Title

Identification of Effective Genes in Feline Infectious Peritonitis and Drug Repurposing Using Systems Biology Approach

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Keywords

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Abstract

Feline Infectious peritonitis (FIP) is a systemic infectious disease of cats of viral origin in the coronavirus. The lack of clear signs of the virus before the clinical form of the disease, as well as the absence of easy and inexpensive diagnostic tests to confirm the virus's presence are other problems in controlling and preventing the spread of the virus. Additionally, has not yet had approved drug or treatment protocol for this disease. In this paper, the gene co-expression network was first reconstructed and modulated using the STRING database and Cytoscape

software. The gene ontology and pathways of the modules were obtained using the DAVID and KEGG databases. The most important possible pathways are: Proteasome, Protein processing in endoplasmic reticulum, Protein export, Aminoacyl-tRNA biosynthesis, Phagosome, Tuberculosis and T cell receptor signaling pathway. In the other part of the study, the gene-drug network regeneration strategy was used to identify a potential drug that was reconstructed using the DGIdb database and Cytoscape software using the drug gene network. BORTEZOMIB, CARFILZOMIB, OPROZOMIB, IXAZOMIB CITRATE, MARIZOMIB, BCG VACCINE, IC14, NELFINAVIR, RITONAVIR, are some of our recommended drugs for this disease. Although our computational strategy predicts repurposable candidate drugs against FIP, more detailed experimental trials and clinical analyses of drug performance, toxicity, and validation are necessary to achieve an accurate and improved treatment protocol.

Abbreviations

BP: Biological processes

CC: Cellular components

FCoV: Feline coronavirus

FIP: Feline infectious peritonitis

FIPV: Feline infectious peritonitis virus

GO: Gene ontology

MF: Molecular functions

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

The text summarizing results with no other divisions

Feline Infectious Peritonitis (FIP) is a severe disease primarily affecting younger cats [1, 2]. Diagnosis is challenging due to the lack of definitive tests and specific symptoms [3]. It is caused by feline coronavirus (FCoV), an RNA virus belonging to the Alphacoronavirus genus with serotypes 1 and 2 [4]. Serotype 1 is more prevalent [2], but research focuses on serotype 2 due to easier laboratory propagation. FCoV can persist in dry environments for up to seven weeks and spreads indirectly [5].

Detecting FIP early is problematic as clinical signs and imaging lack of specificity. Real-time polymerase chain reaction tests for viral RNA are inconclusive. Due to its rapid progression and diagnostic limitations, prevention outweighs treatment options [5–7].

Efforts to develop a vaccine have been hindered by antibody-dependent enhancement [8]. Thus, identifying effective treatments is critical. This study employs computational biology to analyze gene expression data (dataset GSE152676) from healthy and FIP-infected cats. Gene ontology (GO) analysis using the DAVID database identifies relevant biological processes [9].

The research aims to pinpoint FIP-related genes and potential drug targets efficiently. By leveraging a drug-gene interaction network, the study rapidly identifies candidate drugs through bioinformatics and gene co-expression network analysis. This approach enhances understanding of FIP mechanisms and aids in developing effective treatments [10].

In this study, gene expression data for FIP was obtained from the NCBI database using the GSE152676 dataset [11], which includes data from healthy and FIP-affected cats. The dataset comprises 19,493 transcripts obtained via Illumina sequencing. Significant gene expression differences (p-value <0.001) between healthy and FIP groups were identified, resulting in 1,332 genes for network construction.

The gene co-expression network was constructed using the String database (version 11.5) [12], focusing on 1,332 genes from the previous step, specifying Felis catus as the species of interest.

The network settings emphasized co-expression interactions with a confidence score of 0.40, excluding unconnected nodes. High-confidence data were obtained by adjusting interaction settings. The network was visualized and refined using Cytoscape software [13], employing graph theory principles to reconstruct the main gene co-expression network (Figure 1).

Clustering:

The cluster analysis of biological networks has become one of the most significant strategies for identifying functional modules and predicting network biomarkers and protein complexes. The visualization of the clustering outcome is highly important for demonstrating the structure of biological networks [14]. The ClusterVis [15] plugin (version 1.0.3) was used to cluster the main network and to analyze this biological network. Cytoscape software is a powerful instrument for drawing and analyzing networks [13]. It is a platform that can be employed to run the ClusterVis plugin. In this step, the gene co-expression network data obtained from the string site were imported into the Cytoscape software, version 3.8.2. Then, five performance modules were obtained using the ClusterVis plugin and the Algorithm: FAG-EC parameters and setting the algorithm parameters to DefinitionWay: Strong and OutputThreshold: 10. The list of cluster genes is provided in the supplementary file.

