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Original article

Integrated multi-omics approach identified molecular mechanism and pathogenetic processes of COVID-19 that affect patient with Parkinson's disorder

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ABSTRACT

The novel coronavirus named SARS-CoV-2 has emerged at the end of 2019, which causes coronavirus disease (COVID-2019). Recent case reports of COVID-19 patients have revealed the onset of Parkinson's disease (PD) symptoms in patients who do not have a family history of the PD. However, till recently, no genetic impact or mechanisms that may induce Parkinsonism in COVID-19 patients or after COVID-19 have been found.. This study aimed to detect the commonly dysregulated genes, transcriptional regulators, and pathways between PD and COVID-19. We integrated genome-wide transcriptomic datasets from peripheral blood mononuclear cells (PBMC) samples from COVID-19 and PD and associated pathways. Our study revealed 81 upregulated and 48 downregulated differentially expressed genes (DEGs) shared between PD and COVID-19. These dysregulated genes were involved in key pathways "mitochondrion structure organization", "cell activation in immune response", and "signalling by interleukins". Our analysis showed RELA, TP53 and SP1 TFs that may regulate the upregulated DEGs. We have discovered key dysregulated genes and characterized the biological processes of commonly dysregulated in COVID-19 and PD, which could be used for the design of personalized treatment of PD following COVID-19.

1. Introduction

At the end of 2019, a novel virus termed SARS-CoV-2 emerged in Wuhan, China. This novel virus is responsible for a respiratory illness called coronavirus disease (COVID-19). The SARS-CoV-2 is a member of coronaviruses, which are single-stranded RNA viruses that usually infect a wide range of vertebrate hosts (Cui et al., 2019). The patients infected with coronaviruses present mild symptoms of cold (Weiss and Navas-Martin, 2005). In the last decades, three types of coronaviruses (SARS-CoV-1, MERS-CoV, SARS-CoV-2) have emerged and caused severe respiratory tract infection. These three viruses have caused the loss of lives of many people, SARS-CoV-1 infected about 8000 people worldwide in 2002–2003 while MERS-CoV infected ~2,500 people. Recent SARS-CoV-2, the causative agent of COVID-19, which has become a massive threats for people worldwide (Li et al., 2019). Several factors including age, comorbid diseases impact the outcome of the disease (Guan et al., 2020).

Parkinson's disorder (PD) is a chronic neurodegenerative disease that shows neurodegeneration of neurons that secrete dopamine in the substantia nigra part of the midbrain. The typical symptoms of PD are shaking, stiffness, tremor, walking imbalance. Various factors including genetics and environment are considered for the development and progression of PD. The influence of SARS-CoV-2 infection and its implications on PD, on the other hand, remains unclear (Schirinzi et al., 2020). Many patients are concerned about the possibility of COVID-19 infection, since a few case

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studies have shown exacerbation of parkinsonian symptoms during infection, as well as poor treatment outcomes in PD patients (Antonini et al., 2020; Cilia et al., 2020; Hainque and Grabli, 2020). Within 2–5 weeks of infection, hospitalized patients with COVID-19 developed acute clinical parkinsonism, according to at least three published case reports (by Méndez-Guerrero et al., Cohen et al., and Faber et al.) (Méndez-Guerrero et al., 2020; Cohen et al., 2020; Faber et al., 2020). Among the three patients, two responded to the treatment of dopaminergic medication (Hainque and Grabli, 2020; Pantell et al., 2013), and the rest of one patient recovered spontaneously (Cilia et al., 2020). These three patients did not have any family history of PD, or prodromal PD (Hainque and Grabli, 2020). Brain imaging of these patients showed the decreased function of nigrostriatal dopamine systems, which is close to PD (Cohen et al., 2020). Brundin et al. has proposed three potential mechanisms for the repaid development of parkinsonism following SARS-CoV-2 as discussed herein (Brundin et al., 2020). Firstly, vascular insults due to COVID-19 in various organs including the brain that may damage the nigrostriatal systems as seen close to vascular parkinsonism (Fabbri et al., 2021). Secondly, inflammation has been considered as risk factors for PD which suggests the acute systemic infection as seen in COVID-19 may trigger neuroinflammation and death of nigral dopamine secreting neurons. Midbrain dopamine secreting neurons are vulnerable to systemic inflammation. A prior research found higher levels of IL-6 in COVID-19, while a study found a disruption in the kynurenine pathway in COVID-19 (Thomas et al., 2020). Both processes have been related to Parkinson's disease (Johnson et al., 2019; Heilman et al., 2020). This evidence supports the idea that COVID-19 infection could trigger Parkinson's disease.. Numerous studies have been published to characterize theCOVID-19 transcriptome dysregulations (Blanco-Melo et al., 2020; Islam et al., 2020; Lieberman et al., 2020; Fagone et al., 2020). However, there are no molecular processes or pathways that could explain the connections between PD and COVID-19.

