig. 6e, the clustergram indicated the overexpression of *MALAT1* and *NEAT1* in relation to PD ($p = 0.019$).[71]

GO analysis and COVID-19

We analyzed the expression of the six genes in the presence of COVID-19 using the Enrichr database (Diseases/Drugs). This section of the Enrichr database (Diseases/Drugs) uses the Gene Expression Omnibus (GEO) dataset and presents the results of a list of genes entered in the Enrichr database. Therefore, we used the results of several GEO datasets from the Enrichr database to report the expression profiles of our candidate genes and lncRNAs in COVID-19.

The GDS1028 dataset reports the differences in the expression of human peripheral blood mononuclear cell (PBMC) genes in 10 adult patients with severe acute respiratory syndrome (SARS) compared to healthy individuals using microarray data analysis. Expression levels of *SNCA* and *PARK7* were higher in patients with SARS than in healthy individuals ($p = 0.004$).

Besides, the associations of candidate lncRNAs with COVID-19 were analyzed using the Enrichr database (Legacy) based on GEO datasets. GSE150847 displayed the gene expression profiling of SARS-CoV-2-infected transduced human ACE2 mouse models using high throughput sequencing. Enrichr database based on GSE150847 also revealed that the up-regulation of *MALAT1*, *NEAT1* and *XIST* was related to SARS-CoV-2 in the lungs of Ad5-ACE2-transduced mice compared to Ad5-Empty-transduced mice ($p = 0.004$). GSE148729 also provided the gene expression profiling of SARS-CoV-1/2 infected human epithelial cell line Calu-3 at bulk and single-cell levels using high throughput sequencing. Enrichr database based on GSE148729 verified the up-regulation of *NEAT1* and *MALAT1* in SARS-CoV-1/2-infected human cell lines compared with that in uninfected cell lines (= 0.046) (Fig. 6f).

CeRNA network of mRNA-miRNA-lncRNA

The ceRNA network for PD was developed by the interaction between mRNA, miRNA and lncRNA. To design a ceRNA network related to PD, three steps were required to select mRNAs, miRNAs and lncRNAs, as detailed above. The final network consisted of 34 nodes, including six mRNAs, 16 miRNAs and 12 lncRNAs that interact with each other (Fig. 7) (Supplementary Excel 3). Moreover, we used the candidate mRNAs (six genes) and lncRNAs (12 lncRNAs) related to PD to construct the PD and COVID-19 ceRNA network. As mentioned, the expression levels of *SNCA* and *PARK7* in the candidate mRNAs were related to COVID-19. Additionally, *MALAT1* and *NEAT1*, among the candidate lncRNAs (12 lncRNAs), were related to COVID-19. The expression levels of the SNCA and PARK7 genes, as well as the expression levels of the NEAT1 and MALAT1 lncRNAs, were upregulated in both PD and COVID-19. This parallel upregulation suggests a positive correlation between the expression of these genes.

At this point, we focused on lncRNAs because several studies have reported their association with COVID-19.[74–76] In this section, *XIST* was omitted because changes in its expression were reported in infected mouse cells (not human cells). In addition, as shown in Figure 6f, several studies have confirmed some differences in the expression of *MALAT1* and *NEAT1* in different human cells or human PBMCs infected with SARS-CoV-2.[77–79] Thus, a PD and COVID-19 ceRNA network was constructed using *SNCA* and *PARK7* as mRNA nodes, and *MALAT1* and *NEAT1* as lncRNA nodes, incorporating the candidate miRNAs linked to these genes and lncRNAs (Fig. 8).

Discussion

PD can be regarded as an age-dependent neurodegenerative disorder affecting movement abilities.[80] The regulation of gene expression is one of the major factors in cellular homeostasis that can be impaired in PD.[81] NcRNAs are risk factors that play a role in altering PD gene expression and PD.[82] There were major differences in the clinical presentation related to age at onset. Juvenile-onset PD is usually defined as the age at disease onset before 20 years. Early-onset PD refers to patients who present motor symptoms before age 40; the most reported age for late-onset PD refers to that after 60 years.[83] Patients with early-onset PD had more benign disease progression, delayed onset of falls and longer survival compared to those with late-onset PD.[84] Additionally, a comparison between early-onset and late-onset patients showed that early-onset patients were less likely to have gait disturbance as the presenting symptom and had more pronounced rigidity and bradykinesia compared to late-onset patients.[84]

