Discovering Common Pathogenic Mechanisms of COVID-19 and Parkinson Disease: an Integrated Bioinformatics Analysis

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Abstract

Coronavirus disease 2019 (COVID-19) has emerged since December 2019 and was later characterized as a pandemic by WHO, imposing a major public health threat globally. Our study aimed to identify common signatures from different biological levels to enlighten the current unclear association between COVID-19 and Parkinson's disease (PD) as a number of possible links and hypotheses were reported in the literature. We have analyzed transcriptome data from peripheral blood mononuclear cells (PBMCs) of both COVID-19 and PD patients, resulting in a total of 81 common differentially expressed genes (DEGs). The functional enrichment analysis of common DEGs are mostly involved in the complement system, type II interferon signaling (IFNG) pathway, oxidative damage, microglia pathogen phagocytosis pathway, GABAergic synapse. The protein-protein interaction network (PPIN) construction was carried out followed by hub detection, revealing 10 hub genes (*MX1*, *IFI27*, *C1QC*, *C1QA*, *IFI6*, *NFIX*, *C1S*, *XAF1*, *IFI35*, and *ELANE*). Some of the hub genes were associated with molecular mechanisms such as Lewy bodies-induced inflammation, microglia activation, and cytokine storm. We investigated regulatory elements of hub genes at transcription factor and microRNA levels. The major transcription factors regulating hub genes are *SOX2*, *XAF1*, *RUNX1*, *MITF*, and *SPI1*. We propose that these events may have important roles in the onset or progression of PD. To sum up, our analysis describes possible mechanisms linking COVID-19 and PD, elucidating some unknown clues in between.

Introduction

According to the statistics provided by WHO, there have been approximately 255 Million cases diagnosed with coronavirus disease in 2019 (COVID-19) with more than 5 million confirmed death cases as of November 2021. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and is considered a worldwide pandemic whose impacts are noticeable across the globe (Chams et al. 2020; Khorsand et al. 2020). COVID-19 is initially viewed as a respiratory disease. However, it was demonstrated that SARS-CoV-2 affects multiple organs such as the central nervous system (CNS). Moreover, neurological manifestation associated with SARS-CoV-2 can potentially occur via direct invasion of the virus into CNS and thus, introduce the brain as a location containing high replicative values for SARS-CoV-2 (Song et al. 2021; Szcześniak et al. 2021).

PD (Parkinson's disease) is a neurodegenerative disease characterized for the first time in 1817 by James Parkinson. However, after nearly two centuries of research, the cause of most of the cases is still unclear (Olsen et al. 2018; Hayes 2019). There are multiple reports regarding the occurrence of neurological complications in individuals with COVID-19 as up to 85%. Additionally, hyposmia, one of the symptoms of PD, has been reported to happen in 65% of cases with COVID-19 (Merello et al. 2021). The prevalence of PD among elderly ages higher than 65 is 1–3% and for the whole population is approximately 0.3% (Raza et al. 2019). Of note, PD is distinguished mainly via degeneration of dopaminergic neurons located in the substantia nigra of the midbrain (Kalia and Lang 2016). Subsequently, a number of theoretical mechanisms such as basal ganglia injury, microglial-induced inflammation, and post-encephalopathy inflammation have been proposed to be the hypothetical link between COVID-19 and PD but there is still a

gap of knowledge in the way of understanding the relationship among them. This hypothesis is also supported by some case reports, stating a rapid onset of PD after infection with SARS-CoV-2 (Eichel et al. 2020; Cartella et al. 2021; Merello et al. 2021).

On the other hand, several viruses including Epstein-Barr, hepatitis C, herpes simplex 1, influenza A, and varicella-zoster have previously been shown to be related to increasing the risk of diagnosing with PD in the distant future (Henry et al. 2010; Merello et al. 2021). These viruses can directly induce neuronal injury after the infection. For instance, it has been demonstrated that there is a marked increased risk of developing PD after hepatitis C virus (HCV) infection. This was enabled by the ability of HCV to replicate in CNS (Tsai et al. 2016). The family of Coronaviridae has been known to cause CNS infection (Bergmann et al. 2006), presumably in the case of SARS-CoV-2 via blood-brain barrier (BBB) due to the cytokine storm (CS) (Eldeeb et al. 2020; Sulzer et al. 2020). Moreover, SARS-CoV-2 signature was detected in the autoptic brains of 21 out of 40 patients (53%) after dying of COVID-19. Although no relationship between the presence of SARS-CoV-2 and the severity of the disease was found, it was proved that SARS-CoV-2 can reach CNS (Matschke et al. 2020). Overall, all the aforementioned pieces of evidence create an urgent need that the possible crosstalk between SARS-CoV-2 and neurodegenerative disorders such as PD should be taken into consideration. Other studies have been carried out assessing other potential comorbidities in respect to COVID-19 including chronic kidney disease (Auwul et al. 2021) and diabetes mellitus (Rahman et al. 2021).