In this study, by examining genome-wide gene expression data from COVID-19 and PD, we have proposed a multi-omics integration approach to uncover dysregulated transcriptomic signatures and pathogenetic mechanisms that may explain the effect of COVID-19 on the development of PD. Furthermore, dysregulated gene signature, molecular pathways, gene ontologies, and transcriptional regulators that may underlie PD in COVID19 were investigated in this study (Fig. 1).

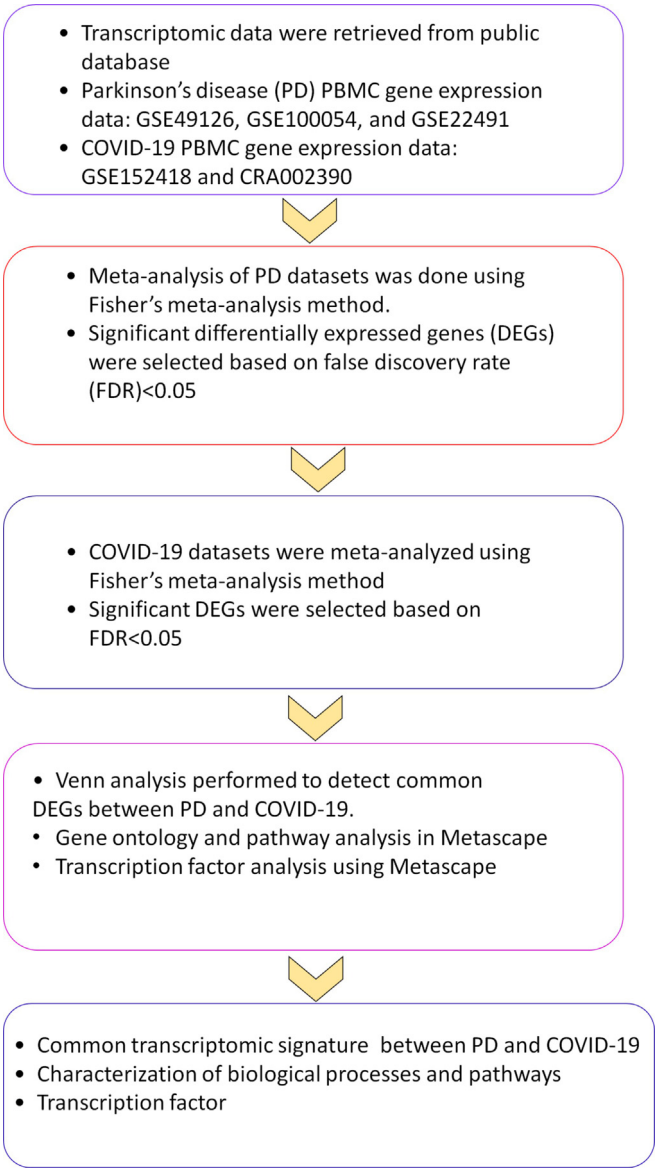


Fig. 1. Diagrammatic representation of the workflow used in this study. The transcriptomic datasets of peripheral blood mononuclear cells (PBMCs) of COVID-19 and Parkinson's disease (PD) were obtained from public gene expression database. Meta-analysis of COVID-19 and PD transcriptomics datasets were performed, respectively. The significant differentially expressed genes (DEGs) obtained from COVID-19 PBMCs meta-analysis and PD PBMCs meta-analysis followed by identification of common DEGs between COVID-19 and PD. The significant common DEGs were assessed for gene ontology, pathways, transcription factors were identified.

2. Materials and methods

2.1. Transcriptomic data acquisitions

We have queried NCBI Gene Expression Omnibus (GEO) database to detect the suitable datasets generated from PBMCs from COVID-19 and PD patients. We retrieved two RNA-Seq datasets (GSE152418) that contained gene expression profiling of 16 PBMC samples of COVID-19 cases and 17 healthy controls (Arunachalam et al., 2020). We also obtained a PBMC COVID-19 dataset (Accession number: CRA002390) from the Genome Sequence Archive. This dataset contained gene expression profiles of 3 COVID-19 cases and 3 controls (Xiong et al., 2020).