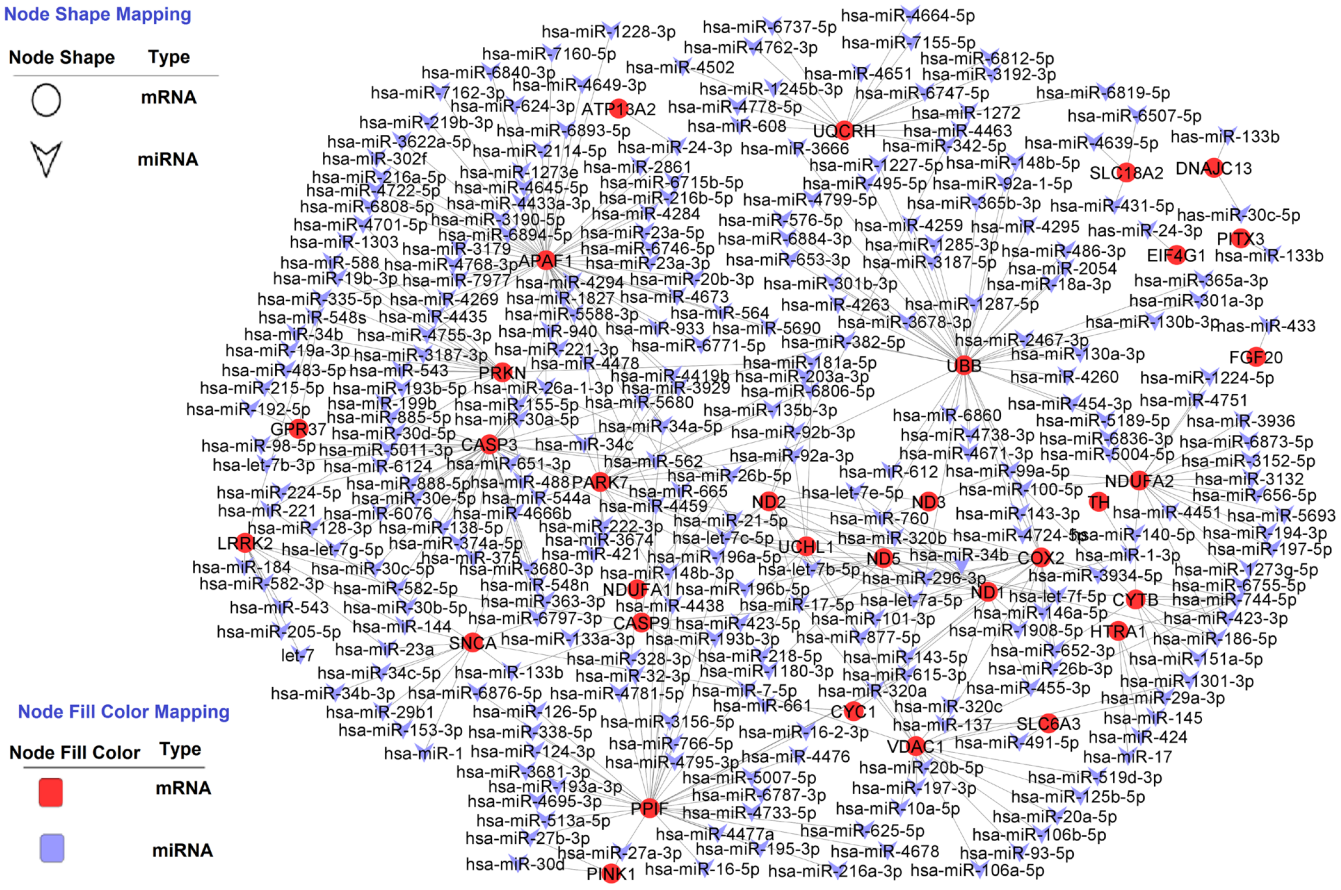

Fig. 4. mRNA-miRNA network analysis revealed that 32 mRNAs were targets of 125 miRNAs. The 23 miRNAs interacted with six candidate mRNAs, namely, *hsa-miR-26b-5p, hsa-miR-7-5p, hsa-miR-335-5p, hsa-miR-148b-3p, hsa-miR-181a-5p, hsa-miR-582-5p, hsa-miR-23a, hsa-miR-144, hsa-miR-221, hsa-miR-488, hsa-miR-133b, hsa-miR-27a-3p, hsa-miR-27b-3p, hsa-miR-4435, hsa-miR-4755-3p, hsa-miR-34c, hsa-miR-92a-3p, hsa-miR-4438, hsa-miR-4478, hsa-miR-4419b, hsa-miR-3929, hsa-miR-30c-5p* and *hsa-miR-24-3p*. mRNA, messenger RNAs; miRNA, microRNAs.

Some studies have reported that the overexpression of *SNCA* and *PARK7* is related to PD. Chiba-Falek *et al*. examined the expression levels of SNCA-mRNA in seven sporadic PD brain samples and seven normal controls using real-time PCR.[85] They reported that, on average, SNCA mRNA levels in PD brains were almost fourfold greater than those in controls. Also, Miller *et al*. showed that the amount of *SNCA* protein in the blood and the level of *SNCA* in the brain tissue were both doubled compared to the controls.[86] However, another study detecting autoantibodies in the serum of patients with PD reported increased serum levels of SNCA-reacting antibodies.[87] Yalçınkaya *et al*. also reported that the *PARK7* (*DJ-1*) expression level was increased in the PBMCs of PD patients.[88] Besides, Hu *et al*. reported the important impact of COVID-19 on neurodegenerative diseases such as PD.[89] On the other hand, proinflammatory cytokine levels, as well as the proinflammatory state, were increased in patients with COVID-19. This was closely followed by *SNCA* dysfunction and accumulation, thus promoting the development and progression of neurodegenerative diseases like PD.[90,91] In fact, some viral infections and other possible factors may be linked to increases in *SNCA* dysfunction or the loss of dopaminergic neurons in PD patients.[92,93] In conclusion, there is a possible relationship between SARS-CoV-2 and the pathogenesis of PD. A review also reported, according to some literature studies, that the upregulation of *SNCA*, which could occur during SARS-CoV-2 infection, would lead to widespread neurodegeneration.[93] Another study investigated mRNA expression in the brain tissues, primary microglia and primary astrocytes of M-CoV (murine β-coronavirus)-infected mice; the analyses of qRT-PCR reported that *DJ-1* mRNA was up-regulated in the brain tissues, primary microglia and primary astrocytes of M-CoV-infected mice compared to Mock (parallel controls were inoculated with PBS-BSA). They also demonstrated that the alteration of *DJ-1*, an oxidant-sensing molecule, was the first instance in M-CoV.[94] Therefore, Enrichr results of the GDS1028 dataset showed higher expression levels of *SNCA* and *PARK7* in the PBMCs of patients with SARS (COVID-19) compared to healthy individuals. It could be argued that the parallel expression of these genes in PD and COVID-19 would probably lead to an increase in PD symptoms due to infection with COVID-19.