In the present study, we adopted an integrated bioinformatics analysis to scrutinize the common molecular mechanisms involved in COVID-19 and PD pathogenesis and how SARS-CoV-2 can possibly contribute to developing PD whether immediately after contracting COVID-19 or years later (an overview of the present study was shown in the Fig. 1).

Materials And Methods

Transcriptomic data analysis

We obtained the transcriptome data from the Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) with accession number GSE152418 (16 PBMCs samples from COVID-19 subjects and 17 normal individuals) (Arunachalam et al. 2020), and GSE165082 (12 PBMCs samples from PD and 14 normal individuals) (Henderson et al. 2021). The R package DESeq2 provided for normalization and differential expression analysis (Love et al. 2014). We used *P*-value < 0.05 and LogFC ≥ 1 as thresholds. Common DEGs between two datasets were obtained using the Venny 2.1.0 tool (https://bioinfogp.cnb.csic.es/tools/venny/index.html).

Gene ontology and pathway enrichment analysis

For the functional annotation and pathway enrichment analysis of the DEGs, Enrichr web utility tools (Kuleshov et al. 2016) were used. WikiPathway and the Kyoto Encyclopedia of Genes and Genomes (KEGG) were used for finding pathway enrichment analysis. Gene Ontology (GO) terms were considered

in three main categories such as biological process (BP), cellular component (CC), and molecular functions (MF).

Protein-protein interaction network construction and analysis

GeneMANIA (Warde-Farley et al. 2010) server was used for protein-protein interaction network (PPIN) construction and then the obtained PPIN was analyzed and visualized by Cytoscape version 3.8. We adopted a Hub detection approach called maximum clique centrality (MCC) via cytoHubba plug-in of Cytoscape to retrieve the top 10 hub nodes. MCC is a local-based algorithm which outperforms other methods in hub identification (Chin et al. 2014).

Identification of transcription factors and microRNAs regulating Hub genes

Transcription factors (TFs) and microRNAs are considered the major regulatory elements of gene expression at both transcription and post-transcription levels (Qin et al. 2020). We have constructed TF-Hub genes and miRNA-Hub genes regulatory networks with the use of NetworkAnalyst 3.0 to detect important regulatory elements (Zhou et al. 2019). As a TFs database, we used ChEA (Lachmann et al. 2010) to create the TF-Hub genes interaction network. To construct the miRNA-Hub genes interaction network, TarBase (Karagkouni et al. 2018) was selected to retrieve interacting miRNAs with regard to hub genes. Following the network's construction, network analysis was carried out to identify core TFs and miRNAs based on the degree.

Results

Identification of common DEGs between COVID-19 and PD

We examined transcriptional signatures between COVID-19 (n = 16) and healthy controls (n = 17). There were 4795 DEGs in COVID-19 versus healthy controls. Also, we obtained DEGs between PD (n = 14) and normal subjects (n = 12). Our results showed 233 DEGs in PD compared to controls. We detected 81 common DEGs between COVID-19 and PD (Fig. 2). Top ten common DEGs are shown in Table 1.

Pathway enrichment analysis

Functional annotations of common DEGs indicated involvement in multiple pathways including the complement system, type II interferon signaling (IFNG) pathway, oxidative damage, microglia pathogen phagocytosis pathway, GABAergic synapse (Table 2a). The GO analysis of common DEGs revealed that enriched BPs were mostly involved in the regulation of complement activation, regulation of immune effector process, regulation of humoral immune response, cell junction disassembly, commissural neuron axon guidance, synapse pruning, complement activation, classical pathway, determination of left/right symmetry, negative regulation of humoral immune response mediated by circulating immunoglobulin, humoral immune response mediated by circulating immunoglobulin. The enriched molecular functions were involved in kinase activator activity, protein kinase activator activity, GABA-A receptor activity, neurotransmitter receptor activity involved in regulation of postsynaptic membrane potential, GABA

receptor activity, transmitter-gated ion channel activity involved in the regulation of postsynaptic membrane potential, protein kinase regulator activity, transmitter-gated ion channel activity, glycerol channel activity, arylesterase activity. CC enriched in GABA-A receptor complex, azurophil granule, collagen-containing extracellular matrix, Golgi lumen, secretory granule lumen, caveola, specific granule lumen, vacuolar lumen, primary lysosome, plasma membrane raft (Table 2b).

