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COVID-19: A Drug Repurposing and Biomarker Identification by Using Comprehensive Gene-Disease Associations through Protein-Protein Interaction Network Analysis — Source link

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COVID-19: A drug repurposing and biomarker identification by using comprehensive gene-disease associations through protein-protein interaction network analysis

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Abstract

COVID-19 (2019-nCoV) is a pandemic disease with an estimated mortality rate of 3.4% (estimated by the WHO as of March 3, 2020). Until now there is no antiviral drug and vaccine for COVID-19. The current overwhelming situation by COVID-19 patients in hospitals is likely to increase in the next few months. About 15 percent of patients with serious disease in COVID-19 require immediate health services. Rather than waiting for new anti-viral drugs or vaccines that take a few months to years to develop and test, several researchers and public health agencies are attempting to repurpose medicines that are already approved for another similar disease and have proved to be fairly effective. This study aims to identify FDA approved drugs that can be used for drug repurposing and identify biomarkers among high- risk and asymptomatic groups. In this study gene-disease association related to COVID-19 reported mild, severe symptoms and clinical outcomes were determined. The high-risk group was studied related to SARS-CoV-2 viral entry and life cycle by using Disgenet and compared with curated COVID-19 gene data sets from the CTD database. The overlapped gene sets were enriched and the selected genes were constructed for protein-protein interaction networks. Through interactome, key genes were identified for COVID-19 and also for high risk and asymptomatic groups. The key hub genes involved in COVID-19 were VEGFA, TNF, IL-6, CXCL8, IL10, CCL2, IL1B, TLR4, ICAM1, MMP9. The identified key genes were used for drug-gene interaction for drug repurposing. The chloroquine, lenalidomide, pentoxifylline, thalidome, sorafenib, pacitaxel, rapamycin, cortisol, statins were proposed to be probable drug repurposing candidates for the treatment of COVID-19. However, these predicted drug candidates need to be validated through randomized clinical trials. Also, a key gene involved in high risk and the asymptomatic group were identified, which can be used as probable biomarkers for early identification.

Keywords: COVID-19, SARS-CoV-2, 2019-nCoV, novel corona virus, drug repurposing, chloroquine, high-risk group, asymptomatic

1. Introduction:

Coronaviruses (CoVs) belong to positive-sense RNA viruses that are crown-shaped having club-like spikes on the outer surface (1). There are several types of coronavirus which infect human (2,3). The outbreak which started from December 2019 was found to be novel

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coronavirus (2019-nCoV) also called Severe Acute Respiratory Syndrome (SARS-CoV-2) causes Coronavirus Disease 2019 (COVID-19) (4). Recent findings suggest that clinical & pathological symptoms caused by COVID-19 resemble SARS, which is caused by the SARS coronavirus (SARS-CoV) (5,6). SARS-CoV and SARS-CoV-2 were both found to be from bat origin(7–11). It is thought that human to human transmission is through an intermediate host (12), while for SARS-CoV it is through civet cat. The SARS-CoV-2 intermediate host is still unknown(13,14). Though some studies predicted intermediate hosts to be though pangolin it is still not proven (15). SARS-CoV-2 and SARS-CoV are also known to infect humans using the same angiotensin-converting enzyme 2 (ACE2) receptor (16). While at the level of the whole genome, SARS-CoV-2 and SARS-CoV were found to be distantly related to sequence identity (79.6 %), but the spike-protein between two viruses was found to be very similar in structure (17).

The Spike protein present in both SARS-CoV and SARS-CoV-2 binds to the host cell through the receptor-binding protein called angiotensin-converting enzyme 2 (ACE2), which is located on the host membrane cell surface. While both SARS-CoV and SARS-CoV-2 bind to the same host cell as ACE2, the SARS-COV-2 binding affinity to ACE2 is significantly higher than that of SARS-CoV. The viral protein responsible for hosting and replication of SARS-CoV-2 entry is identical in structure to SARS-CoV (18,19). To date, there are no antiviral agents and vaccines available for SARS-CoV-2, although the possible antiviral drugs such as remdesivir, chloroquine, hydroxychloroquine, ritonavir/lopinavir with inteferon beta are used as preventive agents for COVID-19 for the treatment of this disease (20–22). Many computational studies are underway to identify potential anti-viral drugs and vaccines (23,24). According to the WHO and CDC, the common symptoms for COVID-19 are runny nose, sore throat, cough, fever, and difficulty in breathing for severe cases. In a recent report from Wuhan hospital based on clinical course and outcome of 107 patients, the clinical progression of COVID-19 is shown as a tri-phasic pattern that involves mild and severe cases of COVID-19 (25). According to the CDC, the severity of cases is mostly for those patients who have high-risk factors like hypertension, diabetes, heart disease, cancer, and lung disease (26).

The popular diagnostic element in the detection of SARS-CoV-2 is in respiratory specimens by next-generation sequencing or RT-PCR methods in real-time. The throat-swab or nasopharyngeal swab specimen collected from patients will be PCR re-examined at every other day. Also performed are regular blood count laboratory review, serum biochemical examination, coagulation profiling, myocardial enzymes, interleukin-6 (IL-6), serum ferritin, and procalcitonin. In addition to that CT scan or chest, radiographs are used for a routine check for the patients. The patient is considered to recover from COVID-19 if fever is absent for at least 3 days, improvement is noted in lung and chest CT, improvement in respiratory symptoms and negative for SARS-CoV-2 RNA for at least 24 hours from the collected throat-swab specimen of the patient (27–29).

Due to the over-welcoming rush of patients to hospitals, many countries have begun to accept COVID-19 patients only with severe conditions, while mild conditions such as fever and cough have been requested to self-quarantine for 14 days to avoid infecting others. Treatment is desperately needed at around 15 percent of COVID-19 patients with serious illness. Scientists are attempting to repurpose drugs that have already been approved for other similar diseases and have proved to be fairly effective rather than coming up with substances from

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scratch that may take years to develop and test (30–32). In this study, a gene-disease association study was performed for COVID-19 by comparing genes involved in causing symptoms, high-risk factors, and clinical outcomes to identify key genes involved in individual high-risk factors and asymptomatic symptoms for COVID-19.

2. Methods

2.1. Data source & retrieval:

DisGeNET(33) is one of the largest and comprehensive databases containing human gene-disease associations. All gene-disease association genes were retrieved from the DisGeNet database. This database contains a collection of genes associated with human diseases that contain integrated data from GWAS catalogs and animal models. All the gene-disease association genes were retrieved using the common Human Genome Organisation (HUGO) gene symbol. The gene-disease association was retrieved based on COVID-19 symptoms, clinical outcomes, risk factors, and SARS-CoV infection. Gene Ontology (GO) is the representation of genes with their biological properties. The all gene ontology related to viral entry and viral life cycle was downloaded from the amigo gene ontology database. The human gene-disease association related to COVID-19 was retrieved as follows:

(i) Gene Dataset (GD) construction from Disgenet (GD1)

1. Cough (n=92 genes)

2. Fever (n=874)

3. Dyspnea/Shortness of breath (n=187)

4. Pneumonia (n=496)

Risk factors

5. Heart Disease (n=324)

6. Kidney Disease (n=638)

7. Lung Disease (n=392)

8. Diabetes (n=1267)

9. Hypertension (n=1309)

10. Cancer (n=1437)

Clinical Outcomes

(i) Mild & Moderate Case

11. Lymphopenia (n=136)

12. Pulmonary infiltrate (n=18)

(ii) Severe Case

13.Leukocytosis (n=32)

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14.Neutrophilia (n=62)

15.Sepsis (n=528)

16.Kidney injury (n=91)

17.Coagulopathy (n=56)

18.Thrombocytopenia (n=340)

19.Multiple organ failure (n=16)

SARS-CoV-2 related homology-based gene-disease association

20. SARS-COV (n=84)

21. Viral entry (n=158)

22. Viral life cycle (n=654)

Asymptomatic gene sets

1. Cough (n=92 genes)

2. Sore throat (n=6 genes)

3. Runny nose (n=3 genes)

4. Diarrhea (n=328 genes)

5. Headache (n=85 genes)

(ii) The curated dataset from Comparative Toxicogenomics Database (CTD) (GD2)

The curated dataset related to COVID-19 gene sets were downloaded from CTD (34). These gene sets were collected from the MeSH terms (C000657245) under category respiratory tract disease & viral disease.

2.2. Data pre-processing

All gene-disease association of 22 lists containing related to COVID-19 **(GD1)** was compared using a multiple comparison tool called multiple list comparator tool available at molbiotools. The tool compares based on pairwise intersections with a full symmetrical matrix based on the Jaccard index. After the comparison, the common gene sets were obtained. All the genes were selected based on the Jaccard index of more than 0.3 from the DisGeNET. All gene sets constructed from disgenet **(GD1)** were compared with a curated dataset of COVID-19 **(GD2)** released from the Comparative Toxicogenomics Database containing 473genes. The overlapping gene sets **(GD3)** were selected for enrichment analysis

2.3. Gene enrichment analysis

The overlapping genes selected from gene set **(GD3)** were enriched for gene ontology mapping using with setting Benjamini and Hochberg with P-value less than 0.05 by using the panther tool(35).

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2.4. Construction of comprehensive Protein-Protein Interaction (PPI) network

The Protein-Protein Interaction network was constructed using the STRING database (36) by using selected enriched genes. The STRING is a database containing information on protein-protein interactions of both known and prediction-based. The selected genes were used to construct a PPI network using the String database with setting to 0.4 and above.

2.5. Protein-Protein network analysis and identification of key genes

The PPI network was visualized and analyzed by Cytoscape (37). The key genes were identified by using the cytohubba (38) app available in Cytoscape. It predicts important nodes or hubs in an interactome network by using several topological algorithms. In this study, Maximum Clique Centrality (MCC) was used to identify key/hub genes from the whole network.

2.6. PPI network construction for high-risk factor group

Apart from the comprehensive network, the PPI network was constructed only for high-risk factor groups separately to understand the mechanism of disease. For these, four separate networks were constructed for hypertension, diabetes, heart disease, lung disease, kidney disease, and cancer by using SARS-CoV disease-gene association, viral and viral life cycle from gene ontology.