Theo *et al*. also conducted a comprehensive analysis of the expression levels of 90 lncRNAs in the brain samples of 20 PD patients and 10 controls.[95] The results demonstrated the significant upregulation of *MALAT1* in PD compared to the controls.[96] The qPCR results of another study showed higher levels of *NEAT1* expression in the substantia nigra of PD brains than in the substantia nigra of control brains (control n = 24; PD n = 29).[97] Also, the Enrichr results of the GSE7621 dataset analysis demonstrated that the overexpression of *MALAT1* and *NEAT1* was related to PD from the substantia nigra of the postmortem human brain compared to

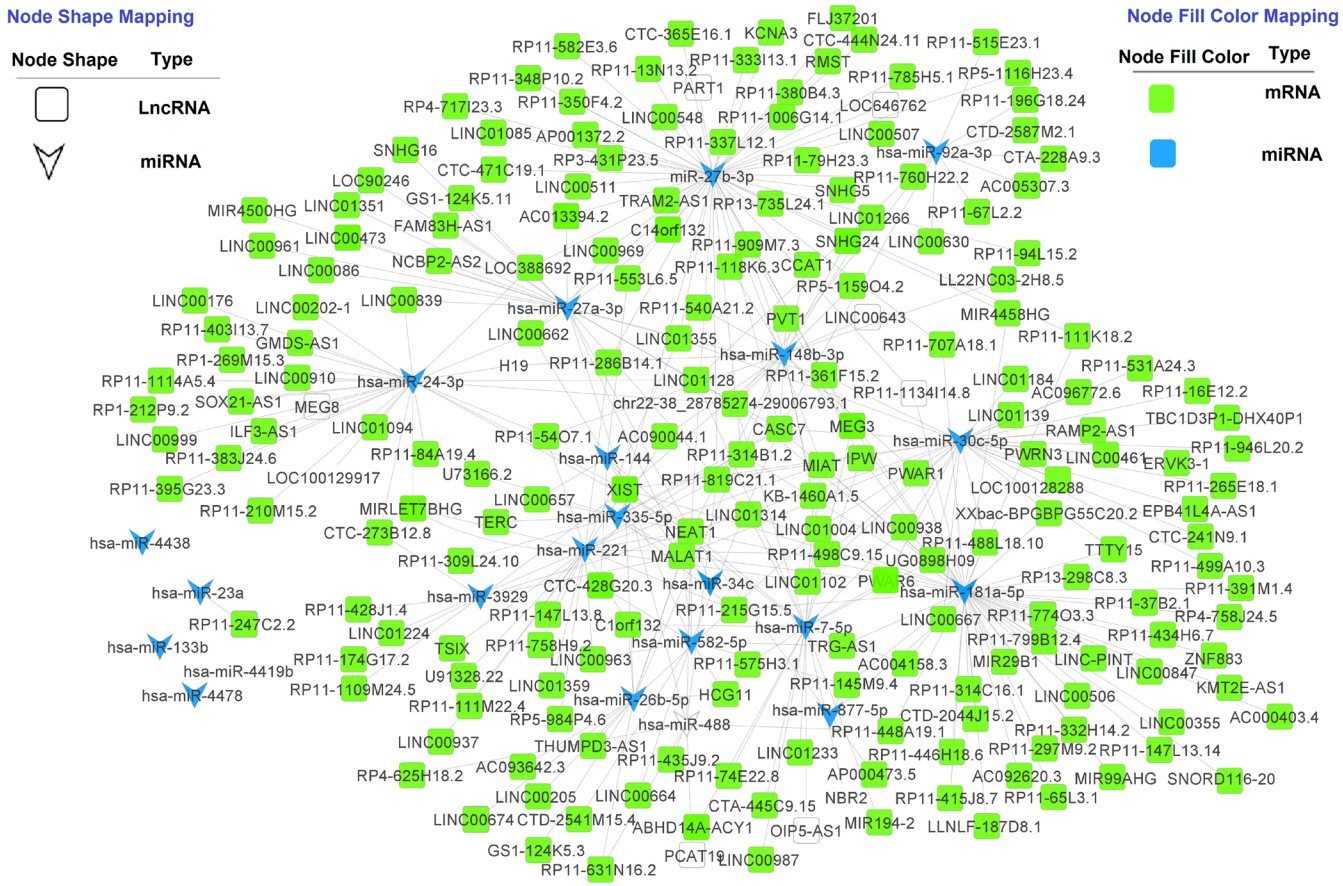

Fig. 5. miRNA-lncRNA network analysis revealed that 18 lncRNAs, *NEAT1, XIST, MALAT1, CASC7, RP11-314B1.2, LINC01355, MEG3, RP11-361F15.2, RP11-819C21.1, IPW, LINC00662, LINC00938, LINC01004, LINC01128, LINC01314, MIAT, RP11-215G15.5* and *RP11-54O7.1,* had the most interactions with miRNAs. lncRNAs, long noncoding RNAs; miRNA, microRNAs.