The GO section, contains information about Biological Processes (BP), Cellular Components (CC) and Molecular Functions (MF).The BP, refers to a biological target that comprises a gene or gene product. The procedure is performed through one or several regular sets of molecular functions. The CC refers to the location and structure in the cell in which the gene product is active. The MFs are defined as the biochemical activity (involving a particular binding of ligands or structures) of a gene product [16].

In this step, the list of functional cluster genes, which were obtained from the previous step, was entered into the DAVID site. Several categories of functional information were obtained after providing the requested information and selecting the species Felis catus as the examined

species. GO and pathway sections were among the objectives of our study. In the GO section, the findings of all BP, CC, and MF categories were presented in different evaluations for each category. Moreover, we loaded and stored data for all categories and clusters in order to select more detailed data. All data were arranged according to the p-value and the pathways of each of the five clusters were separately loaded for reviewing and reporting purposes. The PATHWAY database is a collection of diagrams ~~that have been~~ drawn manually. They are called KEGG reference pathway diagrams (maps), each of which is related to a known network of functional importance. The KEGG site was used to gain access to the pathway database [16–19].

The Drug-Gene Interaction Database (DGIdb) is a web resource that collects and presents information on gene-drug interactions from papers, databases, and other web-based sources [20]. It is not a source of information on animal drugs and includes human drugs. Nonetheless, this study could suggest suitable drug candidates for further progressive studies. The set of all involved genes was entered into the clusters in this database. All the predicted drugs for these genes were extracted, and the drugs were examined based on their effects on the involved genes and their participation in the main pathways.

GO and Pathway Enrichment Analysis:

Pathway analysis identified key pathways for each module based on p-value and gene participation:

- Module 1: Proteasome, Influenza A, Measles, Hepatitis C, Herpes simplex infection.
- Module 2: Protein processing in the endoplasmic reticulum (26/56 genes, p-value 1.81e-34) and protein export.
- Module 3: Aminoacyl-tRNA biosynthesis.
- Module 4: Phagosome, Tuberculosis.
- Module 5: T-cell receptor signaling pathway.

Complete pathway details and participating genes are in the supplementary files.

Functional Interpretation of GO Co-expression Networks in FIP:

GO analysis using DAVID categorized information into Biological Processes (BP), Cellular Components (CC), and Molecular Functions (MF) for all five clusters, reported with p-values <0.0 .

Key BPs included:

- Module 1: Response to virus, defense response, proteolysis.
- Module 2: Intracellular protein transport, protein targeting to the membrane.
- Module 3: tRNA aminoacylation, amino acid activation.
- Module 4: Regulation of cytokine production, immune response.
- Module 5: Positive regulation of leukocyte-mediated immunity.

Detailed BP, CC, and MF data are provided in the supplementary files to manage complexity and maintain study focus.

This study employed a bioinformatics approach to unravel genes and pathways involved in FIP, proposing repurposable drugs. Expression-modified genes from healthy and FIP-infected groups were sourced from NCBI [11]. A gene co-expression network was constructed and analyzed, revealing five gene clusters. Drugs targeting these genes were identified from the DGIdb human drug database.

Proposed Candidate Drugs:

Genes from identified modules underwent analysis using the DGIdb database to pinpoint potential drugs, visualized via Cytoscape (Figure 2). Notably, BORTEZOMIB and CARFILZOMIB (linked to nine genes), OPROZOMIB and IXAZOMIB CITRATE (eight genes), and MARIZOMIB (four genes) emerged as proteasome inhibitors [21–25]. Other drugs with significant genetic associations include BCG VACCINE, IC14, NELFINAVIR, and RITONAVIR. Comprehensive drug predictions are detailed in the supplementary files.