Protein-protein interaction network construction and analysis

We constructed PPIN, containing 71 nodes and 1369 edges as it was shown in Fig. 3. The PPIN depicts the interaction of common DEGs and was visualized by Cytoscape software. According to Table 3, the ten hub genes based on MCC score are MX Dynamin Like GTPase 1 (MX1), Interferon-alpha inducible protein 27 (IFI27), C1CQ, C1QA, Interferon-alpha inducible protein 6 (IFI6), NFIX, C1S, X-linked inhibitor of apoptosis-associated factor-1 (XAF1), Interferon-alpha inducible protein (IFI35), and Elastase, Neutrophil Expressed (ELANE). These hub genes can potentially be used as drug targets and play a crucial role in maintaining the stability of the network. Therefore, further analysis of these genes is of great importance. For instance, scrutinizing the regulatory interaction of hub genes is recommended.

Regulatory networks

In order to gain deeper insights into our hub genes, we sought to construct TF-Hub genes and miRNA-Hub genes networks. Figure 4 and Fig. 5 displayed the regulators of the hub genes; TFs and miRNAs respectively. From these regulatory networks, it can be concluded that some regulatory elements are more important and can subsequently interact with more hub genes. In the TFs-Hub genes network, 16 TFs were identified with 3 or more interactions, whereas in miRNAs-Hub genes 29 miRNAs were detected with at least 3 or more interactions. The most connected TFs were *SOX2* and *XAF1* with the degree of 6, and *RUNX1*, *MITF*, *SPI1*, and *MYC* with 5 interactions. The most significant miRNA related to hub genes is hsa-mir-129-2-3p with a degree of 8. Other major miRNAs are hsa-mir-124-3p, hsa-mir-34a-5p, hsa-mir-21-3p and hsa-mir-27a-5p; each has 6 edges with Hub genes.

Discussion

The COVID19 outbreak has undoubtedly become an international concern (2021). Some case reports hypothesized rapid onset of PD happens after SARS-CoV-2 infection (Cartella et al. 2021; Merello et al. 2021). However, there is no study aimed to investigate common links between covid-19 and PD yet in an in-silico manner.

In this study, we adopted a network-based approach following transcriptome analysis to detect the common molecular pathways involved in COVID-19 and PD pathogenesis. The analysis demonstrated 81 common DEGs between COVID-19 and PD. We then performed the pathway enrichment analysis of common DEG. Our results showed the complement and coagulation cascades are one of the pathways that are enriched by the common DEGs. The complement system plays a double role in the immune response against SARS-CoV-2 and the pathogenesis of COVID-19 tissue involvement (Gao et al. 2020;

Diao et al. 2021). Several studies reported complement components to alter within the blood of PD patients (Goldknopf et al. 2006). The type II interferon signaling (IFNG) pathway was also identified. The interferon (IFN) responses constitute the main first line of defense against SARS-CoV-2 (Park and Iwasaki 2020). IFN-γ has a role in inflammation and neurodegeneration in PD, as an increase of IFN-γ was detected in the serum of PD patients (Baba et al. 2005). Another common pathway was oxidative damage. Oxidative stress most likely impacts COVID-19 pathogenesis by accompanying cell activation (Chernyak et al. 2020). Oxidative stress is one of the mechanisms mentioned in the etiopathogenesis of PD (Dorszewska et al. 2021). Oxidative stress causes damage to key cellular components in the substantia nigra (SN) of PD patients (Dias et al. 2013). We detected microglia pathogen phagocytosis pathway in which microglia by some pathogenic mechanisms, could contribute to the development of post-COVID-19 neurological sequelae and disorders, including PD (Awogbindin et al. 2021). Another enriched pathway was GABAergic synapse. COVID-19-associated inflammation may induce a cortical impairment of GABAergic neurotransmission, possibly representing cognitive fatigue, apathy, and executive deficits (Ortelli et al. 2021). GABA has also been reported to be involved in neurodegenerative disorders such as PD (Muñoz et al. 2020).

The hub genes have been identified from the PPIN to detect major signaling elements that may be used as therapeutic targets for the development of novel drugs to treat COVID-19 patients with PD comorbidity. MX1 is one of the myxovirus resistance genes (*MX*) which has the antiviral effect against RNA viruses. MX1 expression has been reported to be elevated in COVID-19 patients and conversely decline as age increases. Plus, it can be stimulated in the cytoplasm by IFNs and participates in the cellular antiviral response to SARS-COV-2 (Bizzotto et al. 2020). Furthermore, the accumulation of α-synuclein (α-SYN) in the brain of PD patients induces the expression of MX1. This molecule is involved in PI3K-Akt signaling pathway, cytokine release, immune response IFNs α, β, and γ signaling pathways (Yamada et al. 1994; Qin et al. 2016). It is also a regulator of IFN systems that contributes to CS (Yang et al. 2021). This might facilitate the entry of virus to CNS via BBB. It is noteworthy that BBB was reported to be disrupted in the animal models of PD which can lead to degeneration of neurons in substantia nigra (Al-Bachari et al. 2020). MX1 localized in self-aggregations and generated Lewy bodies and swelling of neuronal processes in the substantia nigra of brain tissues in Parkinson's patients (McDonough et al. 2017). Lewy bodies which contain misfolded proteins can then trigger activation of T-cells (Sulzer et al. 2017). IFN-alpha inducible (IRI) family members are closely related to the inflammatory immune response in COVID-19 and PD (Shaath et al. 2020). IFI6 is an Immune-associated early predictor for PD (Lei et al. 2020; Yu et al. 2020). IFI35 involved in Type I interferon signaling pathway and have a vital role in inflammation response in SARS-CoV-2 infected cells (Hachim et al. 2020; Ziegler et al. 2020; Ong et al. 2021). On the other hand, IFI35 upregulated in PD patients in response to INFs response (Yu et al. 2020). IFI35 gene is expressed in the stratum and substantia nigra regions of brain and its de novo mutation is contributed to early-onset of PD pathogenesis (Guo et al. 2018). IFI27 is an early predictor for SARS-COV-2 infection and high-level expression of IF127 is associated with the presence of a high viral load (Shojaei et al. 2021). One study found elevated expression of IFI27 after microglial activation and neuroinflammation in progressive neurodegenerative disorders such as PD (Zhou et al. 2015). SARS-CoV-2 infection induces a