We then queried the GEO database with the keyword Parkinson's disorder peripheral blood mononuclear cells that result in three microarray transcription datasets with criteria 1) mRNA expression data ii) should contain cases and controls iii) human peripheral blood mononuclear cells (PBMCs) samples (Table 1). GSE49126 dataset contained 50 samples, where 30 PD cases and 20 healthy controls from PBMC. GSE100054 contained 19 PBMC samples, which 10 PD cases and 9 healthy controls. GSE22491 contained gene expression of 18 PBMC samples, which 10 PD cases and 8 healthy controls. The detailed characteristics of the datasets are presented in Table 1.

2.2. Data processing and differential expression analysis

We have preprocessed the COVID-19 PBMC two datasets in the DESeq2 R package. The individual datasets were analyzed and identified differentially expressed genes (DEGs) using a statistical threshold an absolute log-fold change (logFC) >=1 and Benjamini-Hochberg corrected adjusted p-value FDR < 0.05. We then performed a meta-analysis of these two datasets using Fisher's meta-analysis method implemented in the metaRNASeq R package.

Table 1
The description and features of the datasets employed in the proposed study.

Accession No.	Cell/ tissue sources	Platform	Samples (Case: Control)
COVID-19 datasets			
GSE152418	PBMC	Illumina NovaSeq 6000	16:17
CRA002390	PBMC	Illumina NovaSeq platform 5000	3:3
Parkinson's disorder			
GSE49126	PBMC	Agilent-014850 Whole Human Genome Microarray 4x44K G4112F (Feature Number version)	30:20
GSE100054	PBMC	Affymetrix Human Clariom D Assay [transcript (gene) version]	10:09
GSE22491	PBMC	Agilent-014850 Whole Human Genome Microarray	10:8

PBMC: Peripheral blood mononuclear cells.

The three microarray datasets of PD PBMC were processed and meta-analyzed using Network Analyst (NA) web utility tool (Zhou et al., 2019). First of all, we used two normalization procedures of datasets, namely variance stabilizing normalization (VSN) algorithm (Konishi, 1985), followed by quantile normalization (Hansen et al., 2012). ComBat procedure embedded into NA was also employed to adjust study batch effect in meta-analysis. The normalized datasets were used for differential gene expression analysis using R package LIMMA (linear models for microarray data) (Ritchie et al., 2015). Finally, we performed a meta-analysis of these three datasets using Fisher's meta-analysis method as used for COVID-19 datasets.

2.3. Functional enrichment analysis into the DEGs

We used a web utility "Metascape" for enrichment analysis (Zhou et al., 2019). The Metascape uses various sources of data including Gene Ontology, KEGG, Reactome, MSigDB for functional enrichment analysis. Metascape provides non-redundant terminology (Zhou et al., 2019). To detect significant ontologies, Metascape uses the hypergeometric test and Benjamini-Hochberg p-value correction algorithm. A Bonferroni corrected p-value < 0.05 was considered for significant terms selection.

2.4. Transcription factor analysis

We also used Metascape to identify the transcriptional regulatory transcription factors (TFs) for the identified DEGs (Zhou et al., 2019). Metascape uses the TRRUST database, which is a manually curated database of human and mouse transcriptional regulatory networks (Han et al., 2015; Han et al., 2018).

2.5. Protein-protein interaction analysis

We have performed protein–protein interaction analysis (PPI) of the proteins, by using protein interactome data via MetaScape (Zhou et al., 2019). The modules of the PPI network was explored using MCODE plugin embedded in MetaScape (Zhou et al., 2019).

3. Results

3.1. Identification of common transcriptional signatures between COVID-19 and PD PBMCs

We retrieved three peripheral blood mononuclear cells (PBMCs) PD data (accession no: GSE49126, GSE100054, GSE22491), for a total of 87 samples that included 50 PD cases and 37 healthy controls. The three datasets were processed and we performed a meta-analysis of three PBMCs datasets using Fisher's method. Our meta-analysis detected 2186 differentially expressed genes (DEGs), where 933 upregulated and 1253 downregulated DEGs (FDR < 0.05) (Table 2 and Table S1).

Table 2
Top 20 differentially expressed genes identified via meta-analysis in Parkinson's disorder PBMCs compared to controls.