The major pathways obtained using bioinformatics databases involved Proteasome, Protein processing in the endoplasmic reticulum, Protein export, Aminoacyl-tRNA biosynthesis, Phagosome, Tuberculosis, and the T-cell receptor signaling pathway. The proteasome pathway, crucial for cellular regulation and quality control (p-value: 4.76E-12), emerged prominently. Proteasome inhibitors like BORTEZOMIB [23], CARFILZOMIB [22], OPROZOMIB [22], IXAZOMIB CITRATE [24], and MARIZOMIB [25], originally used in cancer therapy [26], were highlighted as potential treatments for FIP. Their role in regulating key cellular proteins via the ubiquitin-proteasome system suggests antiviral potential, crucial for various stages of coronavirus infection and potentially reducing antiviral resistance [27, 28]. The study recommends these drugs as robust therapeutic options for FIP.

The Tuberculosis pathway (p-value: 5.86E-04) shares similarities with FIP, involving expression-modified genes CD14, TLR4, and TLR2 [11, 29, 30], also in the Toll-like receptor signaling pathway (p-value: 0.001873) [31]. One of the drugs targeting the CD14 gene is IC14 [32], could thus serve as a potential FIP treatment by inhibiting its activity, as seen in studies on SARS-CoV-2 [33].

In addition to the tuberculosis pathway, the Toll-like receptor signaling and phagosome pathways (p-value: 3.92E-07) also share common genes with tuberculosis (i.e., LTR4), the drugs suggested on the Tuberculosis pathway can be effective on the two mentioned pathways. NELFINAVIR, a protease inhibitor, shows promise in reducing HIV viral load and increasing CD4+ cells [34], demonstrating antiviral effects on FIP in vitro [1] and potential with Galanthus nivalis agglutinin for FIP [35] and SARS-CoV-2 inhibition [36].

RITONAVIR, another HIV protease inhibitor [37], was tested with LOPINAVIR for SARS-CoV-2 but did not reduce mortality [38]. GC376 [39] and GS-441524 [40] show promise in FIP treatment, though concerns about resistance and tissue distribution remain. Effective

treatments for FIP are crucial due to the toxicity of FIPV inhibitory doses and the absence of approved therapies [41, 42].

REMDESIVIR (GS-5734), a nucleoside analog with broad antiviral activity including FIPV [42], MERS CoV, and SARS CoV [43], has FDA approval for SARS-CoV-2 treatment [44]. XRAPHCONN®, containing GS-441524, shows promise in FIP treatment but lacks widespread approval, despite being easier to synthesize than REMDESIVIR [5, 45].

The development of drugs for treating FIP and other animal coronaviruses can prevent animal deaths and future virus spread. However, this study's computational approach and limited experimental resources could not validate the drugs or confirm the analyzed pathways in vitro and in vivo. Experimental validation and clinical trials are necessary to ensure the effectiveness and safety of the identified candidate drugs for FIP treatment.