2.7. PPI network construction for the asymptomatic group (without fever)

The PPI network was constructed for very mild symptoms like cough, runny nose, diarrhea to understand the mechanism of the asymptomatic group.

2.8. Drug-gene interaction analysis

The identified hub genes were predicted for therapeutic target or drug-using drug-gene interaction database (39) (DGIdb2.0; Http: //www.dgidb.org/). The setting was limited to the FDA approved drug database.

2.9. STITCH drug-gene network construction

The predicted FDA approved drugs from hub genes through the drug-gene interaction database were used for drug-protein network construction through the STITCH database (40). The drug was prioritized based on a network score of more than 0.9.

3. Results & Discussion

3.1. Identification of common genes for COVID-19

Based on symptoms, clinical outcomes of mild, moderate & severe cases of COVID-19 related disease, the high-risk factor involved in the COVID-19 severe cases-based disease-associated genes were selected for the study. The overall framework of workflow is shown in **Figure 1**. As the human disease-gene association is lacking for SARS-CoV-2 infection, gene sets related to SARS-CoV was used to relate various symptoms. A clinical outcome of other gene sets of viral entry and viral life cycle was included from the amigo gene ontology database (41). This comprehensive gene set was compared with the pairwise intersection method by using the Jaccard index. These genes selected based on the Jaccard similarity

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score, Jaccard score, disease-gene association score, and disease-disease association score based on the DisgeNet database.

Although these gene-disease associations cannot exclude false-positives, some diseases are better studied than others which can affect the gene-set. Because of this reason, the datasets probably will be noisy and incomplete due to the nature of the curation process. For this reason, the gene sets are selected only from human-data and any gene related to mouse and rat model is discarded. The common genes selected based on the Jaccard similarity score were 1930 **(Supplementary Table 1)**. These genes were compared with the curated list of COVID-19 from the CTD database containing 473 genes **(Supplementary Table 2)**. The non-redundant overlapping genes were selected for gene enrichment **(Figure 2)**.

The common genes are mapped through gene ontology and genes are selected based on the statistical significance of p-value less than 0.05. The selected genes were also compared with the STRING protein-protein interaction database and only the genes which have greater than 0.4 interactions were further selected for network construction. Based on the above criteria, 279 genes were selected as statistically significant enriched genes **(Table 1).**

3.2. Protein-Protein interaction network analysis for COVID-19 related genes

The process by which two or more proteins from a complex through non-covalent bonds is called protein-protein interaction (PPI). The molecular mechanisms of disease or new drug targets can be identified by using PPI network analysis. Moreover, this gene was used to construct Protein-Protein interaction and genes were selected based on the interaction score of more than 0.4 **(Figure 3)**. The PPI network was constructed using the STRING database and analyzed by Cytoscape. The hub genes were identified by using cytohubba using the MCC method **(Table 2)**. This method uses 11 centrality measures to identify the hub genes from the network. The identified top genes function predicted through gene mania webserver revealed that most of the genes were involved in an inflammatory response, cell chemotaxis, cytokine activity, cytokine receptor binding, regulation of inflammatory response and adaptive immune response **(Figure 4)**. The identified top 10 hub genes are as follows:

VEGFA

This is important for viral infection and its associated pathology(42). Vascular Endothelial Growth Factor promotes SARS-CoV viral entry.

TNF

Inflammation is a biological reaction resulting in a possible threat. This response may be natural but, under some circumstances, the immune system may attack the normal cells or tissues of the body that cause an abnormal inflammation due to viral entry. TNF- has been identified as a key inflammatory response regulator. TNF signaling responses in the lung to promote viral entry and persistence, pro-inflammatory cytokine tumor necrosis factor-alpha can be readily detected after infection (43,44).

IL-6

Interleukin 6 (IL-6) is developed in response to induced infection and tissue damage. It is stated that the up-regulation of IL-6 can promote viral survival or alleviation of the disease during viral infections (45).

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CXCL8

ELR-containing CXC chemokines CXCL8 promotes Neutrophil infiltration. Neutrophil (PMN) infiltration plays a central role in inflammation and is a major cause of tissue damage. This neutrophil infiltration may perform phagocytosis and cause adverse effects of inflammation due to viral associated damage (46).

Interleukin-10 (IL-10) is an immunoregulator to prevent tissue damage, however, the virus evolves to exploit immunoregulatory mechanisms for their survival in the infected host (47).

CCL2

The CCL2 gene significantly enhances the pathogenesis and replication of viruses (48–50)

IL1B

IL-1B gene is reported to be mediating acute pulmonary inflammation through inflammation of lung cells during viral infection (51)(52).

TLR4

The TLR4 Toll-like receptor 4 activation helps to create a defensive immune response but an excessive inflammatory response can lead to damage to the host during viral infection (53,54).

ICAM1

ICAM-1 (Intercellular Adhesion Molecule 1) gene is stated to play a major role in infectious disease in viral replication modulation and also as a site for the cellular entry of certain viruses. ICAM-1 is caused by interleukin-1 and tumor necrosis factor (TNF) and expressed by the lymphocytes and vascular endothelium (55,56).

MMP9

MMP9 is developed by a variety of cells in the respiratory tract and has been reported to play a key role during pulmonary viral infection due to immune response modulation. MP9 has anti-Respiratory Syncytial Virus properties that enhance viral clearance, neutrophil recruitment, and loss of MMP9 expression (57). It will be interesting to study the role of MMP9 in innate responses to SARS-CoV-2 infections further.

3.3. Protein-Protein Interaction network analysis for high-risk factor

To understand the genes associated during SARS-CoV-2 infection, **a** separate network was constructed for each risk factor groups like hypertension, diabetes, kidney disease, lung disease, cancer with SARS-CoV diseases associated gene, viral entry, and viral life cycle gene ontology-based gene sets and compared with curated the CTD dataset. The top 10 key genes for hypertension high-risk groups were VEGFA, IL6, TNF, CCL2, MMP9, ALB, IL10, PTGS2, CXCL8, CASP3, and the predicted drugs were paclitaxel, thalidomide, and rapamycin. The top key genes for the diabetic high-risk group were IL, TNF, CXCL8, IL10, CCL2, ICAM1, IFNG, IL2, FN1, CXCR4, and the predicted drugs were plerixafor, quinine, pentoxifylline, and rapamycin. The key genes involved in heart disease high-risk group of COVID-19 were IL6, TNF, CXCL8, CCL2, MAPK1 EGFR, ICAM1, CCL5, CXCR4, AGT, and the predicted drugs were plerixafor, afatinib, gefitinib, paclitaxel, and Cortisol. The key

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genes involved in lung disease high-risk group of COVID-19 were IL6, TNF, CXCL8, IFNG, CCL5, IL10, CCL2, ICAM1, CXCL1, CXCR4, and the predicted drugs were plerixafor. The key genes involved in kidney disease high-risk group of COVID-19 were IL6, TNF, CXCL8, CCL2, IL10, ICAM1 CCL5, FN1, EGFR, CXCR4, and the predicted drugs were plerixafor afatinib bosutinib erlotinib lapatinib vendetanib and pentoxifylline. The key genes involved in cancer high-risk group of COVID-19 were VEGFA, STAT3, IL6, TNF, MAPK3, MAPK1, CASP3, MMP9, PTGS, EGF, and the predicted drugs were gentamicin, hydroxychloroquine sorafenib sulindac thalidomide erlotinib and vandetanib **(Table 3)**.

An inflammatory cytokine is a signaling molecule secreted from helper T Cells which includes interleukin-1. Tumor necrosis factor-alpha plays an important role in mediating the innate immune response. The excessive production of inflammatory cytokines due to COVID-19 disease contributes to inflammatory disease. Such cytokines include interferons, interleukins, chemokines, colony-stimulating factors, and tumor necrosis factors and lead to coronavirus infection symptoms such as redness, swelling/edema, fever, and pain. The overproduction of pro-inflammatory cytokines can lead to a "cytokine storm," during which inflammation spreads throughout the body through the circulation (58,59). This pro-inflammatory cytokine has negative adverse effects such as inflammation of the kidney, lungs, and heart, which is the reason for patients to be prone to a high-risk group for COVID-19 (60).

3.4. Protein-Protein Interaction network analysis for asymptotic person

The protocol is usually practiced at all entry points to assess body temperature for fever and is isolated for laboratory research. However, for people who have no symptoms or very mild, cold-like symptoms like runny nose, cough, and sore throat are overlooked. In general, asymptomatic infections cannot be identified until they are confirmed by RT-PCR. Yet it is treated as a silent carrier. Finding genes related to asymptomatic showing just sore throat, cough, runny nose, headache without fever will improve understanding of COVID-19 transmission and spectrum of the disease it causes and it will provide insight into the pandemic cause. The protein-protein network was constructed with symptoms like cough, runny nose, sore throat along with SARS-CoV, viral entry and viral life cycle gene sets and compared with CTD curated COVID-19 gene data set. The key genes involved in an asymptomatic group of COVID-19 predicted genes are IL6, TNF, CXCL8 IL1B, IL10, CCL2, ICAM1, IL2, STAT3, and CCL5. These IL1B and STAT3 can only be found in the asymptomatic group when compared to other groups. Upregulation of STAT5 dimers gene expression has been observed for inflammation-related genes. Signal transducer and transcription activator 3 (STAT3) is a central regulator of many physiological functions, including immune response. Interleukin 1 beta (IL-1β) also known as leukocytic pyrogen is a cytokine protein encoded by the IL1B gene in humans. This cytokine is an essential mediator of inflammatory reactions and is involved in several cellular activities, including cell proliferation, differentiation, and apoptosis. These genes can be used as biomarkers to identify COVID-19 in the asymptomatic group **(Table 3)**.