Entrez ID	Name	Combined T stat	FDR
64403	CDH24	74.32	8.69E−10
84552	PARD6G	68.27	6.95E−09
10313	RTN3	67.6	6.95E−09
50674	NEUROG3	65.20	1.50E−08
3975	LHX1	64.53	1.50E−08
388630	TRABD2B	64.49	1.50E−08
29101	SSU72	63.84	1.75E−08
6656	SOX1	62.76	2.28E−08
23120	ATP10B	62.26	2.28E−08
125950	RAVER1	62.22	2.28E−08
83855	KLF16	62.14	2.28E−08
64839	FBXL17	62.04	2.28E−08
84634	KISS1R	61.95	2.28E−08
7070	THY1	60.78	3.65E−08
285601	GPR150	60.39	4.09E−08
284346	ZNF575	59.94	4.74E−08
27158	NDOR1	59.64	5.14E−08
2020	EN2	59.40	5.43E−08
3196	TLX2	59.09	5.94E−08
57863	CADM3	58.68	6.84E−08

Two PBMCs COVID-19 RNA-Seq transcriptomic datasets (accession no: GSE152418 and CRA002390) contained a total of 39 samples, 19 cases, and 20 healthy control. These two datasets were processed and we performed a meta-analysis to identify DEGs using the same Fisher's methods. Our meta-analysis of PBMC COVID-19 showed 3272 significant (FDR < 0.05) genes (Table 3 and Table S2).

In order to identify concordant overlapped DEGs between two pathologies (Table S3) namely, PD and COVID-19, we compared the DEGs. Our analysis identified a total 129 DEGs, 81 upregulated DEGs (*COX15, NOL8, SSU72, B3GNT7, RCSD1, RNF167, G6PD, ABHD8, EMC6, TRIM46, KMT2C, STARD7, TRIM62, PGBD4, UAP1L1, APOL4, LETM1, ARPC5, HELZ2, TMEM106A, TMEM63B, KRI1, RAB11B, CUL1, PRDX3, CIC, ZDHHC5, MRPS23, SPATA2L, ACVR1B, CIZ1, SHARPIN, CAMKK2, KCTD12, CTSZ, PNKD, RAB7A, SPPL2B, GPR153, OGDH, USP7, BCAM, PTMS, ZNF467, PFKL, HAGH, BARD1, CREB3L4, NRROS,*

Table 3
Top 20 differentially expressed genes identified via meta-analysis of COVID-19 PBMCs compared to controls.

Ensemble ID	Gene symbol	FDR	Fold change
ENSG00000211896	IGHG1	0.00	5.46
ENSG00000211972	IGHV3-66	0.00	5.09
ENSG00000253451	IGLV2-28	0.00	5.04
ENSG00000165948	IFI27L1	0.00	4.79
ENSG00000211676	IGLJ2	0.00	4.69
ENSG00000211678	IGLJ3	0.00	4.63
ENSG00000211974	IGHV2-70D	0.00	4.62
ENSG00000211949	IGHV3-23	0.00	4.42
ENSG00000159189	C1QC	0.00	4.35
ENSG00000211946	IGHV3-20	0.00	4.34
ENSG00000253818	IGLV1-41	0.00	4.13
ENSG00000253998	IGKV2-29	0.00	4.11
ENSG00000276566	IGKV1D-13	0.00	4.00
ENSG00000136315	AL355922.1	0.00	3.89
ENSG00000282651	IGHV5-10-1	0.00	3.88
ENSG00000211964	IGHV3-48	0.00	3.75
ENSG00000241351	IGKV3-11	0.00	3.68
ENSG00000211598	IGKV4-1	0.00	3.66
ENSG00000211968	IGHV1-58	0.00	3.64
ENSG00000243063	IGKV3-7	0.00	3.59

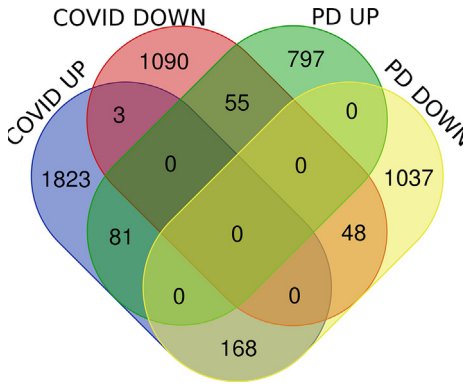


Fig. 2. The commonly differentially expressed genes (DEGs) were identified in PBMCs from COVID-19 and Parkinson's disorder (PD) patients. The Venn diagram shows the common upregulated and downregulated DEGs between COVID-19 and PD PBMCs.