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Figure legends

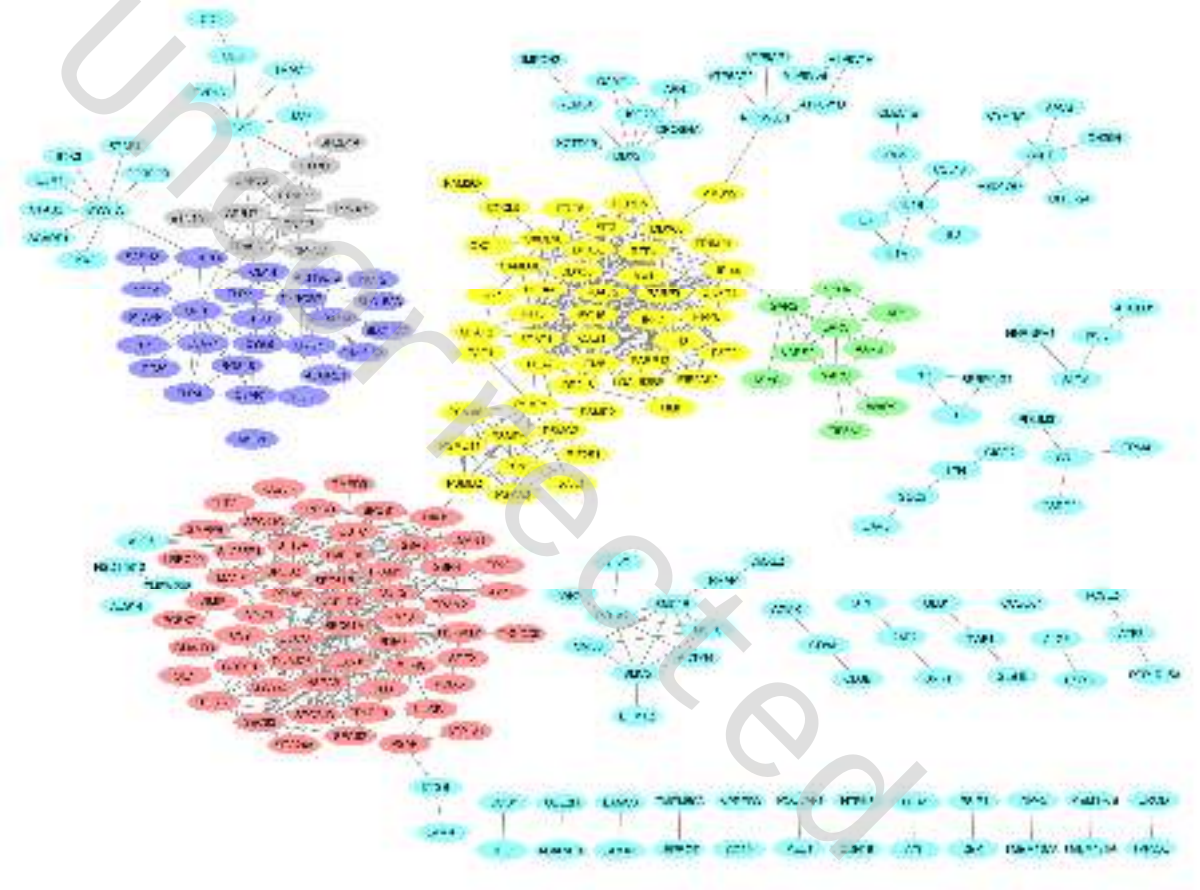

Figure 1. Gene co-expression network for the primary gene list. In this network, there are 263 nodes (genes) and 698 edges (co-expression). Edges represent the interactions between nodes. Genes are shown in different colors according to their clusters. Cluster 1 is represented in pink, Cluster 2 in yellow, Cluster 3 in green, Cluster 4 in blue, and Cluster 5 in gray. Genes that are not assigned to any clusters are shown in light blue.

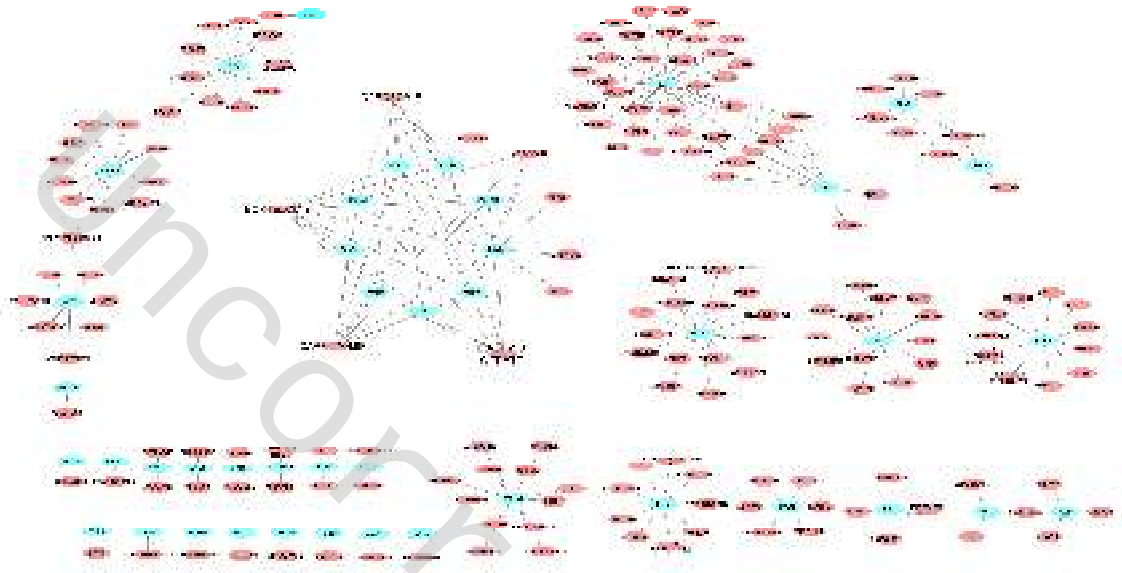

Figure 2. Drug-Gene interaction network. Circle and hexagon nodes indicate genes and drugs, respectively.