3.5. Drug-gene interaction analysis of COVID-19

Based on the drug-gene interaction database (DGIdb2.0), the identified FDA approved drugs with the gene were used for STITCH prediction for each drug-gene association **(Figure 5-**

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14). The drugs were selected based on the network interaction score above 0.9 as follows **(Table 2)**:

TNF

Chloroquine (0.969)

Chloroquine is a medication used to prevent and treat malaria (61) and is suggested for COVID-19 treatment. Chloroquine has antiviral effects that work by increasing endosomal pH resulting in impaired virus/cell fusion that requires a low pH. The presence of nitrogens in chloroquine and the number of related isoquinoline and quinoline drug family members prevent the endosome from acidifying and thereby disrupt viral replication. When more nitrogens are added, either by making extra branches of ionizable nitrogens or by lengthening one of the chains by adding extra carbons and other nitrogens around it which can have an even greater effect.

lenalidomide (0.940)

Over the past ten years, lenalidomide has been used widely to treat both inflammatory conditions and cancers.

Penicillin (0.933)

Penicillin is a group of antibiotics. The combination of antibiotics with an anti-viral drug is proved effective in controlling viral replication.

Pentoxifylline (0.990)

This is used as a drug to treat muscle pain in people with peripheral artery disease. Studies have demonstrated a reduction in the risk of hepatorenal syndrome. Pentoxifylline, a phosphodiesterase inhibitor potently suppresses cytokine production as a neonatal anti-inflammatory agent. It is reported to be more effective at improving blood vessel function and reducing inflammation than antiretroviral medications alone in people infected with HIV(62,63).

Thalidome (0.980)

Thalidome used for cancer diagnosis is also used for treating a variety of HIV-related conditions(64).

VEGFA

Sorafenib (0.909)

This is used for treating cancer of the kidneys, liver, and lung (65). It is reported sorafenib inhibited replication of New World alphaviruses and two Old World alphaviruses, Sindbis virus, and chikungunya virus, leading to a reduction in viral protein production and overall viral replication (66).

IL8

Paclitaxel (0.947) is used to treat several types of cancer and reported to have anti-viral activity (67).

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IL10

Rapamycin (0.985)-Rapamycin, a powerful mTOR inhibitor, has proven effective in the treatment of some diseases. Immunomodulatory drug rapamycin (RAPA) possesses anti-HIV properties and can be a valuable medication that should be used for viral infection prevention and treatment(68).

IL1B

Cortisol (0.958)

Cortisol medication used to treat conditions arising from the B-Cell mediated antibody response due to overactivation and prevents the cause of inflammation by limiting the release of inflammatory substances. Corticosteroids are used in the treatment of severe acute respiratory syndrome (SARS-CoV) and it may suppress the “cytokine storm"(69).

ICAM1

Statins (0.987)

They are the most common cholesterol-lowering drugs. It is hypothesized to prevent cardiovascular disease through modulation of inflammatory response. Lipophilic statins like fluvastatin are efficient to use anti-zika virus drugs are reported (70). Statins have lowered the occurrence of severe infections or have improved health results for those diagnosed with viral or bacterial infections, including pneumonia. Statins modulate the antiviral response of the first line of protection against invading pathogens in human bronchial and epithelial cells (71).

4. Conclusion and limitation of the study

In this study, by using gene-disease association, genes related to COVID-19 symptoms, clinical outcomes, and risk factors were studied using the network-based methodology for identification of drug repurposing and also network analysis for the high-risk group and asymptomatic to identify biomarkers. Based on this analysis, drug targets for prioritized and genes were identified as biomarkers. These results were validated by literature data, but this study has several limitations. All predicted drugs must be validated either through randomized clinical trials or through experimental assays before being used in patients. The network was constructed based on the gene-disease associations and from the curated data set from the disgenet and CTD database, which were based on literature mining. However, it is noted during the writing of this manuscript that the network analysis of this study reported chloroquine as already used in the treatment of COVID-19.

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Figure legends

Figure 1: Overall framework for prioritizing COVID-19 key genes using network-based approaches. The workflow contains 5 steps including (A) retrieving COVID-19 disease-gene list from DisgeNet and The Comparative Toxicogenomics Database (CTD) –Curated COVID-19 gene-sets (B) The overlapping common genes enriched for gene ontology with a p-value less than 0.05 (C) Protein-Protein interaction of statistically significant genes with setting greater than 0.4 (D) Identification of key genes using Cytohubba (E) Identification drugs from the druggable genome by using DGIdb and STITCH.

Figure 2: Gene ontology (BO) analysis of COVID-19 genes for selection of statistically significant genes using gene enrichment analysis

Figure 3: Protein-protein interaction of all 279 disease-gene association of COVID-19 showing 261 nodes and 2542 edges with average node degee 19.5by using STRING database with setting greater than 0.4

Figure 4: The predicted function of top 10 hub disease-gene network association of COVID-19 using gene mania

Figure 5: Drug-gene network of TNF and its druggable FDA approved drugs. The network shows cholorquine, hydrocholorquine and penicillin and other related drugs to the TNF network.

Figure 6: Drug-gene network of VEGFA using STITCH database

Figure 7: Drug-gene network of IL6 using STITCH database

Figure 8: Drug-gene network of IL8 (CCL8) using STITCH database

Figure 9: Drug-gene network of IL10

Figure 10: Drug-gene network of CCL2

Figure 11: Drug-gene network of IL1B

Figure 12: Drug-gene network of TLR4

Figure 13: Drug-gene network of ICAM1

Figure 14: Drug-gene interaction of MMP9

Figure 15 : PPI network of (A) Cancer (B) Diabetes (C) Heart Disease (D) Hypertension (E) Kidney Disease (F)Lung Disease (G) Asymptomatic

Table legends

Table 1 : The 279 enriched gene based on gene ontology (GO Slim) – Biological process selected based on criteria P-Value less than 0.05

Table 2: Identified top 10 druggable genes, showing gene-disease association and predicted of STITCH & DGIdb2.0 of FDA drugs from drug-gene association

Table 3: Top 10 key genes of high risk with predicted FDA approved drug and asymptomatic group identified from Protein-Protein interaction network by using Cytohubba

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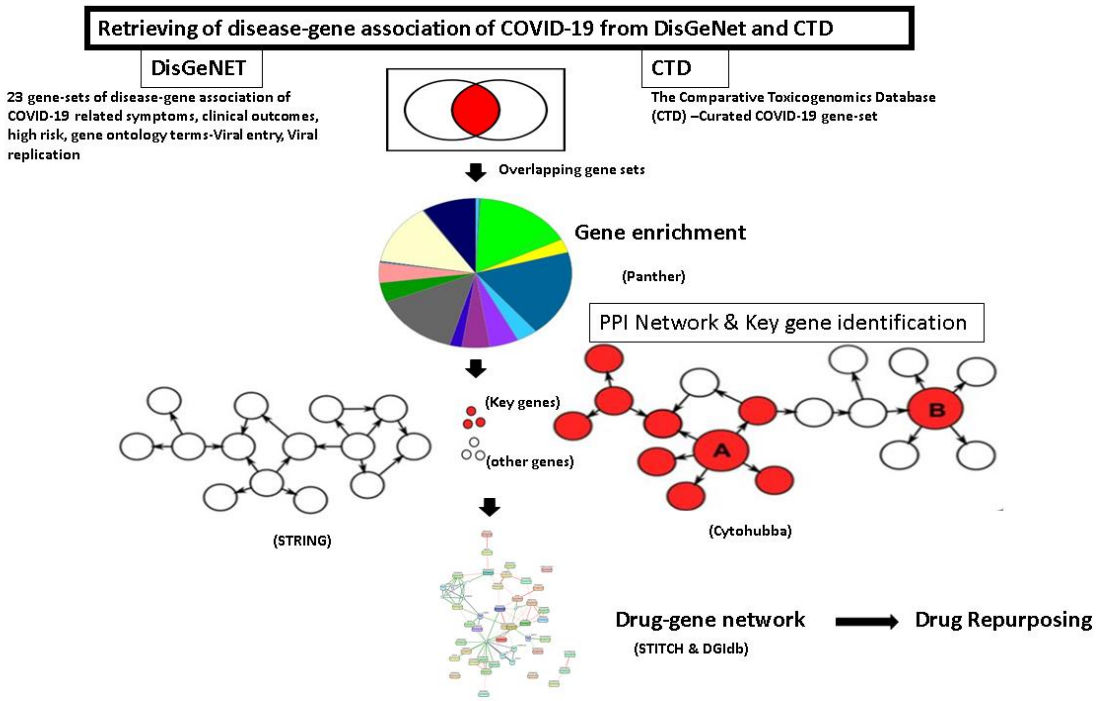

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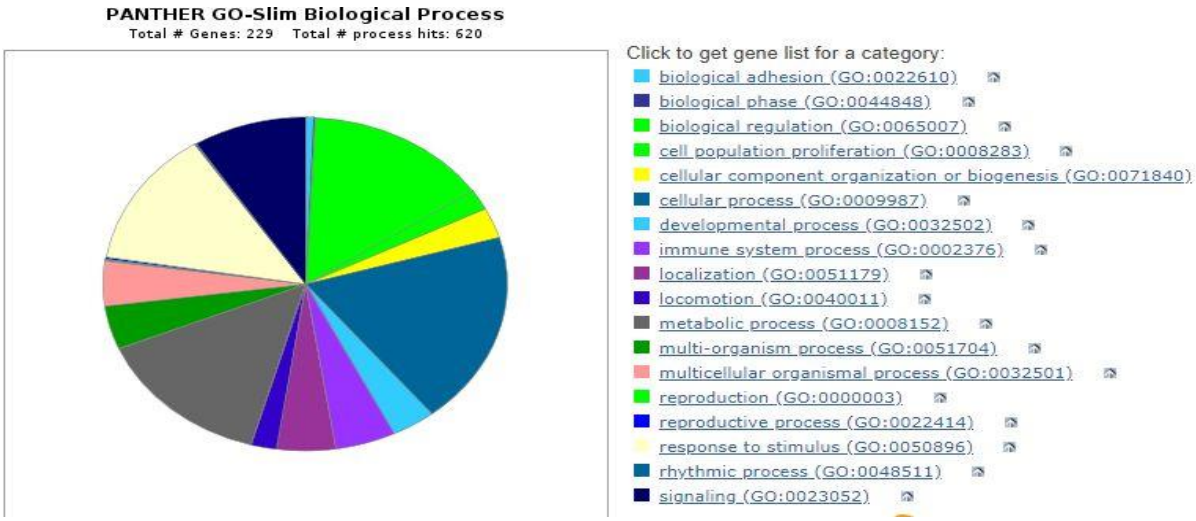