SBF1, ARHGAP1, SLC37A2, UBXN11, ARPC1B, RAB34, CYB5R3, N4BP1, PRKACA, SHISA7, VSIG2, BMP8B, NFE2, DUSP7, SLC27A1, CCR2, TFG, SLC37A4, DVL3, MBD6, DOK3, ITPA, MDK, HECTD3, OGFR, RUSC2, PORCN, ALG3, CPTP, PEX10, HEMGN, SMCR8) were commonly modulated between COVID-19 and PD.

Our analysis identified 48 downregulated DEGs (*PDCD5, CDCA4, ZNF227, CCR3, RBM6, FAM8A1, RPRD1A, ZNF121, DDX21, RNF139, ACP1, OTULIN, PHF11, CHRNE, PSMA1, BORA, LSG1, RNF103, CAMP, ZBTB1, CCDC82, IDI1, DCP2, TMEM201, CD3G, TRMT12, SGCE, FAM76B, CHI3L1, MITD1, RCHY1, CLEC7A, METTL2A, CEP70, TAF5L, CENPH, HSDL1, HNRNPH3, HSP90AA1, MCM9, AP4S1, SCRN3, SLC45A4, WTAP, THUMPD1, NMI, TM7SF3, DBR1*) were commonly modulated between PD and COVID-19 (FDR < 0.05) (Fig. 2).

3.2. Identification of common functional gene ontology terms in COVID-19 and Parkinson's disorder PBMCs

To illustrate the biology of the overlapping DEGs found, we conducted an enrichment analysis of genes. In this way, we identified several ontologies and pathways that overlapped between PD and COVID-19 (Figs. 3B–4). Our analysis showed the common gene ontologies of the upregulated DEGs between PD and COVID-19 "mitochondrion organization", "cellular protein catabolism", "cofactor metabolic process", "cellular component disassembly", "apoptotic signalling pathways", "positive regulation of organelle organization ", "nervous system development", "negative regulation of cellular component organization", "organelle localization" (Figs. 3–4). Among the significant ontologies enriched by downregulated DEGs were "Cell activation in immune systems", "Signalling by interleukins", "Metabolism of RNA", "Positive regulation of cell death" (Figs. 3–4).

3.3. Prediction of transcription factor overlapping between COVID-19 and Parkinson's disorder PBMCs

To provide putative transcriptional regulators of the common modulated DEGs between PD and COVID-19, we identified that RELA, TP53, and SP1 were involved in the expression of commonly upregulated genes in COVID-19 and PD. However, we did not obtain any significant TFs that may be involved in the regulation of DEGs which were downregulated DEGs (Fig. 5).

3.4. Functional module analysis of proteins encoded by the DEGs

To dismantle the molecular interactions of the proteins encoded by the DEGs which were commonly modulated in COVID-19 and PD, we investigated protein–protein interaction (PPI) analysis. Our analysis showed the presence of four modules in the PPI networks (Fig. 6). The modules were found involved in various infection and metabolism associated pathways (Fig. 6B,C).

4. Discussion

Comorbidities are considered as immense risk factors for increased vulnerability to COVID-19 and poor therapeutic outcome. Among the comorbidities, neurological disorders came into