the controls. On the other hand, Huang *et al*. demonstrated that the proinflammatory lncRNA *NEAT1* was overexpressed in the epithelial/basal cells of mild patients with severe COVID-19 compared with those of healthy controls[98]; *NEAT1* expression was also significantly higher in severe patients than in mild patients. However, they found that *MALAT1* was overexpressed in the bronchoalveolar lavage fluid of severe patients but not in that of mild patients. Furthermore, they indicated that the specific changes in the activity of *NEAT1* and *MALAT1* lncRNAs were involved in the COVID-19-related hyperinflammatory process. Therefore, the results of the GSE148729 dataset indicated that the expression levels of *NEAT1* and *MALAT1* were higher in SARS-CoV-1/2 infected human cell lines compared with that in uninfected cells. So, it could be argued that these lncRNAs probably have parallel expression in PD and COVID-19. It is possible that COVID-19 infection can regulate *NEAT1* and *MALAT1* lncRNAs. Consequently, these lncRNAs may act as sponges for their target miRNAs (*hsa-miR-7-5p*, *hsa-miR-148b-3p*, *hsa-miR-26b-5p, hsa-miR-34c, hsa-miR-3929, hsa-miR-144, hsa-miR-221, and hsa-miR-488*), thereby increasing the expression of the *SNCA* and *PARK7* genes, which worsens PD symptoms in the presence of COVID-19 infection.

As shown in Figure 9, the interactions of *NEAT1* and *MALAT1* lncRNAs with their target miRNAs were identified. One of the important miRNAs identified in this study is *miR-7*, which can decrease *SNCA* stability and regulate target mRNA degradation.[99] Shen *et al*. validated the direct interaction between *miR-7* and *SNCA* with a dual luciferase reporter assay.[100] Tatura *et al*. analyzed *miR-7* expression in the frontal cortex by SYBR Green qRT-PCR assays and reported the significant down-regulation of *miR-7* in PD compared to the control.[41] Using a luciferase activity assay, Zhang *et al*. reported that *NEAT1* can bind with *miR-7* competitively, blocking its function through regulating protein tyrosine kinase 2,[101] which also leads to altered *SNCA* expression (Fig. 9a).

Tatura *et al*. also reported an upregulation of miR-26b expression in the cerebellum of PD patients compared to controls. *MiR-26b* binds to the *PARK7* gene and alters its expression.[41] As shown in Fig. 9b, *MALAT1* binds directly to *miR-26b* and acts as a sponge for *miR-26a/26b*, as determined by dual luciferase assays in several studies.[102–107] Additionally, some studies have demonstrated the direct interaction between *NEAT1* and both *miR-26a* and *miR-26b*, using a luciferase assay.[108,109] Thus, *NEAT1* can act as a sponge for *miR-26a* and *miR-26b*.

Hsa-miR-148b-3p can regulate the expression of the *SNCA* and *PARK7* genes in PD.[50] The *hsa-miR-148b-3p* level is lower in PD serum compared to control serum.[50,110] Vallelunga *et al*. reported that miR-148b was downregulated in PD patients compared to healthy controls using TaqMan low-density array technology.[45] As shown in Fig. 9c, *NEAT1* lncRNA interacts with hsa-*miR-148b-3p,* regulating its functions. However, a few studies have focused on the interaction between lncRNAs and *miR-148b*.[111]