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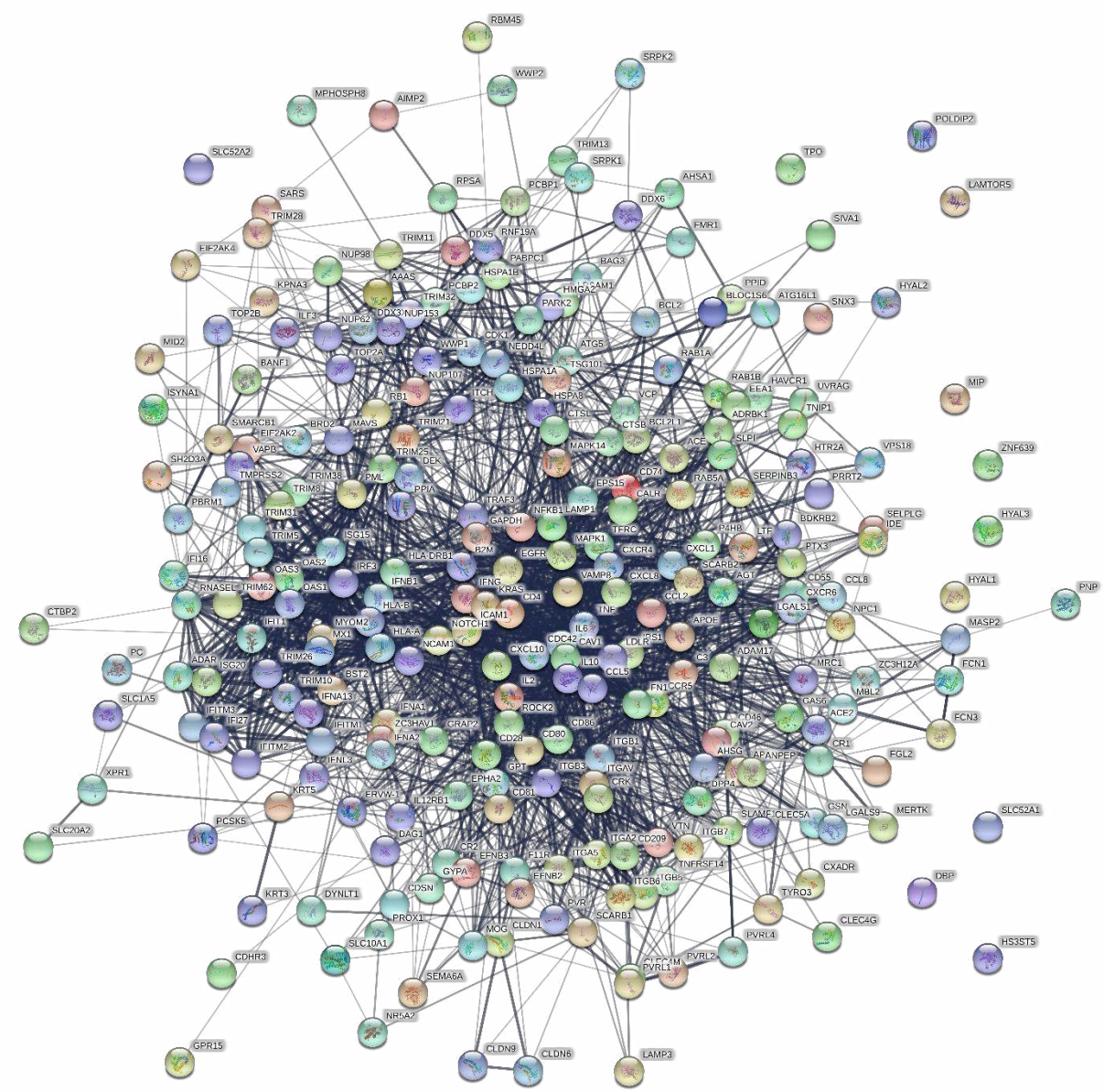

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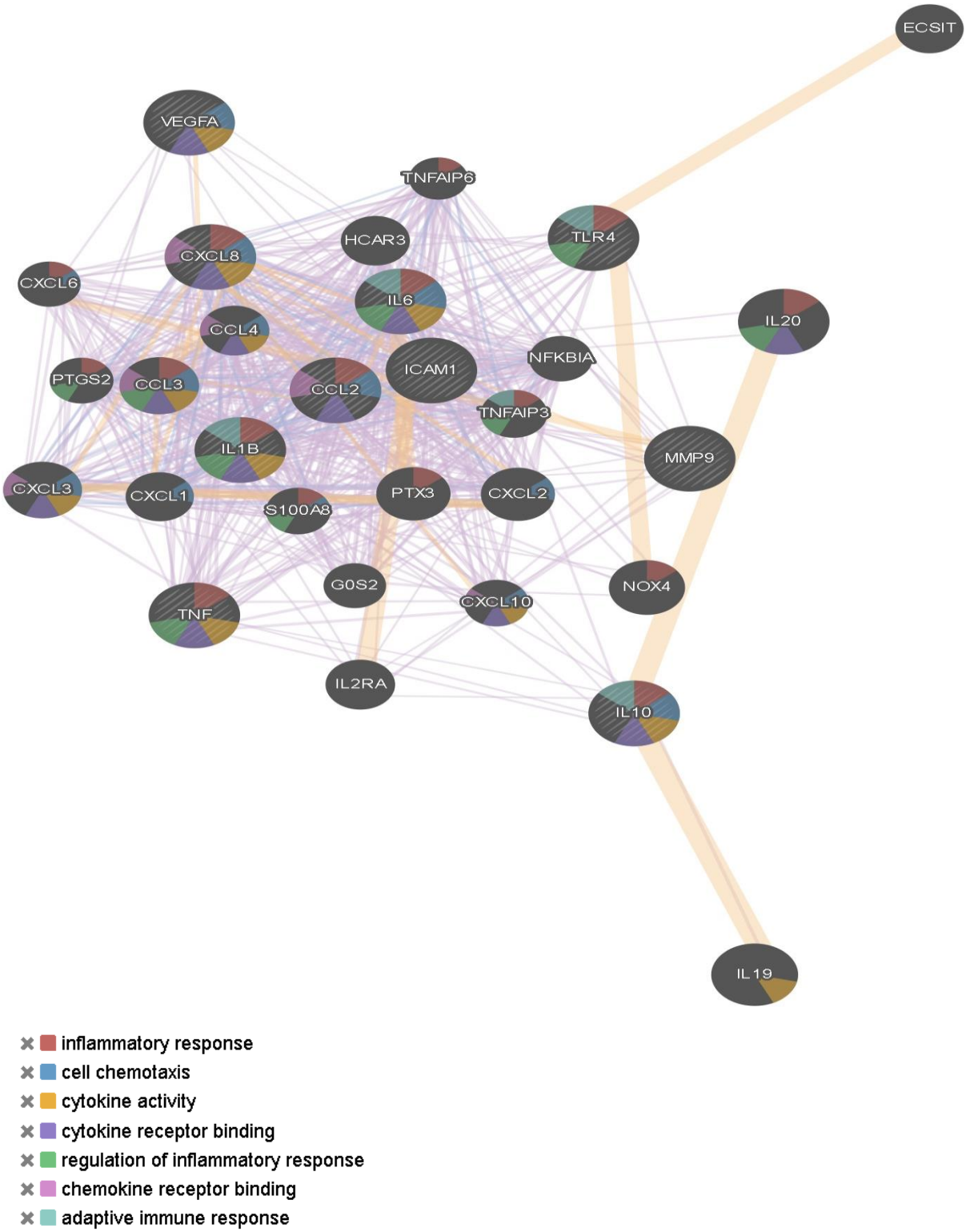

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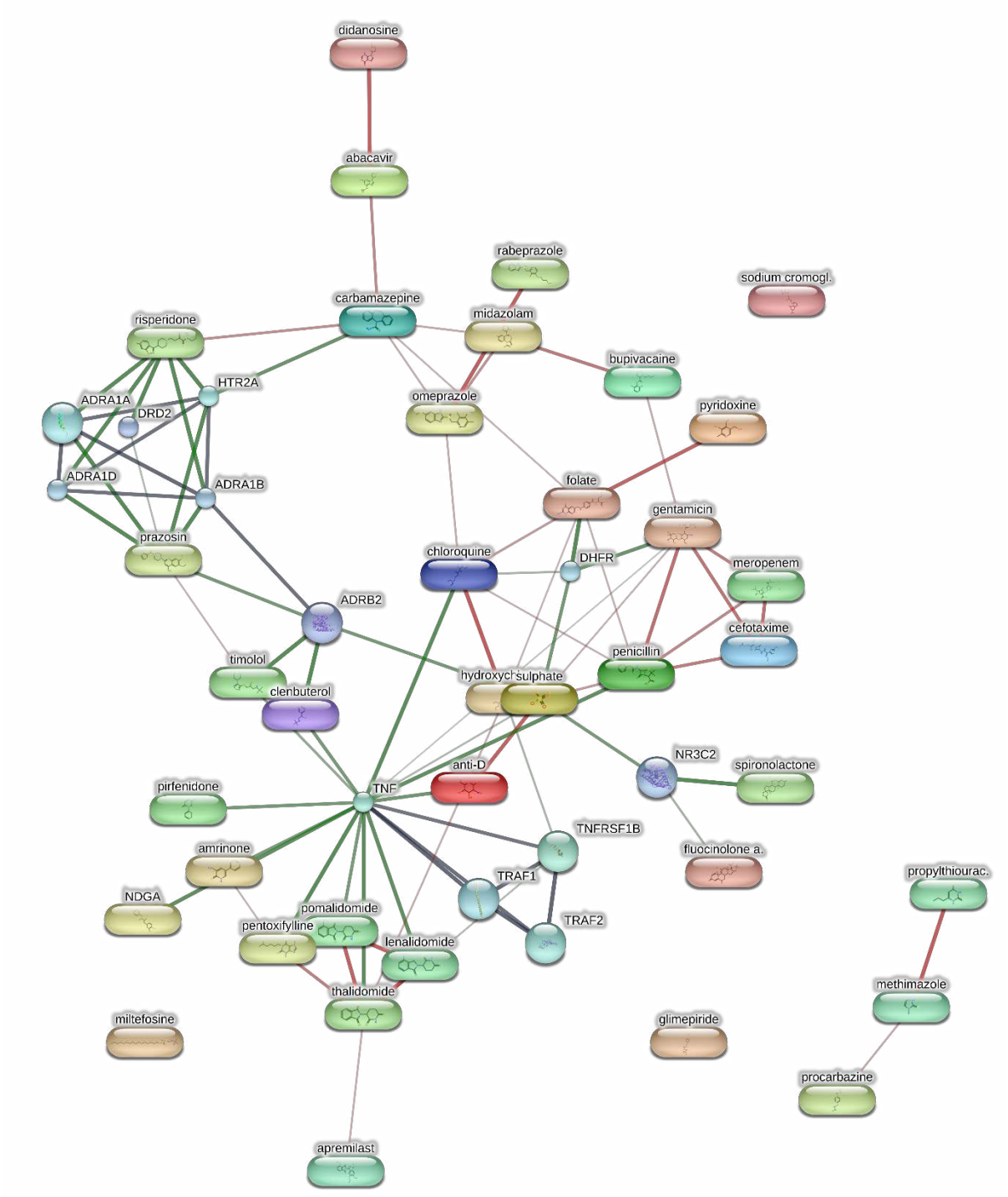