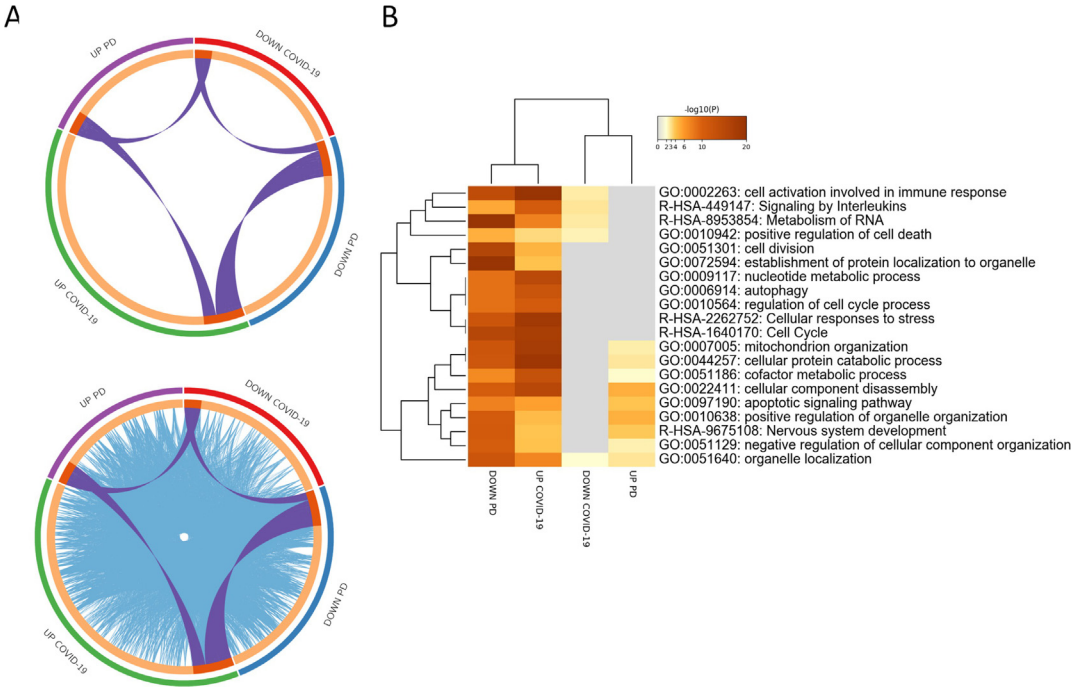


Fig. 3. Functional annotations and characterization of processes of the detected commonly differentially expressed genes in COVID-19 and Parkinson's disorder (PD). A) Circos plot representing commonly differentially expressed genes (DEGs) between COVID-19 and PD. B) The heatmap displaying the clustering of the significantly enriched terms.

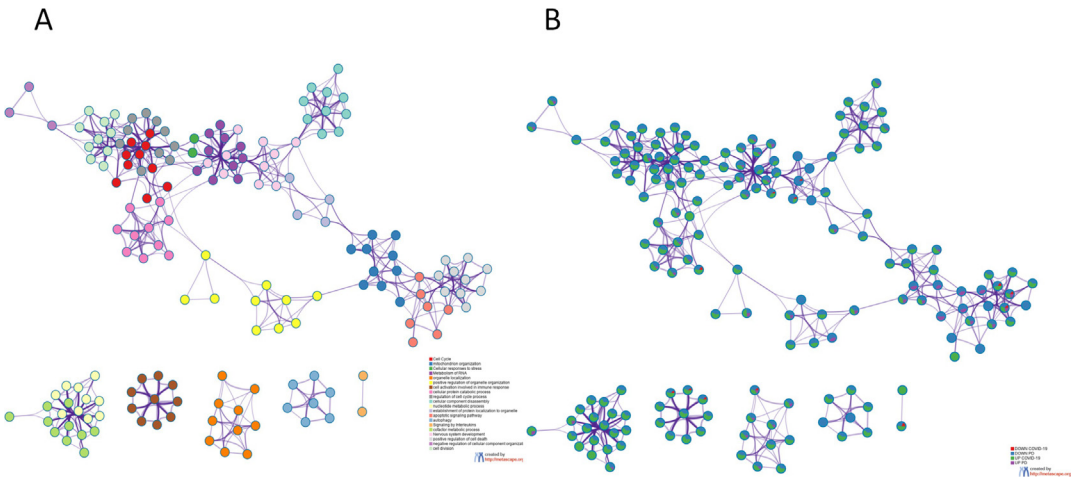


Fig. 4. The network of functional analysis on the differentially expressed genes (DEGs) in COVID-19 and Parkinson's disorder (PD). A) The network displaying the mutual connections of enriched terms by the DEGs. B) The same previous network where nodes are displayed as pies that are proportional to the number of hits represented by the DEGs belonging to each gene term.