Online supplemental material

Supplementary Excel file. The complete information of all modules separately for BP, CC, MF and phatways, as well as Gene-Drug network data, is provided in this supplementary excel file.

Table 1. The details of the gene co-expression modules.

Table 2. The significant biological pathways for all five clusters.

Table 3. The candidate drugs.

Visual abstract. Visual abstract of the research process

Table 1.
The details of the gene co-expression modules.

module no.	No.	List of genes
co-expression-module-1	49	EIF2AK2, PSMD11, NMI, TXNL1, PSMB2, PSME2, PSMA6, PSMD3, PSMD4, FAM26F, CXCL11, STAT1, IFIT3, IFIT2, IRF1, UBA7, CXCL9, TRIM21, RSAD2, DHX58, CXCL10, TAP1, SAMD9L, PARP12, ISG15, STAT2, MX1, IRF7, IFI35, RTP4, LGALS3BP, OAS1, HERC6, BST2, IFI44L, HERC5, IFI44, MMS19, DTX3L, PARP9, DDX58, ZNFX1, DDX60, PSMA3, UBE2L6, PSMC2, EIF2S1, IFI6, PSMB9
co-expression-module-2	56	SRPRB, TMED10, LRRC59, TRAM2, SSR3, P4HB, MANF, KDELR2, SPCS1, SEC62, SSR2, PPIC, SLC33A1, PCSK7, SSR4, DNAJC3, OS9, DAD1, HSP90B1, ERLEC1, SLC35B1, SEC61B, SDF2, HSPA5, TXNDC5, VIMP, HDLBP, DNAJB9, SEC61A1, SEC24D, PDIA5, PDIA3, SEC63, DDOST, CANX, LMAN1, TRAM1, SND1, SSR1, HM13, SIL1, SEC24A, SEC23B, COPG1, NUCB1, STT3A, CLTCL1, GMPPB, RAB5IF, PSAP, ATP1A1, PDIA6, TMED9, SPCS2, OSTC, SEC11C
co-expression-module-3	10	ASNS, MARS, HARS, AARS, WARS, EIF5A2, VARS2, GARS, NARS, LARS
co-expression-module-4	26	WAS, SASH3, TLR2, CD14, CORO1A, NCF2, TYROBP, SPI1, BLK, CTSS, SLC11A1, ADGRE1, CYBB, SLC15A3, CD80, PTAFR, FGR, C5AR1, ARHGDIB, TLR4, SRGN, MSR1, RGS18, C1orf162, ALOX5AP, C3AR1
co-expression-module-5	10	CD247, TRAF3IP3, BTN1A1, GRAP2, SH2D1A, P2RX7, GPR174, INPP5D, CD3D, ZAP70

Table 2.
The Significant Biological Pathways for all Five Clusters.

Cluster no.	PATHWAY	*p*-Value
co-expression-module-1	Proteasome	4.76E-12
	Influenza A	1.06E-08
	Measles	7.51E-07
	Hepatitis C	8.76E-07
	Herpes simplex infection	6.34E-06
co-expression-module-2	Protein processing in endoplasmic reticulum	1.81E-34
	Protein export	6.96E-12
co-expression-module-3	Aminoacyl-tRNA biosynthesis	2.44E-15
co-expression-module-4	Phagosome	3.92E-07
	Tuberculosis	5.86E-04
	Toll-like receptor signaling pathway	0.001873
co-expression-module-5	T cell receptor signaling pathway	0.002116

Table 3.
The candidate drugs.

Drug	No.	Gene
BORTEZOMIB	9	PSMD11, PSMB2, PSME2, PSMA6, PSMD3, PSMD4, PSMA3, PSMC2,PSMB9
CARFILZOMIB	9	PSMD11, PSMB2, PSME2, PSMA6, PSMD3, PSMD4, PSMA3, PSMC2,PSMB9
OPROZOMIB	8	PSMD11, PSMB2, PSMA6, PSMD3, PSMD4, PSMA3, PSMC2, PSMB9
IXAZOMIB CITRATE	8	PSMD11, PSMB2, PSMA6, PSMD3, PSMD4, PSMA3, PSMC2, PSMB9
MARIZOMIB	4	PSMB2, PSMA6, PSMA3, PSMB9
RITONAVIR	2	CXCL10, TLR4
NELFINAVIR	1	TLR4
IC14	1	CD14
BCG VACCINE	1	EIF2AK2