strong activation of major constituents of the human complement subcomponent C1q (*C1QA*, *C1QB*, *C1QC*) (Ramlall et al. 2020; Santiesteban-Lores et al. 2021). These genes are upregulated in the microglia cells in the brain of PD patients. Activation of the complement system improves the removal of pathogens and products of tissue damage from the brain and is related to neuronal cell death in PD (Depboylu et al. 2011; Mariani et al. 2016; Itoh and Voskuhl 2017). ELANE gene codes destructive enzymes named neutrophil elastase that play key role in host defense mechanism. This enzyme is highly overexpressed in naso-oropharyngeal and blood samples of COVID-19 patients. Neutrophil elastase can activate the spike (S) protein and mediate viral entry and pathogenesis of SARS-COV-2 (Belouzard et al. 2010; Akgun et al. 2020; Guéant et al. 2021). After an inflammatory insult to the CNS structure, the expression of neutrophil elastase increases, then degrades basal lamina and extracellular matrix (ECM) molecules, and suppress neurobehavioral recovery mechanisms (Stowe et al. 2009; Stock et al. 2018). Neutrophil Elastase Inhibitors could be new treatment options for COVID-19 patients (Mohamed et al. 2020).

Among these transcription factors, sex-determining region Y-box 2 (SOX2) has a critical role in the development and maintenance of neural stem/progenitor cell populations committed to becoming glial cells. SOX2 inhibits myelination in the peripheral nerves and maintains Schwann cells in a proliferative state, which is also associated with the influx of macrophages and increased neuroinflammation (Roberts et al. 2017). Interestingly, the expression level of SOX2 was found be elevated in the brains of PD patients (Vedam-Mai et al. 2014). Nerve inflammation is one of the important factors in the onset or progression of PD (Pajares et al. 2020). XAF1 is a mitochondrial apoptosis activator that is upregulated in immune cells (T, B, natural killer, and dendritic cells) of COVID-19 patients that may be associated with increased apoptosis of these cells (Zhu et al. 2020; Gao et al. 2021). Furthermore, *XAF1* expression is higher in the midbrain of PD patients (Gispert et al. 2015; Santiago and Potashkin 2017). IFN-α and IFN-β induced XAF1 mRNA expression and therefore induced cell apoptosis (Leaman et al. 2002). The expression of Runt-related transcription factor 1 (RUNX1) increases after SARS-CoV-2 infection (O'Hare et al. 2021). Interestingly, its overexpression is related to the progression of PD. RUNX1 increases the expression of leucine-rich repeat kinase 2 (*Lrrk2*) gene in immune cells and has a critical role in the pathogenesis of familial PD due to developing hyperactive inflammatory phenotype, neuronal toxicity, and cell apoptosis (Cook et al. 2017; Thomsen et al. 2021). Microphthalmia-associated transcription factor (MITF) is one of the key TFs with varying functions in cell homeostasis, cell cycle, and apoptosis. MITF is upregulated in immune cells and worsens severity of infection in an unknown way in COVID-19 patients (Bost et al. 2020; Ding et al. 2021; Jeong et al. 2021). Ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) is expressed in neural cells and inhibits the stability of MITF by binding to the ubiquitinated protein. The ligase activity of UCHL1 is disrupted in PD, resulting in MITF overexpression and cell damage in these patients (Liu et al. 2002; Seo et al. 2017). The E26 transformation-specific (ETS) family transcription factor SPI1 upregulated in PBMCs of COVID-19 patients and is involved in the inflammatory process and modulates host immune systems of these patients (Fagone et al. 2020; Rahman et al. 2021). SPI1 plays a key role in the identity, differentiation, and specialized functions of microglia. Microglia rapidly activates in response to proinflammatory response. These activated microglia are accumulated in