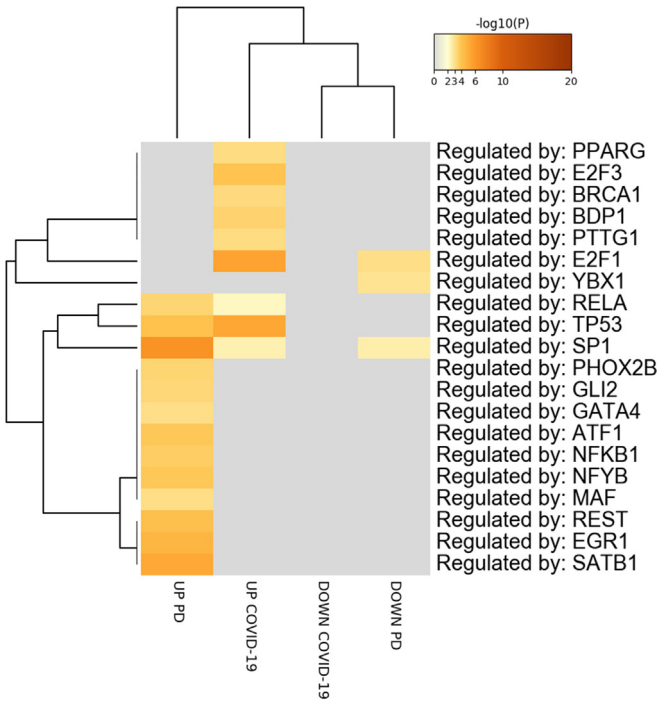
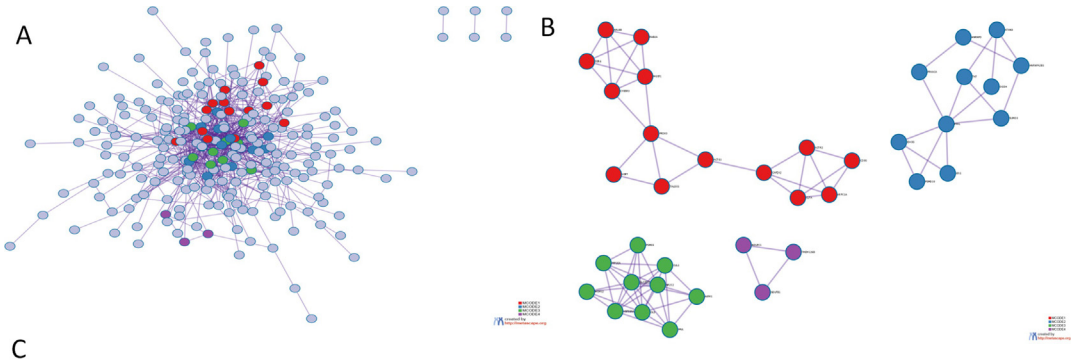


Fig. 5. Transcription factors analysis that may regulate the common differentially expressed genes in PBMCs from Parkinson' disease patients and COVID-19. The heatmap showing the transcription factors are displayed as hierarchical clustering. The colour corresponds to the p-value where grey cells show insignificant enrichment.

a greater risk for PD since some case reports showed the development of PD following COVID-19. The neurological symptoms in COVID-19 patients appear to be severe to mild. Despite the three case reports described the development of PD after COVID-19 presenting a great threat to the massive development of PD in response to COVID-19 (Méndez-Guerrero et al., 2020; Cohen et al., 2020; Faber et al., 2020).

The cellular and mechanism that may lead to COVID-19 induced PD are not understood yet. Therefore, characterizing critical genes and pathogenetic pathways in COVID-19 and PD is very important to understand the possible links of development of PD following COVID-19. In this study, for the first time, we identified commonly modulated common genes and molecular processes altered between PD and COVID-19 in PBMC. To this aim, we utilized whole-genome PBMC transcriptomic datasets of COVID-19 and PD via systems biology analysis. Our analysis detected 81 upregulated and 48 downregulated significant DEGs were common between two pathologies suggesting a possible molecular link between COVID-19 and PD. The upregulated genes were involved in several biological processes including "mitochondrion structure organization" among others. There is substantial evidence has been presented that suggests the mitochondrial dysfunction is involved in the aetiology and pathogenesis of PD since the inhibitor of electron transport chain complex I cause PD (Winklhofer and Haass, 2010; Perier and Vila, 2012; Keane et al., 2011). The mitochondria are involved in crucial cellular processes including energy metabolism, calcium homeostasis, and program cell death. Disruption of mitochondria is involved in the neuronal cell death of substantia nigra of PD, substantia nigra is the part of the brain mainly involved in PD development. In line with this evidence, our study suggests impairment of mitochondrial structure organization pathways might be involved in PD and COVID-19.

Our study demonstrated that the downregulated common genes are predominantly involved in immune systems related processes namely, "cell activation in immune response", "Signalling by interleukins". There is much compelling evidence that suggests the increased expression of genes in central nervous systems and peripheral nervous systems, infiltration of immune cells into CNS, the altered composition of immune cells in peripheral nervous systems, etc are implicated in the development of PD as discussed herein (Kannarkat et al., 2013; Tansey and Romero-Ramos, 2019). Moreover, various attempts have been taken to decipher inflammatory molecules, cells involved in the development of PD. Investigation of post-mortem brain and cerebrospinal fluids of PD showed the presence of inflammatory cytokines suggesting neuroinflammation in affected brain regions of PD (Tiwari and Pal, 2017). Alterations of various interleukins including IL-6 have been suggested as a marker of increased mortality in PD (Dufek et al., 2015). In line with this evidence, we hypothesized that alteration of signalling by interleukins pathways is involved in COVID-19 induced PD. Increasing evidence also has been suggested the impaired activation of immune systems, specifically the "cytokine storm" found in COVID-19 results from uncontrolled host immune response that is considered to be associated with COVID-19 complications, which supports that systemic immune systems alter-