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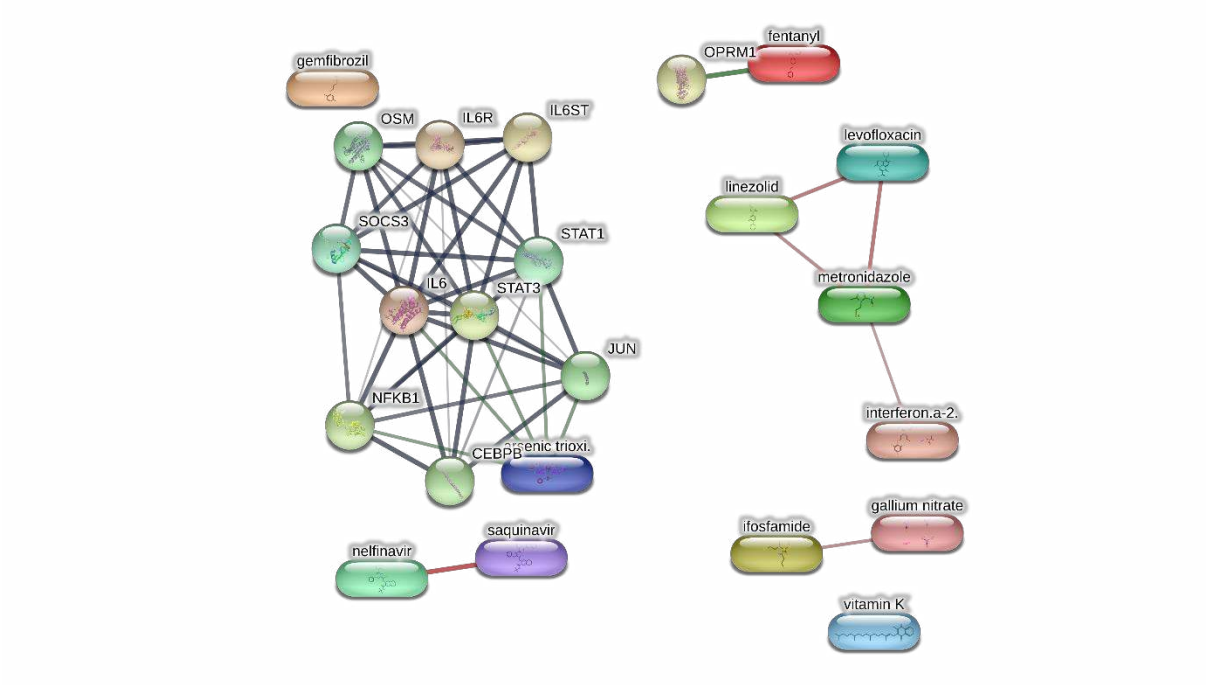

Figure 7: Drug-gene network of IL6 using STITCH database

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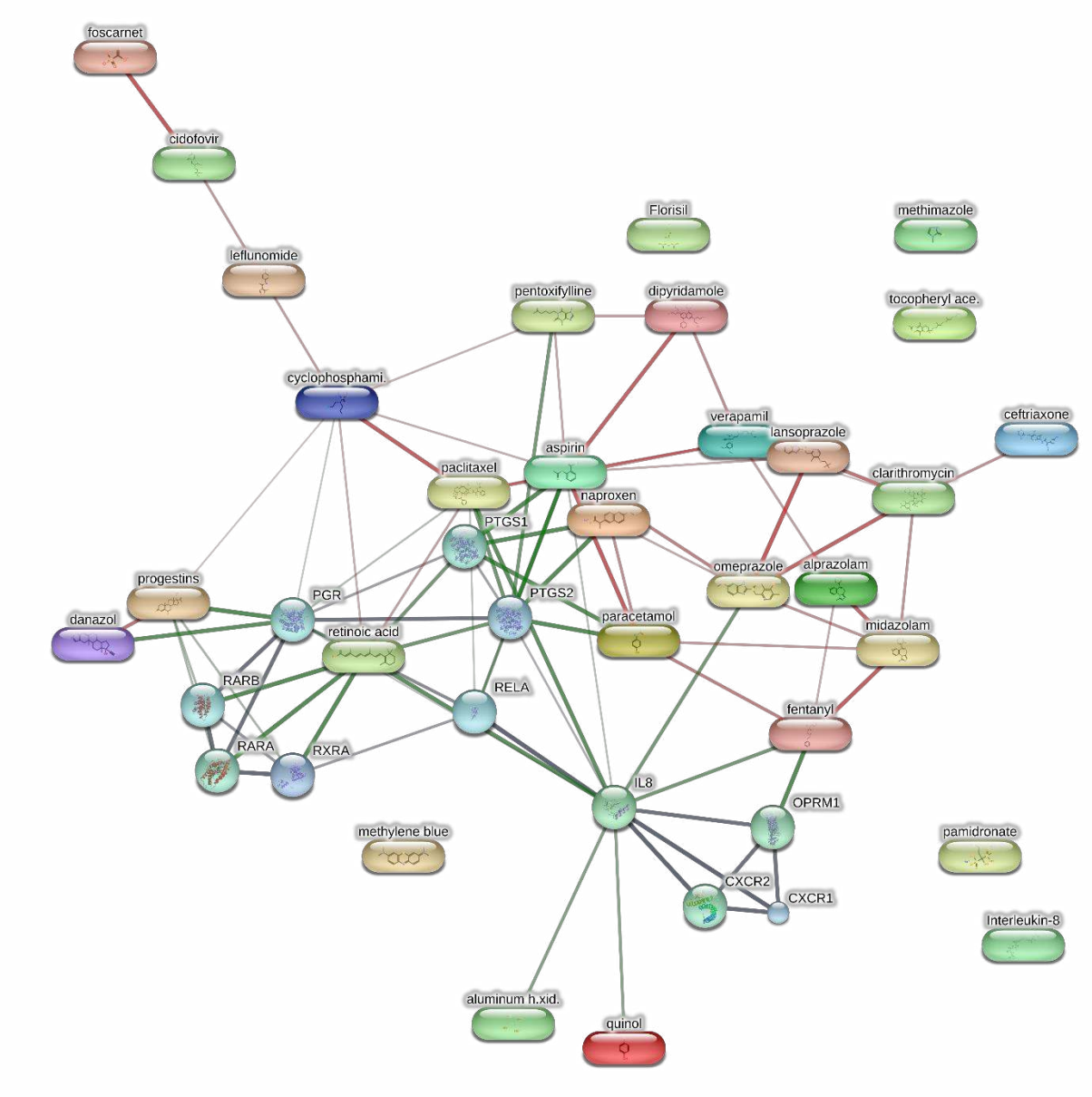

Figure 8: Drug-gene network of IL8 (CCL8) using STITCH database

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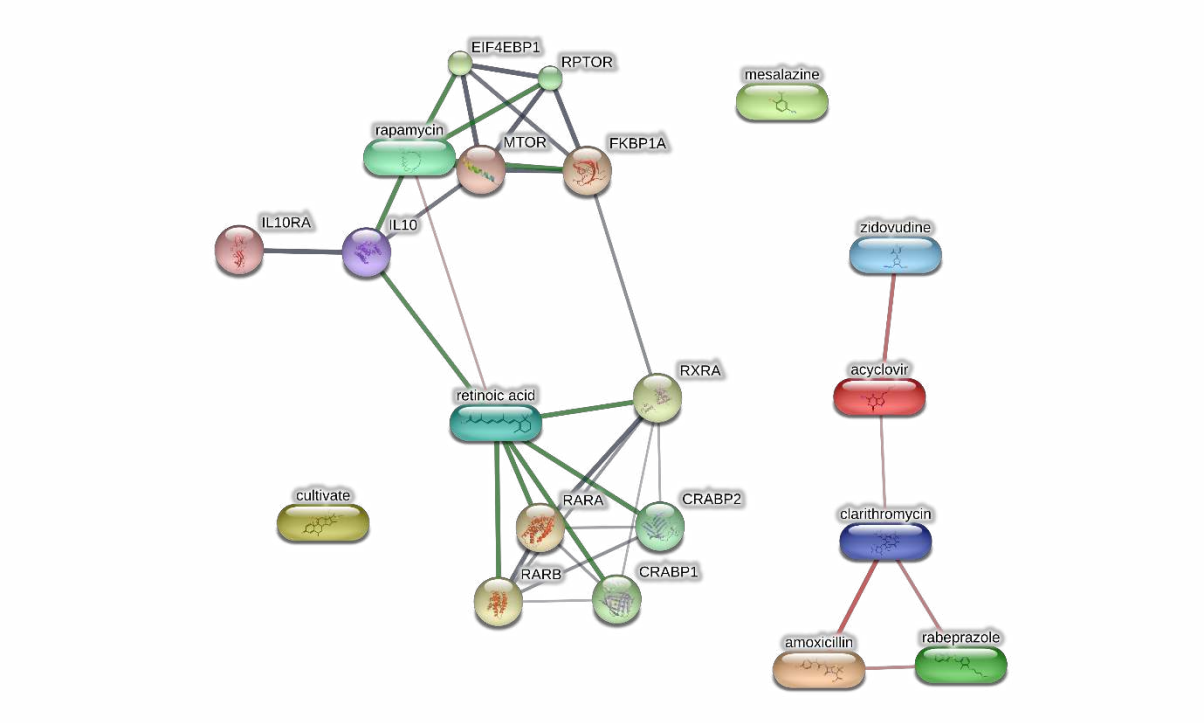