brain lesions of PD patients. SPI1 has many target functional genes in microglial cells including *Spi1, Runx1, Irf8, Il34, Aif1*, *Csf1r, Csf1, Cx3cr1, Tyrobp*, and *Trem2* (Satoh et al. 2014). SPI1 induces cytokine release and microglial pro-inflammatory response (Pimenova et al. 2021). Therefore, misregulation of SPI1 target genes might lead to the establishment or development of PD due to the accumulation of activated microglia (Satoh et al. 2014). In addition, one multi-omic study identifies a Single-Nucleotide Polymorphism, rs10130373, within a microglia-specific peak, interrupts a SPI1 motif, and interfaces effectively with the promoter of the Rab interactor 3 (RIN3) gene. RIN3 plays an important role in the early endocytic pathway that needs microglial function, thereby, has a particularly critical role in progressive neurodegenerative disease (Kajiho et al. 2003; Corces et al. 2020).

hsa-mir-129-2-3p is the most significant miRNA in miRNA-Hub gene regulatory networks. miR-129 is a brain-enriched miRNA and its level increases in the peripheral blood lymphocytes of PD patients (Qin et al. 2016).

In the present study, an integrated bioinformatics approach was adopted to explore the possible risk of PD development after COVID-19 infection by investigating the common molecular mechanisms. By taking advantage of the holistic viewpoint of systems biology, we were able to consider every aspect of both diseases and infer novel hypotheses. Further supplementary studies need to be conducted to clarify the association between COVID-19 and PD, as at the moment, there is little known regarding both of these disease entities. It is worth mentioning that contracting PD is a complex and age-dependent neurodegenerative disorder. Thus, it is encouraged to investigate infected COVID-19 patients' years after their infection to estimate the probability of getting PD.

Conclusion

The current study aimed to investigate common regulators between COVID-19 and PD. Overall, our analysis highlights multiple mechanisms such as complement system, oxidative stress, activation microglia, cytokine storm and activation of T-cells by misfolded proteins which might be the potential links between both comorbidities. Nonetheless, as this is a thorough in-silico analysis, the results of this work should be taken into account carefully. Further case reports and follow-up experiments of COVID-19 patients can corroborate these links.

Abbreviations

COVID-19: coronavirus disease 2019, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, PD: Parkinson's disease, CNS: central nervous system, HCV: hepatitis C virus, cytokine storm (CS), PBMCs: peripheral blood mononuclear cells, GEO: Gene Expression Omnibus, GO: Gene Ontology, KEGG: Kyoto Encyclopedia of Genes and Genomes, MF: molecular functions, BP: biological process, CC: cellular component, TFs: Transcription factors, PPIN: protein-protein interaction network, ETS: E26 transformation-specific, GABA: gamma-aminobutyric acid, MX1: MX Dynamin Like GTPase 1, myxovirus resistance genes (MX), IFN: interferon, IFI6: Interferon-alpha inducible protein 6, IFI27: Interferon-alpha

inducible protein 27, IFI35: Interferon-alpha inducible protein 35, XAF1: X-linked inhibitor of apoptosis-associated factor-1, SOX2:sex determining region Y-box 2, RUNX1: Runt-related transcription factor 1, Lrrk2: leucine-rich repeat kinase 2, MITF: Microphthalmia-associated transcription factor, UCHL1: Ubiquitin carboxyl-terminal hydrolase L1, RIN3: Rab interactor 3

Declarations

Availability of Data and Materials

The data used in this study were downloaded from the GEO database.

Compliance with Ethical Standards

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Code Availability

The code that supports the findings of this study is available on request from the corresponding author.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Aria Jahanimoghadam and Hadis Abdolahzade. The first draft of the manuscript was written by Aria Jahanimoghadam, Hadis Abdolahzadeh, Niloofar Khoshdel rad, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1
Top ten common DEGs between COVID-19 and PD

The common DEGs	Log FC	
	GSE152418 (COVID-19 versus healthy control)	GSE165082 (Parkinson versus healthy control)
ISG15	1.2	-1.3
GABRD	1.8	-2.1
C1QC	3.5	-1.05
C1QB	2.9	-1.2
IFI6	2.05	-1.2
A3GALT2	2.08	1.04
VCAM1	-1.2	2.9
AQP10	1.9	-1.2
ACTG1P25	1.1	-1.2
C4BPA	1.1	-1.4

Table 2a
Top ten molecular pathways enriched by 81 common DEGs in COVID-19 and PD