C

Network	Annotation
Overall network	GO:0038093|Fc receptor signaling pathway|-9.0;R-HSA-449147|Signaling by Interleukins|-8.1;hsa01200|Carbon metabolism|-8.0
MCODE_1	R-HSA-8856828|Clathrin-mediated endocytosis|-8.2;R-HSA-9664407|Parasite infection|-7.8;R-HSA-9664417|Leishmania phagocytosis|-7.8
MCODE_2	ko01200|Carbon metabolism|-7.1;hsa01200|Carbon metabolism|-7.1;ko01230|Biosynthesis of amino acids|-5.5
MCODE_3	hsa04217|necroptosis|-6.6;R-HSA-449147|Signaling by Interleukins|-6.6;R-HSA-69275|G2/M Transition|-6.3
MCODE_4	R-HSA-6799198|Complex I biogenesis|-8.1;GO:0010257|NADH dehydrogenase complex assembly|-7.9;GO:0032981|mitochondrial respiratory chain complex I assembly|-7.9

Fig. 6. The protein interaction analysis (PPI) proposes the key modules altered in COVID-19 and Parkinson's disorder (PD). A) The global PPI network of the commonly modulated in COVID-19 and PD. B) The modules identified from PPI network. C) The functional annotations of the genes involved in PPI and modules.

ations as observed in our study is involved with COVID-19 (Geerlings and Hoepelman, 1999; Catanzaro et al., 2020).

Finally, we identified TFs (RELA, TP53, and SP1) that may regulate the common DEGs between COVID-19 and PD. Our results identified RELA TFs, a major component of NF-kB, which are considered as the master regulators of inflammation and apoptosis (Bellucci et al., 2020; Lanzillotta et al., 2015). The NF-kB/RELA is involved in neurodegenerative diseases including PD (Lanzillotta et al., 2015). Many lines of evidence showed the crucial role of RELA/NF-kB in PD (Lanzillotta et al., 2015). Previous studies showed the dysregulated increased expression of RELA in nigral dopaminergic neurons and glial cells in PD patients (Lanzillotta et al., 2015; Ghosh et al., 2007). Inhibition of RELA prevents loss of dopaminergic neurons and downregulated expression of RELA provides neuroprotection in PD suggesting a critical role of RELA in neurodegeneration in PD (Ghosh et al., 2007). We also identified Tp53, which is associated with cell death pathways, and its activation is involved in the pathogenesis of PD (Lu et al., 2017). It is important to note that our study has some limitation that findings were based on bioinformatics analysis and experimental validations should be done to establish solid conclusions regarding the associations between COVID-19 and PD. We should now like to propose some wet-lab experiments e.g., quantitative polymerase chain reaction, immunohistochemistry, western-blotting to validate the identified hub biomolecules

5. Conclusions

This study was aimed to identify dysregulated common transcriptional signature and molecular pathways between PD and COVID-19. Our integrative analysis suggested 81 upregulated and 48 downregulated DEGs were concordantly common between PD and COVID-19. Our study highlighted the major biological pathways altered in PD and COVID-19 involved in "mitochondrion structure organization" and immune systems related processes namely, "cell activation in immune response", and "Signalling by interleukins". We also detected key TFs namely RELA, TP53 which were involved in the expression of common DEGs. The detected pathways and genes in this study could be therapeutic targets in PD patients with COVID-19. Considering crucial importance of presented hub genes and pathways shared between COVID-19 and PD, experimental assessment of hub genes and pathways in clinical samples in COVID-19 and PD are proposed to further clarify the shared mechanism.

Funding

This research received no external funding.

Data availability statement

All data utilized in this manuscript are available online from their respective databases. GSE152418 and GSE49126 were downloaded from NCBI Gene Expression Omnibus (NCBI-GEO) available at https://www.ncbi.nlm.nih.gov/geo/ and CRA002390 from the Genome Sequence Archive database (https://ngdc.cncb.ac.cn/gsa/).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sjbs.2021.07.074.

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