Figure 9: Drug-gene network of IL10

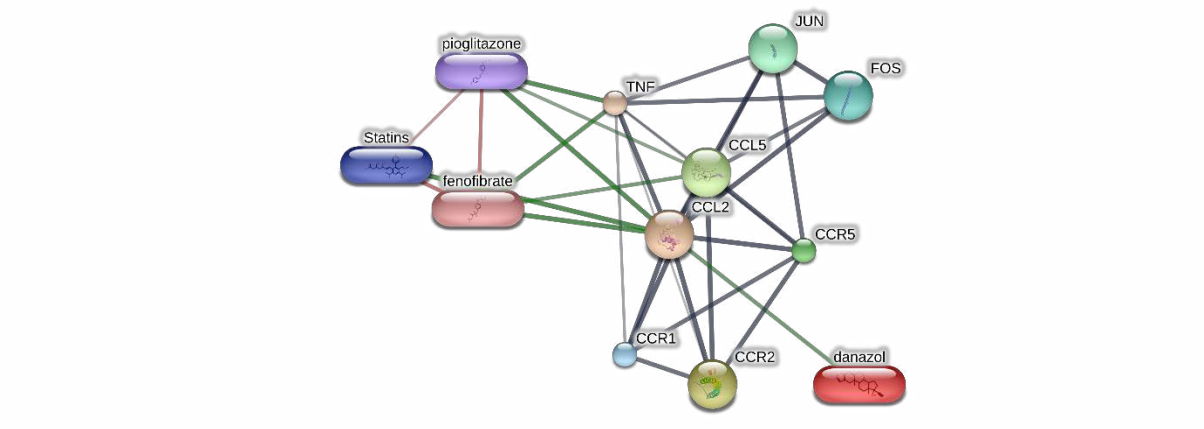

Figure 10: Drug-gene network of CCL2

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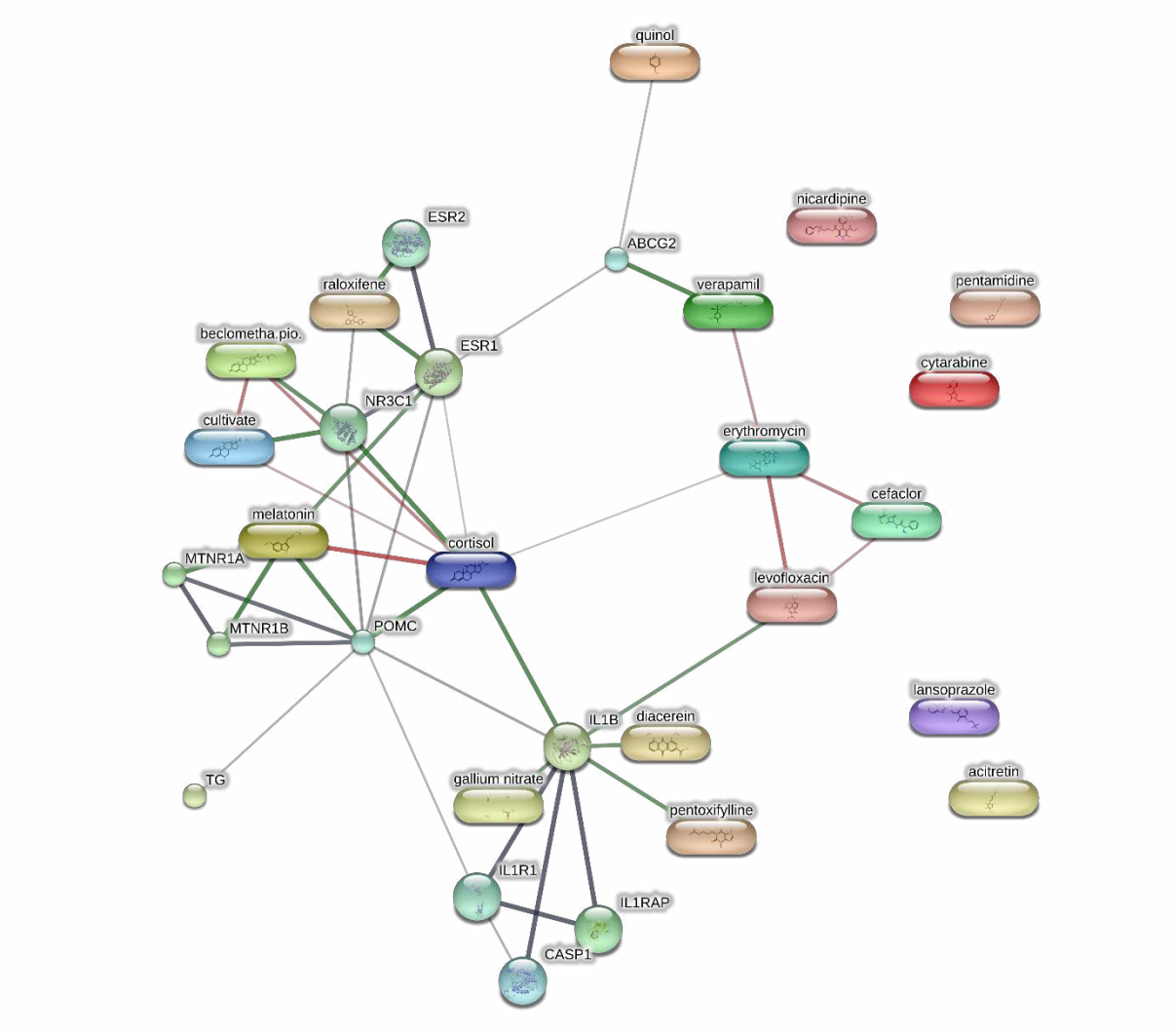

Figure 11: Drug-gene network of IL1B

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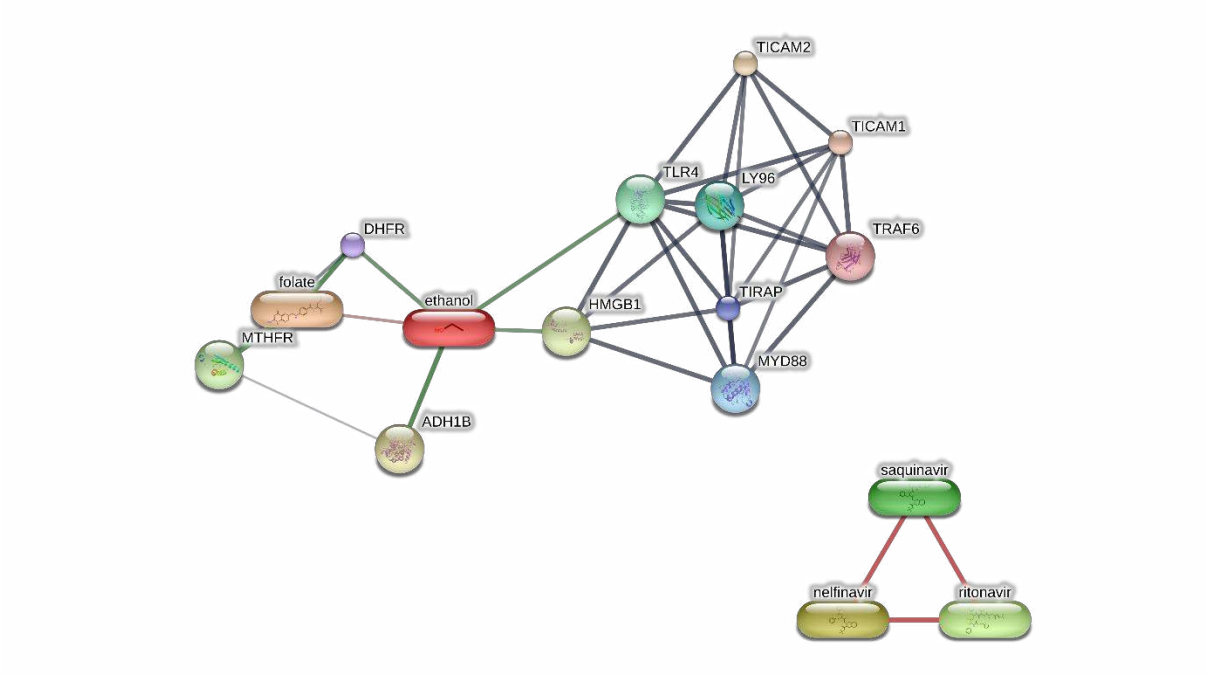

