

A systems biology analysis of protein-protein interaction of digestive disorders and Covid-19 virus based on comprehensive gene information

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ABSTRACT

Aim: Analysis of networks of digestive disorder and their relationship with Covid-19 based on systems biology methods, evaluation similarity, and usefulness of networks to give a new treatment approach.

Background: Digestive disorders are typically complex diseases associated with high treatment costs. They are related to the immune system and inflammation. With the outbreak of Covid-19, this disease was shown to have signs like diarrhea. Some signs of Covid-19 are similar to those of digestive disorders, like IBD and diarrhea. Both of them are accompanied by inflammation and induce disorders in the digestive system.

Methods: DisGeNET and STRING databases were sources of disease genes and constructing networks and were used to construct the network of digestive diseases and Covid-19. Three plugins of Cytoscape software, namely ClusterONE, ClueGO, and CluePedia, were used to analyze cluster networks and enrichment pathways. To describe the interaction of proteins, information from KEGG pathway and Reactome was used.

Results According to the results, IBD, gastritis, and diarrhea have common pathways. The CXCL8, IL-6, IL-1 β , TNF- α , TLR4, and MBL2 molecules were identified as inflammatory molecules in all networks.

Conclusion: It seems that detecting genes and pathways can be useful in applying new approaches for treating these diseases.

Keywords: Digestive system disorders, Covid-19, IBD, Systems biology, Diarrhea, Gastritis.

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Introduction

Coronavirus from the large Coronaviridae family can cause diseases in humans and birds. SARS-CoV2 (Covid-19) was detected for the first time in 2019 in Wuhan, China, and three months later, it was widespread in the world and led to a pandemic (1). To date, physicians have reported many signs and symptoms of Covid-19, such as its effects on the

digestive tract, nervous system, blood circulation, heart, lung, and kidney (2, 3). Studies have also reported that the coronavirus implicates 1844 genes, some of which are common among other diseases. The genes involved in digestive disorders like cholecystitis, diarrhea, gallstone, gastritis, irritable bowel disease, stricture, and acid reflux also are common for Covid-19 (4).

Cholelithiasis is inflammation of the gallbladder; this disease is not well understood, but some similarities between cholelithiasis and gall stone disease have been discovered (5). Diarrhea is a disease defined by abnormal fluidity in stools, and this is common in developing countries, specifically Africa, shown by the high mortality rate in children (6). A

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recent study done by Li et al. (2020) described diarrhea as the most common symptom (fifth main symptom) in Covid-19 patients (7). Gastritis is known as the acute or chronic inflammation of the stomach lining (8). There are many reasons for gastritis, such as alcohol abuse and the long-term intake of non-steroidal anti-inflammatory drugs (9). Recently, studies have shown patients with gastritis and inflammatory bowel disease (IBD) are at high risk of Covid-19 because of the high activity of ACE2 in their plasma (10-12). Sometimes Covid-19 can weaken patients with IBD, and it may lead to their death (13, 14).

A stricture occurs in intestinal fibrosis and collagen accumulation (15). The main reasons for stricture are cancer and inflammatory bowel disease; Crohn's disease is also a cause of stricture in the small bowel (16). Based on recent findings, there are some common genes between stricture and Covid-19 (4). Gastroesophageal reflux is a common digestive disorder that affects millions of people worldwide (17). In addition to risk factors like diet, smoking, and body mass index, it has been suggested that some genes are important for acid reflux (18, 19). This study aims to investigate common genes and protein-protein interactions among the mentioned diseases and Covid-19 infection to find the similarities between gene pathways. It seems that finding the same gene pathway in those diseases can help find an approach to treating Covid-19 infection.

Methods

DisGeNET is an available platform that includes one of the largest collections of genes and variants associated with human disease (20). The related genes of digestive disorders (mentioned in the introduction) and Covid-19 were exported from the DisGeNET database and used to construct the PPI network. The Search Tools for Detecting Interacting Genes/Proteins (STRING), a database for predicted protein-protein interactions at EMBL, clusters the elicited results from

many protein-protein interactions databases, like Mint, BioGrid, etc. To describe the interaction of proteins, information from the KEGG pathway at the address www.genome.jp/kegg/ and Reactome at address www.reactome.org was used (21). We constructed digestive disorders and Covid-19 networks by submitting the list of genes to the STRING database at the address www.string-db.org and analyzed the networks by Cytoscape software at the address www.cytoscape.org (22).

A network includes nodes (e.g., genes or proteins) and links/edges (e.g., co-expression relationships or physical interactions). In biology, network terms, degree, and betweenness are central parameters for analyzing network topology. Edges/links of a node are named the degree of that node. Nodes with high degrees are called hubs, and nodes that achieve top-ten or top-five percent of betweenness centrality are called bottlenecks (both based on the researcher's definition) (23). Therefore, the nodes that simultaneously have hubs and bottlenecks are called hub-bottlenecks (24). The standard deviation (SD) and average degree (AD) were calculated, and nodes with more than two *SD + AD were selected as hub proteins in each network. In addition, the top five percent of betweenness centrality measures were selected as bottleneck proteins. Common genes, hubs, and bottleneck proteins of these Covid-19 and digestive disorder gene networks were extracted and used for more analysis. The common networks were constructed by importing common genes in the STRING database and clustered by the ClusterONE plugin of Cytoscape software (25). This software found overlapping protein complexes in a protein interaction network uploaded into Cytoscape (overlap threshold = 1, node penalty = 0, haircut threshold = 0) (26). By ClueGO and CluePedia plugins of Cytoscape software, pathway enrichment and the relation between pathways were accomplished (27, 28) (table 1).