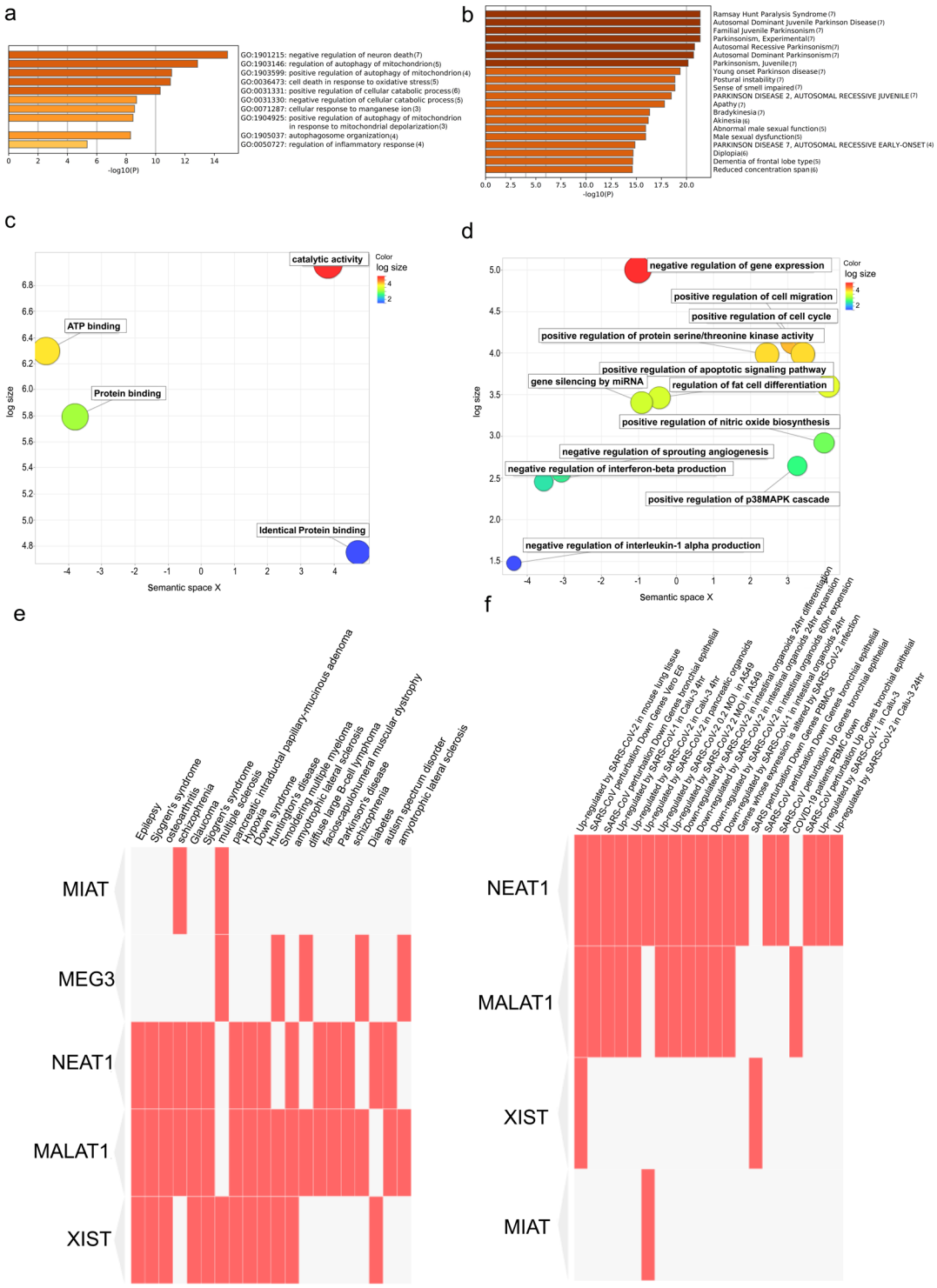

Fig. 6. Gene ontology and pathway enrichment analysis. Metascape bar graphs showing (a) biological processes and (b) a summary of the enrichment analysis of the candidate mRNAs related to different diseases. (c, d) GO enrichment analysis results were summarized and visualized as a scatter plot using REVIGO by clustering the significant genes (adjusted $p < 0.05$). The size of each bubble shows the GO terms with more significant p-values, (c) molecular functions of the candidate mRNAs, and (d) the GO biological processes of the candidate miRNAs. (e, f) Clustergrams showing related diseases such as PD and COVID-19 with differential expression of the candidate lncRNAs using the Enrichr database, (e) the relationship between the overexpression of lncRNAs and PD, and (f) the association between COVID-19 and differential expression of lncRNAs. ATP, Adenosine triphosphate; MALAT1, Metastasis associated in lung adenocarcinoma transcript 1; MEG3, maternally expressed 3; MIAT, myocardial infarctionassociated transcript; NEAT1, Nuclear Enriched Abundant Transcript 1; P38MAPK, p38 mitogen-activated protein kinases ; PD, Parkinson's disease; REVIGO, REduce and Visualize Gene Ontology; XIST, X-inactive specific transcript.