Figure 12: Drug-gene network of TLR4

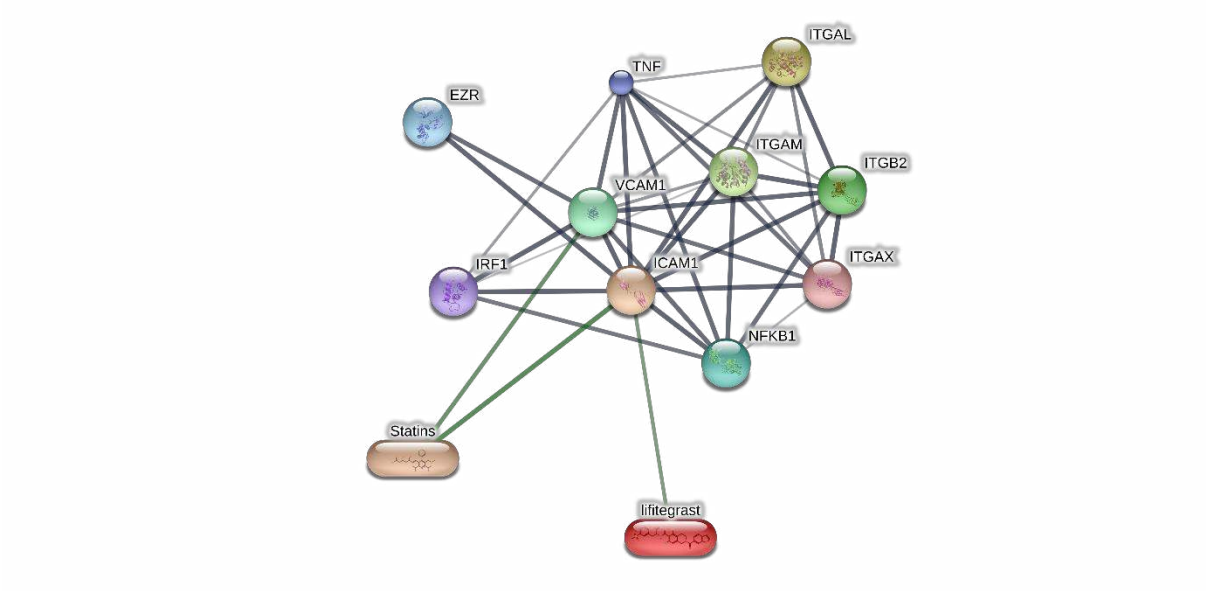

Figure 13: Drug-gene network of ICAM1

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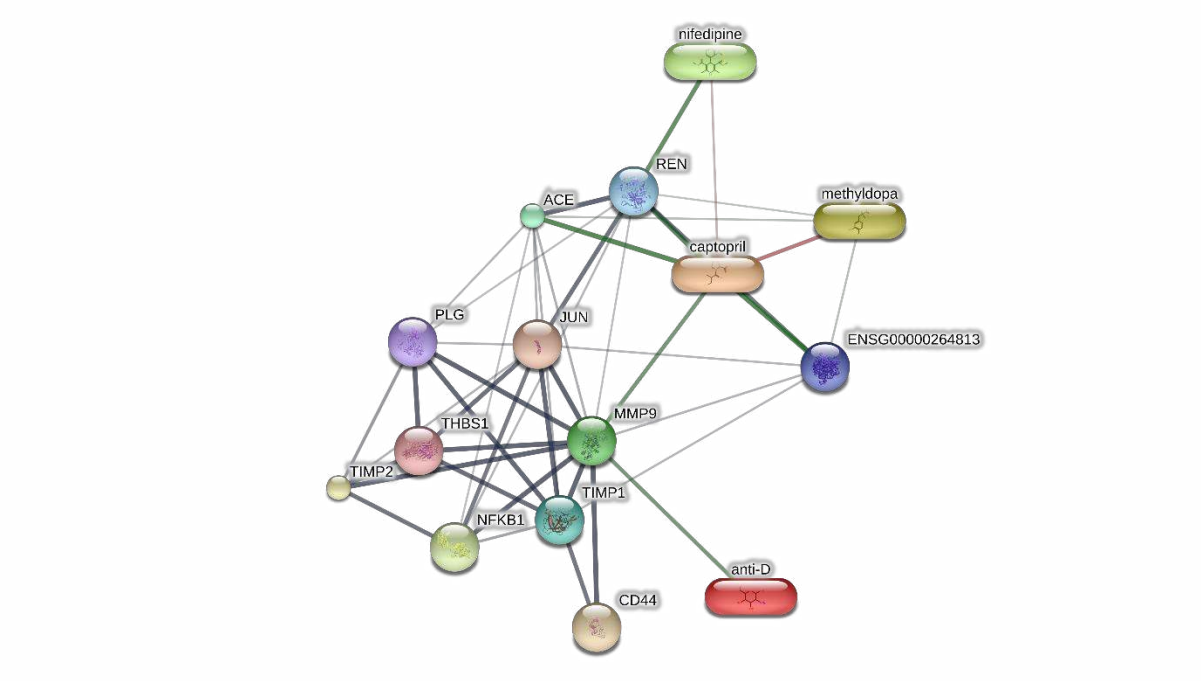

Figure 14: Drug-gene interaction of MMP9

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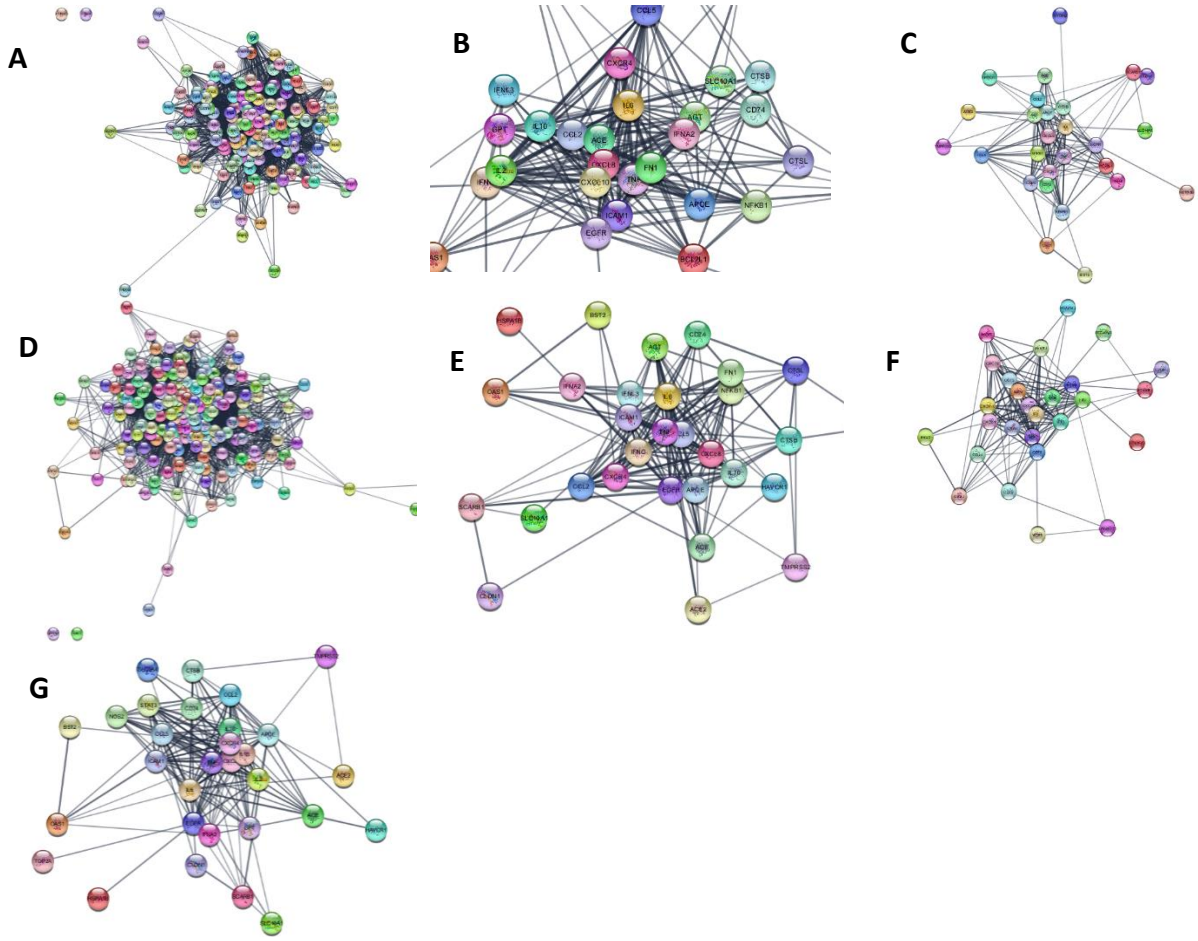

Figure 15: PPI network of high-risk and asymptomatic group of COVID-19. (A) Cancer (B) Diabetes (C) Heart Disease (D) Hypertension (E) Kidney Disease (F)Lung Disease (G) Asymptomatic