Table 1. The enrichment of three modules for diseases.

Disease	Adjusted p-Value	Module
Immunodeficiency	4.070772946660061E-4	Blue module
Macular Degeneration	2.447422407186003E-6	Green module
Anemia	5.473352213598934E-9	Red module

Results

Using the DisGeNET database, we extracted 844 genes for Covid-19, 56 genes for cholecystitis, 631 genes for diarrhea, 52 genes for gallstone, 293 genes for gastritis, 428 genes for irritable bowel disease (IBD), 29 genes for stricture, and 51 genes for acid reflux; 219 genes were shared among all diseases. Three diseases, i.e. IBD, gastritis, and diarrhea, showed some common genes with Covid-19, but the other three diseases showed no common gene. Using the STRING database, the common genes network was constructed. The Covid-19 network showed 219 nodes and 4932 edges (Figure 1).

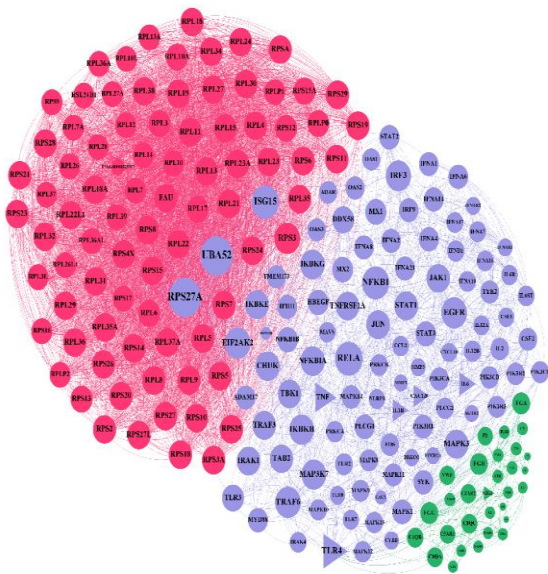


Figure 1. Common gene network containing 219 nodes and 4932 Edges. This network includes three modules that are shown by blue (cluster one), red (cluster two) and dark green (cluster three).

The nodes have been colored in green; Covid-19 genes and some of those were colored red, because they were common with IBD, gastritis, and diarrhea genes.

In the next step, the general network of Covid-19 genes was illustrated in which common genes with diarrhea are shown in red (Figure 2). The network of Covid-19 genes showed that some of these genes were common with gastritis. The nodes colored green are Covid-19 genes, and common genes with gastritis are colored in red (Figure 3). The association of Covid-19 genes and IBD has been shown. The nodes in green color are Covid-19 genes, and common genes with IBD are in red (Figure 4). The genes that are common

between the three diseases are shown by a triangular shape.

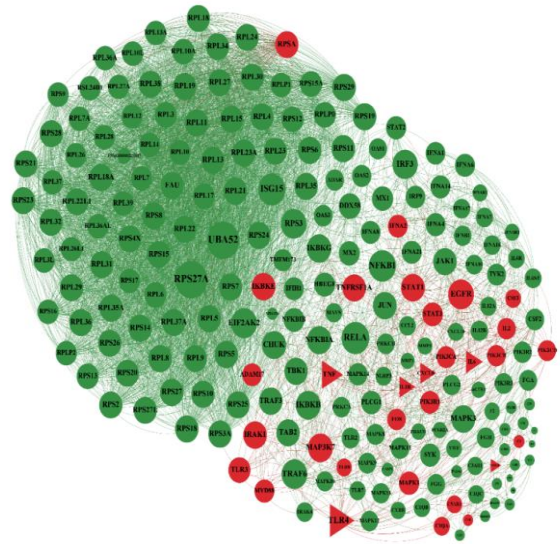


Figure 2. Common genes between Covid19 and diarrhea. Involved genes in covid19 are shown with green and common genes with diarrhea are red

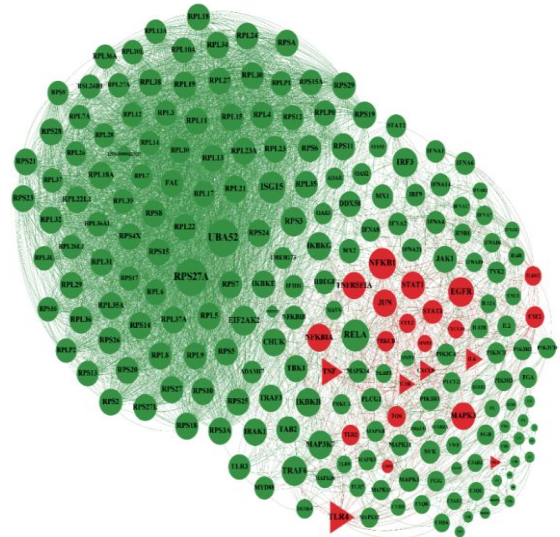


Figure 3. Common genes between Covid19 and gastritis. The genes were colored by green are involved in covid19 and common genes with gastritis are in red.

Discussion

In systems biology science, PPI network analysis and pathway enrichment have been broadly used for discovering main proteins and pathways underlying complex diseases (29). Different types of disorders such as neurodegenerative and many cellular conditions have been analyzed (30, 31, 32, 33, 34, 35).

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