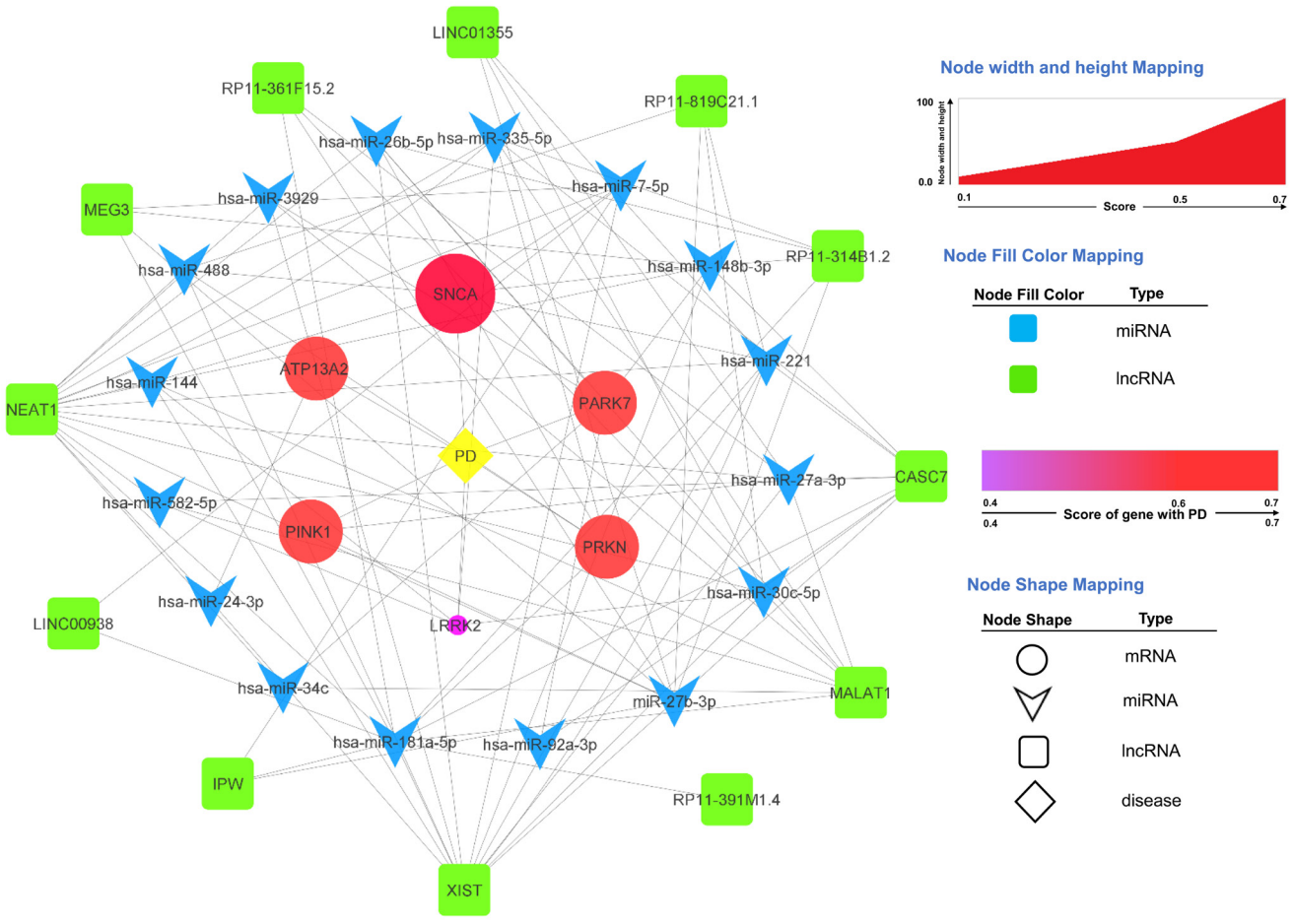

Fig. 7. The PD ceRNA network showing six mRNAs common to PD types, 16 miRNAs interacting with the mentioned mRNAs, and 12 lncRNAs having the most interactions with the mentioned miRNAs. ceRNA, competing endogenous RNA; lncRNAs, long noncoding RNAs; MALAT1, Metastasis associated in lung adenocarcinoma transcript 1; miRNAs, microRNAs; mRNAs, messenger RNAs; NEAT1, Nuclear Enriched Abundant Transcript 1; PD, Parkinson's disease.

Kabaria *et al*. reported that *miR-34c* could repress *SNCA* expression, as confirmed by Western blot analysis and luciferase assay.[112] Additionally, they demonstrated that *hsa-miR-34c* levels were reduced in the brains of PD patients. The *NEAT1* and *MALAT1* lncRNAs were identified as sponges for *miR-34c* (Fig. 9d).[113,114] On the other hand, a dual luciferase assay demonstrated the direct interactions between *NEAT1* and *miR-34c*,[115] as well as between *MALAT1* and *miR-34c*.[116]

The MiRTarBase database based on the Next generation sequencing (NGS) method showed that *hsa-miR-3929* was involved in PD, with the *miR-3929* targets being *PARK7* and *SNCA*. However, very few experiments have focused on this miRNA and its interaction with lncRNAs (Fig. 9e).

Hsa-miR-144, hsa-miR-488 and *hsa-miR-221* are associated with PD via altering the *SNCA* expression.[41] *MALAT1* and *NEAT1* lncRNAs bind directly to *miR-144-3p* and act as sponges for this miRNA as confirmed by the dual luciferase assay. Additionally, qRT-PCR results show that *MALAT1* and *miR-144-3p* suppress each other's expression (Fig. 9f).[117–120] Dual-luciferase reporter assays and RNA immunoprecipitation assays revealed a direct interaction between *NEAT1* and *miR-221* (Fig. 9g).[121] However, some studies have revealed the interaction between *NEAT1* and *miR-488* using dual luciferase assays (Fig. 9h).[122,123]

We identified regulatory networks involving 12 lncRNAs, 16 miRNAs, and 6 mRNAs that play critical roles in PD. By elucidating the regulatory interactions within this network, researchers can uncover novel pathways and processes involved in disease development and progression. This knowledge can help identify key molecular targets for therapeutic interventions. Additionally, by identifying specific lncRNAs and miRNAs associated with PD, researchers can potentially develop noninvasive diagnostic tests. These biomarkers could aid in early disease detection, differential diagnosis, and disease monitoring, enabling timely interventions and personalized treatment approaches.

Exploring the regulatory network between PD and COVID-19 can reveal common molecular pathways and the potential interplay between these diseases. This knowledge can provide insights into the possible impact of COVID-19 on PD pathogenesis and the exacerbation of PD symptoms. It may also shed light on the potential neurological complications of COVID-19 and guide the development of strategies for improving patient outcomes.

One of the limitations of our study was the utilization of the MiRTarBase database, which does not provide information about the source of miRNAs. Due to our limited access to studies with the same platforms, we had to use studies with different platforms to select miRNAs. Since MiRTarBase does not involve the source