Source	Pathways	P-value	Count	Genes
Wiki Pathway	Complement and Coagulation Cascades WP558	0.001682	3	C1QB;SERPING1;C1QC
	Complement Activation WP545	0.003550	2	C1QB;C1QC
	Complement system WP2806	0.007179	3	SERPING1;C4BPA;ELANE
	Type II interferon signaling (IFNG) WP619	0.009842	2	IFI6;ISG15
	miRNAs involvement in the immune response in sepsis WP4329	0.009842	2	VCAM1;ELANE
	Oxidative Damage WP3941	0.011437	2	C1QB;C1QC
	Microglia Pathogen Phagocytosis Pathway WP3937	0.011437	2	C1QB;C1QC
	Development of ureteric collection system WP5053	0.015565	2	WNT11;SMO
	Prader-Willi and Angelman Syndrome WP3998	0.025409	2	GABRR2;GABRD
	Non-genomic actions of 1,25 dihydroxyvitamin D3 WP4341	0.033623	2	RSAD2;ISG15
KEGG	Pertussis	0.000256	4	C1QB;SERPING1;C4BPA;C1QC
	Complement and coagulation cascades	0.000394	4	C1QB;SERPING1;C4BPA;C1QC
	Systemic lupus erythematosus	0.002210	4	C1QB;CTSG;ELANE;C1QC
	Neuroactive ligand-receptor	0.002609	6	GABRR2;CHRND;GRID1;LPAR1;CTSG;GABRD
	Staphylococcus aureus infection	0.006778	3	C1QB;DEFA4;C1QC

Source	Pathways	P-value	Count	Genes
	Transcriptional misregulation	0.007708	4	ETV7;DEFA4;ERG;ELANE
	Nicotine addiction	0.011437	2	GABRR2;GABRD
	Basal cell carcinoma	0.026977	2	WNT11;SMO
	GABAergic synapse	0.050585	2	GABRR2;GABRD
	Morphine addiction	0.052626	2	GABRR2;GABRD

Table 2b

GO enrichment analysis of 81 common DEGs in COVID-19 and PD

	Term	P-value	Count	Genes
BP	regulation of complement activation (GO:0030449)	0.000049	4	C1QB;SERPING1;C4BPA;C1QC
	regulation of immune effector process (GO:0002697)	0.000062	4	C1QB;SERPING1;C4BPA;C1QC
	regulation of humoral immune response (GO:0002920)	0.000067	4	C1QB;SERPING1;C4BPA;C1QC
	cell junction disassembly (GO:0150146)	0.00024	2	C1QB;C1QC
	commissural neuron axon guidance (GO:0071679)	0.00044	2	SMO;NFIB
	synapse pruning (GO:0098883)	0.00057	2	C1QB;C1QC
	complement activation, classical pathway (GO:0006958)	0.00057	2	C1QB;C1QC
	determination of left/right symmetry (GO:0007368)	0.00065	3	DNAH11;SMO;FOXJ1
	negative regulation of humoral immune response mediated by circulating immunoglobulin (GO:0002924)	0.00071	2	FOXJ1;C4BPA
	humoral immune response mediated by circulating immunoglobulin (GO:0002455)	0.00087	2	C1QB;C1QC
MF	kinase activator activity (GO:0019209)	0.00026	3	WNT11;SPDYA;GPRC5D
	protein kinase activator activity (GO:0030295)	0.002133	3	WNT11;SPDYA;GPRC5D
	GABA-A receptor activity (GO:0004890)	0.002649	2	GABRR2;GABRD

Note: BP, biological processes; MF, molecular functions; CC, cellular components

	Term	P-value	Count	Genes
	neurotransmitter receptor activity involved in regulation of postsynaptic membrane potential (GO:0099529)	0.003236	2	CHRND;GRID1
	GABA receptor activity (GO:0016917)	0.00355	2	GABRR2;GABRD
	transmitter-gated ion channel activity involved in regulation of postsynaptic membrane potential (GO:1904315)	0.006547	2	CHRND;GRID1
	protein kinase regulator activity (GO:0019887)	0.007384	3	WNT11;SPDYA;GPRC5D
	transmitter-gated ion channel activity (GO:0022824)	0.008356	2	CHRND;GRID1
	glycerol channel activity (GO:0015254)	0.020088	1	AQP10
	arylesterase activity (GO:0004064)	0.024058	1	CA1
CC	GABA-A receptor complex (GO:1902711)	0.002649	2	GABRR2;GABRD
	azurophil granule (GO:0042582)	0.003635	4	CEACAM6;DEFA4;CTSG;ELANE
	collagen-containing extracellular matrix (GO:0062023)	0.004433	6	C1QB;SERPING1;CTSG;CSPG4;ELANE;C1QC
	Golgi lumen (GO:0005796)	0.007805	3	DEFA4;CSPG4;MUC5B
	secretory granule lumen (GO:0034774)	0.009194	5	DEFA4;SELENOP;SERPING1;CTSG;ELANE
	caveola (GO:0005901)	0.02464	2	SMO;KCNA5
	specific granule lumen (GO:0035580)	0.026188	2	DEFA4;ELANE
	vacuolar lumen (GO:0005775)	0.027664	3	CTSG;CSPG4;ELANE