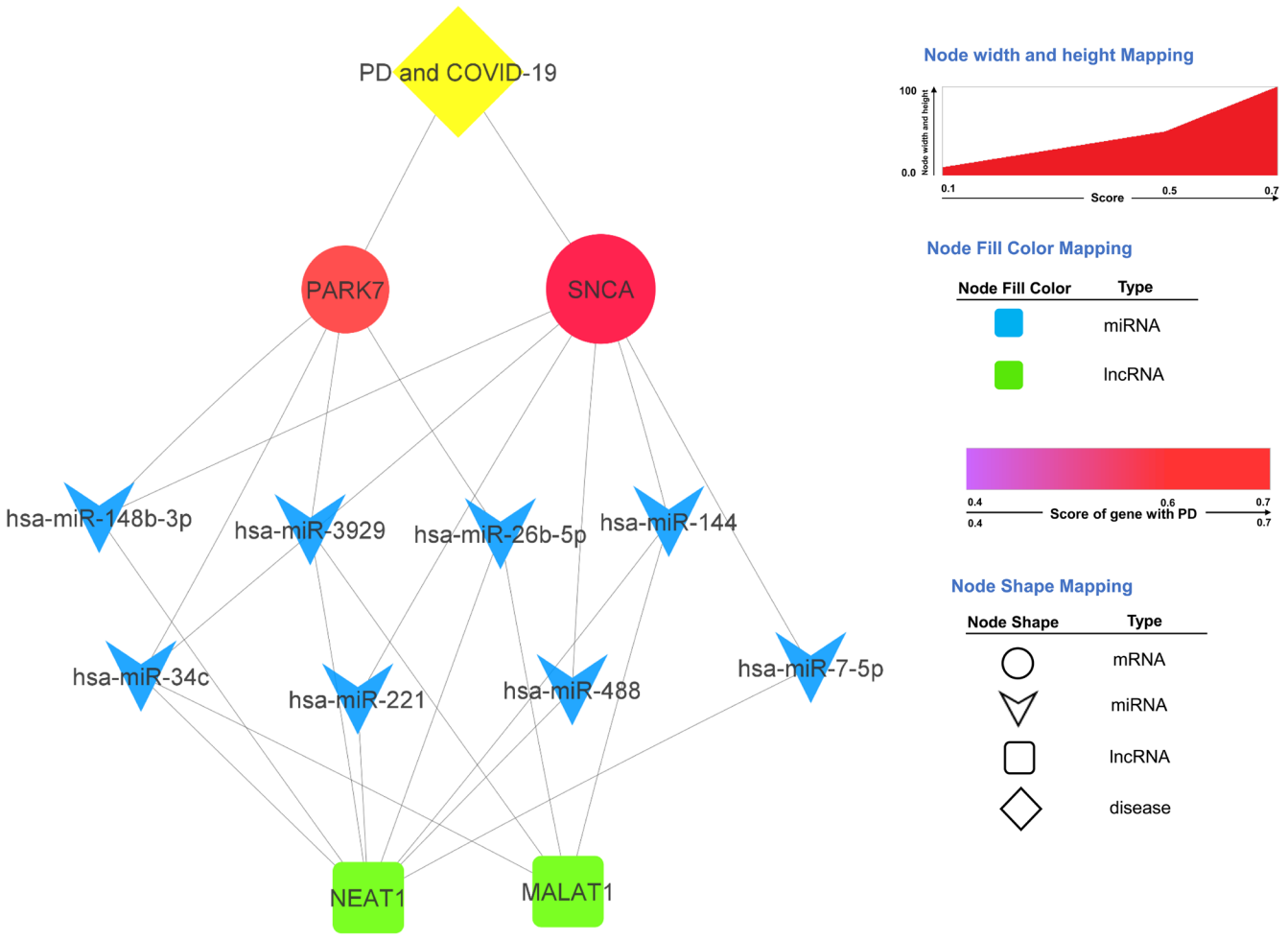

Fig. 8. The PD and COVID-19 ceRNA network showing two mRNAs, eight miRNAs and two lncRNAs related to PD and COVID-19. lncRNAs, long noncoding RNAs; MALAT1, Metastasis associated in lung adenocarcinoma transcript 1; miRNAs, microRNAs; NEAT1, Nuclear Enriched Abundant Transcript 1; PARK7, parkinsonism associated deglycase; PD, Parkinson's disease; SNCA, synuclein alpha.

of tissues, we chose these miRNAs without considering specific tissues. Additionally, ethical considerations imposed several limitations on tracking RNA trends in COVID-19 patients with PD.

Conclusions

In this study, two regulatory networks were constructed. The first network consisted of six mRNAs (*PINK1*, *LRRK2*, *PARK7*, *SNCA*, *PRKN* and *ATP13A2*), 16 miRNAs (*hsa-miR-26b-5p, hsa-miR-7-5p, hsa-miR-335-5p, hsa-miR-181a-5p, hsa-miR-582-5p, hsa-miR-148b-3p, hsa-miR-144, hsa-miR-221, hsa-miR-488, hsa-miR-27a-3p, miR-27b-3p, hsa-miR-34c, hsa-miR-92a-3p, hsa-miR-3929, hsa-miR-30c-5p* and *hsa-miR-24-3p*) and 12 lncRNAs (*MALAT1*, *NEAT1*, *RP11-314B1.2*, *XIST*, *IPW*, *LINC00938*, *MEG3*, *CASC7*, *RP11-361F15.2*, *RP11-391M1.4*, *LINC01355* and *RP11-819C21.1*), which may serve as potential biomarkers for PD diagnosis and progression. Therefore, the findings of this network should be explored in future investigations of PD.

The second network was designed using the first network and nodes involved in COVID-19. This network comprised *NEAT1* and *MALAT1* as important lncRNAs that interacted with eight candidate miRNAs (*hsa-miR-148b-3p, hsa-miR-3929, hsa-miR-26b-5p, hsa-miR-144, hsa-miR-34c, hsa-miR-221, hsa-miR-488* and *hsa-miR-7-5p*) and regulated *SNCA* and *PARK7* genes, thus affecting COVID-19. In this study, based on bioinformatics studies, we found that the expression levels of the *SNCA* and *PARK7* genes in both PD disease and COVID-19 infection were upregulated, as were the expression levels of *NEAT1* and *MALAT1*. Therefore, the parallel expression of these mRNAs and lncRNAs in PD and COVID-19 leads to worsened PD symptoms in the presence of COVID-19. Our study provides insights into specific genes that may serve as biomarkers for PD and highlights the potential interaction between PD and COVID-19. These findings have implications for early diagnosis, disease monitoring, and understanding the impact of COVID-19 on PD symptoms. Further research and validation are needed to confirm these findings and explore their clinical applications.

Acknowledgments

We gratefully thank the Science and Research Branch, Islamic Azad University, Tehran, for supporting this study.