Note: BP, biological processes; MF, molecular functions; CC, cellular components

Term	P-value	Count	Genes
primary lysosome (GO:0005766)	0.043669	1	DEFA4
plasma membrane raft (GO:0044853)	0.043678	2	SMO;KCNA5

Note: BP, biological processes; MF, molecular functions; CC, cellular components

Table 3
Summary of hub nodes

Hubs	MCC
MX1	5
IFI27	4
C1QC	3
C1QA	3
IFI6	3
NFIX	2
C1S	2
XAF1	2
IFI35	2
ELANE	2

Note: MCC, maximum clique centrality

Figures

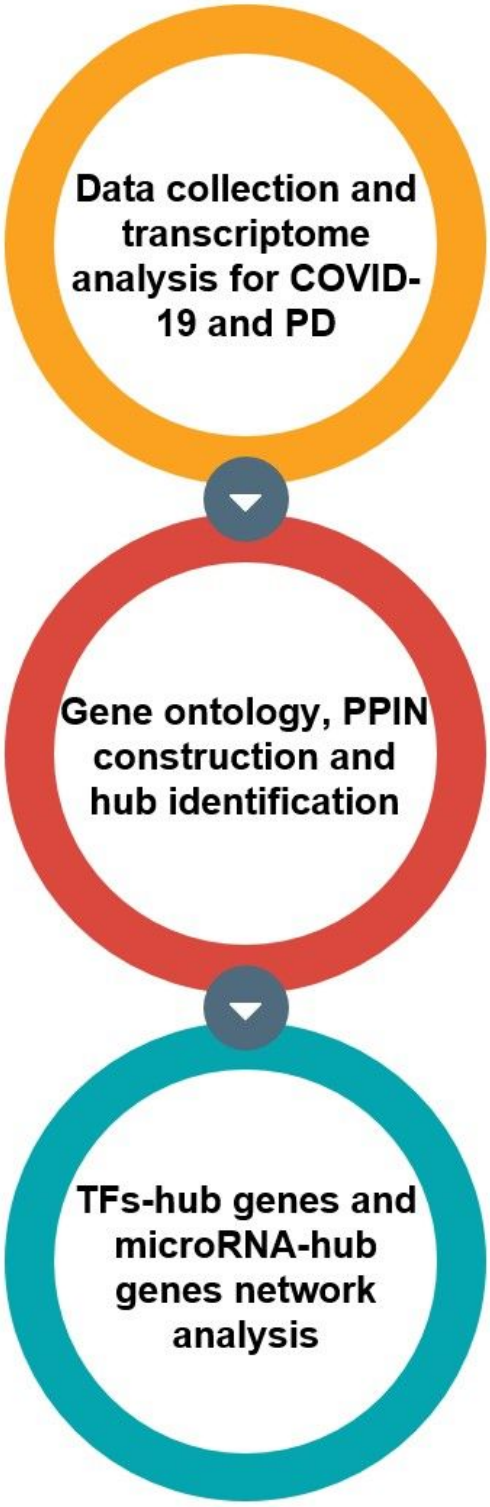

Figure 1

Flow chart of steps conducted in the study