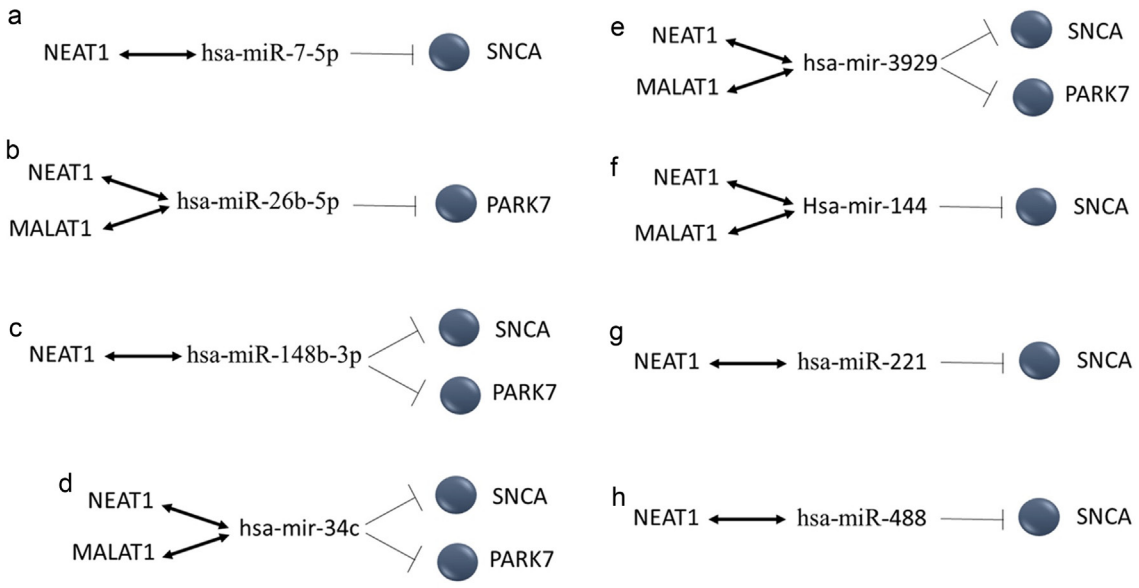

Fig. 9. Interactions between lncRNAs and target miRNAs and the regulation of miRNAs in PD and COVID-19. PD, Parkinson's disease; MALAT1, Metastasis associated in lung adenocarcinoma transcript 1; NEAT1, Nuclear Enriched Abundant Transcript 1; PARK7, parkinsonism associated deglycase; SNCA, synuclein alpha.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Conflict of interest

The authors declare that there are no conflict of interests that could be perceived as prejudicing the impartiality of the research reported.

Author contributions

The design and conceptualization of the study were done by MY, MSH and MP. Data mining, formal analysis and investigation were performed by MY Supervision, validation and visualization were done by MP, KG, and ME. The manuscript was written by MY. Reviewing, editing and proofing were done by MP, KG, and SI. All the authors have read and approved the final manuscript.

Data sharing statement

The information of the genes associated to "Parkinson" is available in the DisGeNET database (https://www.disgenet.org/browser/0/1/0/C0030567/); The information of the genes associated to "AD juvenile" is available in the DisGeNET database (https://www.disgenet.org/browser/0/1/0/C0752097/); The information of the genes associated to "Parkinson disease 2, AR juvenile" is available in the DisGeNET database (https://www.disgenet.org/browser/0/1/0/C1868675/); The information of the genes associated to "young onset Parkinson's disease" is available in the DisGeNET database (https://www.disgenet.org/browser/0/1/0/C4275179/); The information of the genes associated to "late onset Parkinson's disease" is available in the DisGeNET database (https://www.disgenet.org/browser/0/1/0/C3160718/); The information of the miRNAs associated to Parkinson is available in the MiRTarBase database (v.8.0) (https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2019/php/search.php?opt=path&path=hsa05012); The verified target lncRNAs of the selected miRNAs were screened using DIANA-LncBase Experimental (v.2) (http://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?r=lncbasev2%2Findex-experimental); The miRNAs' seed position and seed type in the target lncRNAs were predicted using miRcode database (v.11) (http://www.mircode.org/); The biological processes and pathways of the genes were obtained from the Metascape database (https://metascape.org/gp/index.html#/reportfinal/t0py580jd); The "molecular functions of the selected genes" were obtained from REVIGO (http://revigo.irb.hr/Results.aspx?jobid=150251458); The GO biological process of the candidate miRNAs was visualized using REVIGO (http://revigo.irb.hr/Results.aspx?jobid=151945504); COVID-19-related gene sets are available in the Enrichr database (Diseases/Drugs). (https://maayanlab.cloud/Enrichr/enrich?dataset=e363e682964ffe4c9133013ff4ad24bf); COVID-19-related lncRNA sets are available in the Enrichr database (Legacy). (https://maayanlab.cloud/Enrichr/enrich?dataset=0d5816d0306ddaa38e8d459facb7856b); The gene expression data from the GSE7621 dataset are available in the Enrichr and NCBI databases (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE7621 and https://maayanlab.cloud/Enrichr/enrich#; the gene expression data from the GDS1028 dataset are available in the Enrichr and NCBI databases (https://maayanlab.cloud/Enrichr/enrich# and https://www.ncbi.nlm.nih.gov/sites/GDSbrowser?acc=GDS1028); the gene expression data from the GSE17400 dataset are available in the Enrichr and NCBI databases (https://maayanlab.cloud/Enrichr/enrich# and https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi); the gene expression data from GSE150847 are available in the Enrichr and NCBI databases (https://maayanlab.cloud/Enrichr/enrich# and https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi); and the gene expression data from GSE148729 are available in the Enrichr and NCBI databases (https://maayanlab.cloud/Enrichr/enrich# and https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE148729).

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