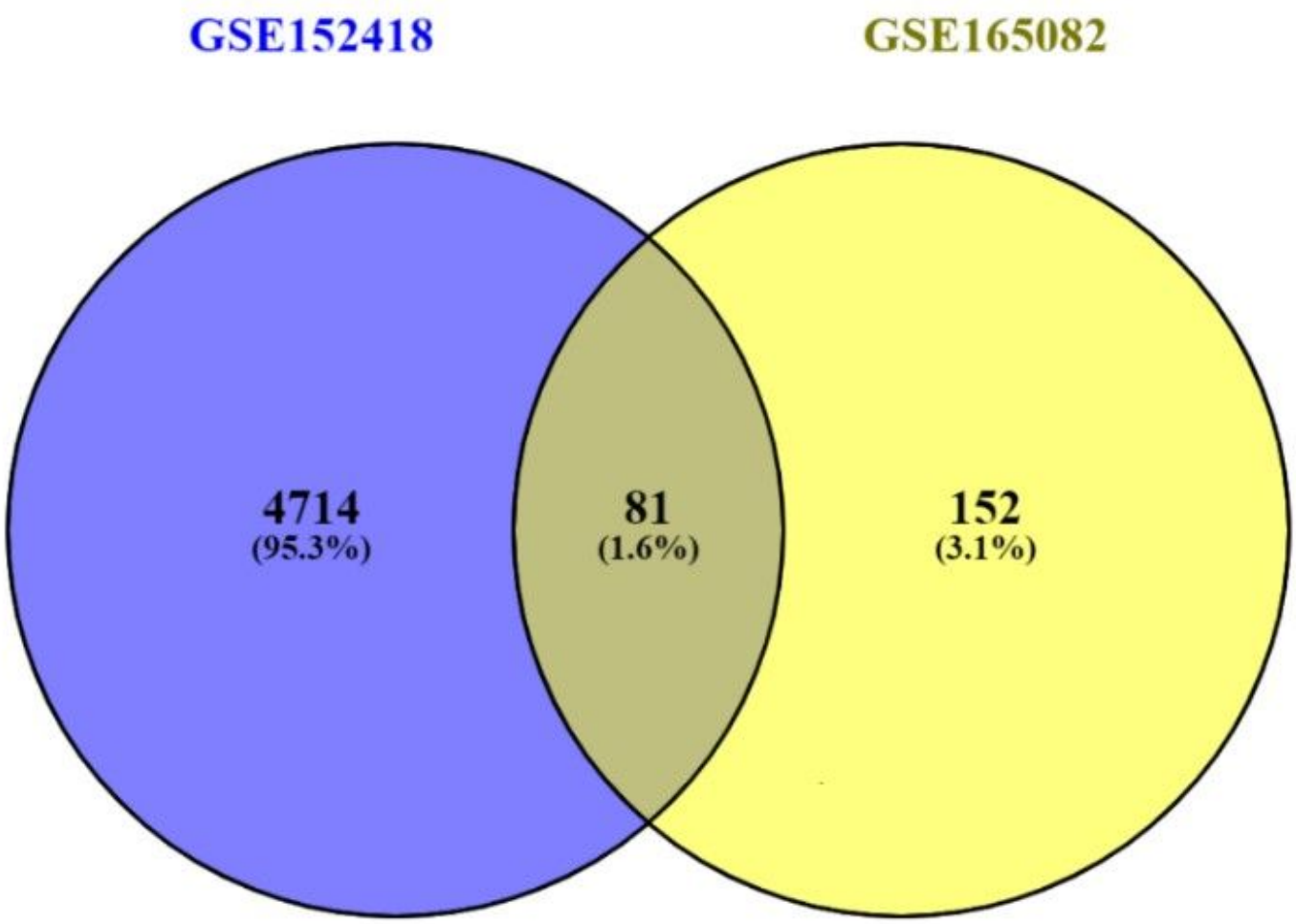

Figure 2

Venn diagram shows common DGEs between Covid-19 and PD

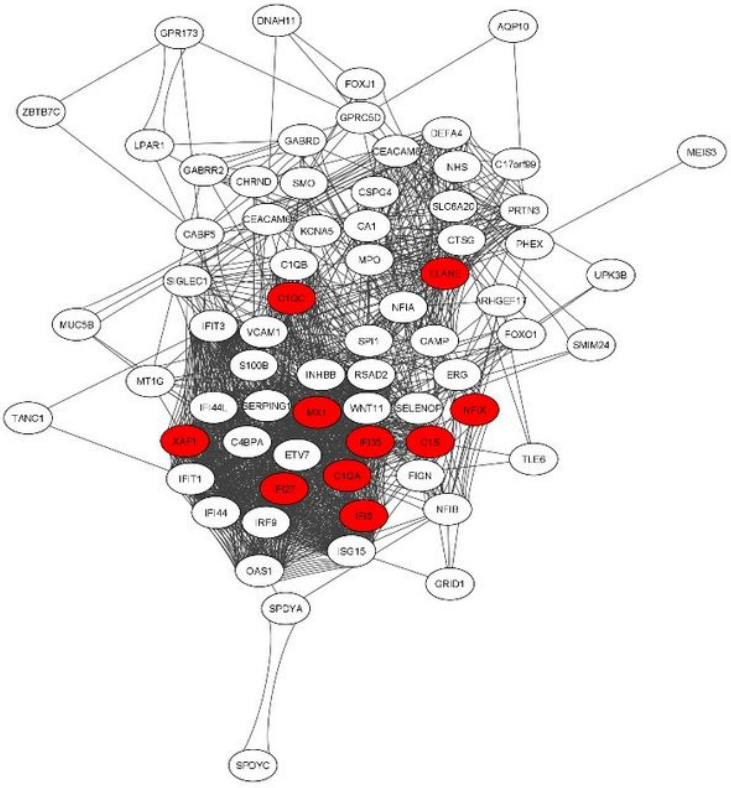

Figure 3

PPIN of common DEGs. Green nodes indicate top 10 hub genes identified by MCC

Figure 4

TFs-hub genes regulatory network acquired from Network Analysis web server. Square nodes representing TFs and circle nodes are stand for Hub genes

Figure 5

miRNAs-hub genes regulatory network acquired from Network Analysis web server. Square nodes represent miRNAs that regulate circle nodes which denote Hub genes