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Uniprot ID	Gene ID	GENE SYMBOL	PANTHER FAMILY/SUBFAMILY	PANTHER PROTEIN CLASS
P78310	CXADR	Coxsackievirus and adenovirus receptor CXADR ortholog	COXSACKIEVIRUS AND ADENOVIRUS RECEPTOR (PTHR44468:SF3)	-
P11226	MBL2	Mannose-binding protein C MBL2 ortholog	COLLAGEN ALPHA-1(XXI) CHAIN-RELATED (PTHR24020:SF20)	extracellular matrix structural protein
Q9H3H5	GPT	UDP-N-acetylglucosamine--dolichyl-phosphate N-acetylglucosaminephosphotransferase DPAGT1 ortholog	UDP-N-ACETYLGLUCOSAMINE--DOLICHYL-PHOSPHATE N-ACETYLGLUCOSAMINEPHOSPHOTRANSFERASE (PTHR10571:SF0)	glycosyltransferase
P01911	HLA-DRB1	HLA class II histocompatibility antigen, DRB1-15 beta chain HLA-DRB1 ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DRB1-15 BETA CHAIN (PTHR19944:SF99)	major histocompatibility complex protein
P29317	EPHA2	Ephrin type-A receptor 2 EPHA2 ortholog	EPHRIN TYPE-A RECEPTOR 2 (PTHR24416:SF306)	-
P01019	AGT	Angiotensinogen AGT ortholog	ANGIOTENSINOGEN (PTHR11461:SF331)	protease inhibitor
Q14258	TRIM25	E3 ubiquitin/ISG15 ligase TRIM25 TRIM25 ortholog	E3 UBIQUITIN/ISG15 LIGASE TRIM25 (PTHR25465:SF17)	-
P05106	ITGB3	Integrin beta-3 ITGB3 ortholog	INTEGRIN BETA-3 (PTHR10082:SF25)	cell adhesion molecule
P18084	ITGB5	Integrin beta-5 ITGB5 ortholog	INTEGRIN BETA-5 (PTHR10082:SF26)	cell adhesion molecule
P13647	K5	Keratin, type II cytoskeletal 5 KRT5 ortholog	KERATIN, TYPE II CYTOSKELETAL 5 (PTHR45616:SF32)	-
P40305	IFI27	Interferon alpha-inducible protein 27, mitochondrial IFI27 ortholog	INTERFERON ALPHA-INDUCIBLE PROTEIN 27, MITOCHONDRIAL (PTHR16932:SF15)	-
P01563	IFNA2	Interferon alpha-2 IFNA2 ortholog	INTERFERON ALPHA-2 (PTHR11691:SF60)	-
Q99797	MIP	Mitochondrial intermediate peptidase MIPEP ortholog	MITOCHONDRIAL INTERMEDIATE PEPTIDASE (PTHR11804:SF5)	metalloprotease
P08648	ITGA5	Integrin alpha-5 ITGA5 ortholog	INTEGRIN ALPHA-5 (PTHR23220:SF3)	-
O75636	FCN3	Ficolin-3 FCN3 ortholog	FICOLIN-3 (PTHR19143:SF373)	intercellular signal molecule
P11142	HSPA8	Heat shock cognate 71 kDa protein	HEAT SHOCK COGNATE 71 KDA PROTEIN	-

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		HSPA8 ortholog	(PTHR19375:SF379)	
P05231	IL6	Interleukin-6 IL6 ortholog	INTERLEUKIN-6 (PTHR10511:SF3)	-
Q15025	TNIP1	TNFAIP3-interacting protein 1 TNIP1 ortholog	TNFAIP3-INTERACTING PROTEIN 1 (PTHR31882:SF3)	-
P11498	PC	Pyruvate carboxylase, mitochondrial PC ortholog	PYRUVATE CARBOXYLASE, MITOCHONDRIAL (PTHR43778:SF2)	ligase
Q96D42	HAVCR1	Hepatitis A virus cellular receptor 1 HAVCR1 ortholog	HEPATITIS A VIRUS CELLULAR RECEPTOR 1 (PTHR47009:SF7)	-
P10145	CXCL8	Interleukin-8 CXCL8 ortholog	INTERLEUKIN-8 (PTHR10179:SF42)	chemokine
P21549	AGT	Serine--pyruvate aminotransferase AGXT ortholog	SERINE--PYRUVATE AMINOTRANSFERASE (PTHR21152:SF24)	transaminase
Q9NY35	CLDN1	Claudin domain-containing protein 1 CLDND1 ortholog	CLAUDIN DOMAIN-CONTAINING PROTEIN 1 (PTHR14347:SF3)	-
P60033	CD81	CD81 antigen CD81 ortholog	CD81 ANTIGEN (PTHR19282:SF214)	-
P13501	CCL5	C-C motif chemokine 5 CCL5 ortholog	C-C MOTIF CHEMOKINE 5 (PTHR12015:SF170)	cytokine
P04406	GAPDH	Glyceraldehyde-3-phosphate dehydrogenase GAPDH ortholog	GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE (PTHR10836:SF111)	dehydrogenase
P46531	NOTCH1	Neurogenic locus notch homolog protein 1 NOTCH1 ortholog	NEUROGENIC LOCUS NOTCH HOMOLOG PROTEIN 1 (PTHR45836:SF12)	-
P08865	RPSA	40S ribosomal protein SA RPSA ortholog	40S RIBOSOMAL PROTEIN SA (PTHR11489:SF17)	ribosomal protein
P17301	ITGA2	Integrin alpha-2 ITGA2 ortholog	INTEGRIN ALPHA-2 (PTHR23220:SF23)	-
P17927	CR1	Complement receptor type 1 CR1 ortholog	COMPLEMENT RECEPTOR TYPE 1 (PTHR19325:SF505)	-
P13164	IFITM1	Interferon-induced transmembrane protein 1 IFITM1 ortholog	INTERFERON-INDUCED TRANSMEMBRANE PROTEIN 1 (PTHR13999:SF6)	-
Q96SB4	SRPK1	SRSF protein kinase 1 SRPK1 ortholog	SRSF PROTEIN KINASE 1 (PTHR24055:SF0)	non-receptor serine/threonine protein kinase
P0DMV9	HSPA1B	Heat shock 70 kDa protein 1B HSPA1B ortholog	HEAT SHOCK 70 KDA PROTEIN 1A-RELATED (PTHR19375:SF223)	-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 March 2020 doi:10.20944/preprints202003.0440.v1

P42081	CD86	T-lymphocyte activation antigen CD86 CD86 ortholog	T-LYMPHOCYTE ACTIVATION ANTIGEN CD86 (PTHR25466:SF2)	immunoglobulin receptor superfamily
O75364	PTX3	Pituitary homeobox 3 PITX3 ortholog	PITUITARY HOMEOBOX 3 (PTHR45882:SF2)	-
P27797	CALR	Calreticulin CALR ortholog	CALRETICULIN (PTHR11073:SF16)	chaperone
Q14314	FGL2	Fibroleukin FGL2 ortholog	FIBROLEUKIN (PTHR19143:SF189)	intercellular signal molecule
Q96J02	ITCH	E3 ubiquitin-protein ligase Itchy homolog ITCH ortholog	E3 UBIQUITIN-PROTEIN LIGASE ITCHY HOMOLOG (PTHR11254:SF66)	ubiquitin-protein ligase
Q12866	MERTK	Tyrosine-protein kinase Mer MERTK ortholog	TYROSINE-PROTEIN KINASE MER (PTHR24416:SF257)	-
Q15366	PCBP2	Poly(rC)-binding protein 2 PCBP2 ortholog	POLY(RC)-BINDING PROTEIN 2 (PTHR10288:SF97)	RNA binding protein
P29590	PML	Protein PML PML ortholog	PROTEIN PML (PTHR25462:SF241)	-
P22897	MRC1	Macrophage mannose receptor 1 MRC1 ortholog	MACROPHAGE MANNOSE RECEPTOR 1 (PTHR22803:SF104)	-
P11388	TOP2A	DNA topoisomerase 2-alpha TOP2A ortholog	DNA TOPOISOMERASE 2-ALPHA (PTHR10169:SF61)	-
P40225	TPO	Thrombopoietin THPO ortholog	THROMBOPOIETIN (PTHR10560:SF0)	-
P18564	ITGB6	Integrin beta-6 ITGB6 ortholog	INTEGRIN BETA-6 (PTHR10082:SF11)	cell adhesion molecule
P06400	RB1	Retinoblastoma-associated protein RB1 ortholog	RETINOBLASTOMA-ASSOCIATED PROTEIN (PTHR13742:SF17)	chromatin/chromatin-binding, or -regulatory protein
P49591	SARS	Serine--tRNA ligase, cytoplasmic SARS ortholog	SERINE--TRNA LIGASE, CYTOPLASMIC-RELATED (PTHR11778:SF7)	aminoacyl-tRNA synthetase
P07237	P4HB	Protein disulfide-isomerase P4HB ortholog	PROTEIN DISULFIDE-ISOMERASE (PTHR18929:SF101)	-
O60858	TRIM13	E3 ubiquitin-protein ligase TRIM13 TRIM13 ortholog	E3 UBIQUITIN-PROTEIN LIGASE TRIM13 (PTHR24103:SF609)	ubiquitin-protein ligase
P52926	HMGA2	High mobility group protein HMGI-C HMGA2 ortholog	HIGH MOBILITY GROUP PROTEIN HMGI-C (PTHR23341:SF4)	endodeoxyribonuclease
P12035	K3	Keratin, type II cytoskeletal 3 KRT3 ortholog	KERATIN, TYPE II CYTOSKELETAL 3 (PTHR45616:SF38)	-

Q8IZI9	IFNL3	Interferon lambda-3 IFNL3 ortholog	INTERFERON LAMBDA-2-RELATED (PTHR31943:SF1)	-
Q10589	BST2	Bone marrow stromal antigen 2 BST2 ortholog	BONE MARROW STROMAL ANTIGEN 2 (PTHR15190:SF1)	-
Q14118	DAG1	Dystroglycan DAG1 ortholog	DYSTROGLYCAN (PTHR21559:SF22)	cell adhesion molecule
P33681	CD80	T-lymphocyte activation antigen CD80 CD80 ortholog	T-LYMPHOCYTE ACTIVATION ANTIGEN CD80 (PTHR25466:SF4)	immunoglobulin receptor superfamily
Q9UJV3	MID2	Probable E3 ubiquitin-protein ligase MID2 MID2 ortholog	E3 UBIQUITIN-PROTEIN LIGASE MID2-RELATED (PTHR24099:SF12)	ubiquitin-protein ligase
Q7Z434	MAVS	Mitochondrial antiviral-signaling protein MAVS ortholog	MITOCHONDRIAL ANTIVIRAL-SIGNALING PROTEIN (PTHR21446:SF6)	-
O00505	KPNA3	Importin subunit alpha-4 KPNA3 ortholog	IMPORTIN SUBUNIT ALPHA-4 (PTHR23316:SF6)	transporter
Q14108	SCARB2	Lysosome membrane protein 2 SCARB2 ortholog	LYSOSOME MEMBRANE PROTEIN 2 (PTHR11923:SF92)	membrane trafficking regulatory protein
P51659	DBP	Peroxisomal multifunctional enzyme type 2 HSD17B4 ortholog	PEROXISOMAL MULTIFUNCTIONAL ENZYME TYPE 2 (PTHR13078:SF56)	-
P27487	DPP4	Dipeptidyl peptidase 4 DPP4 ortholog	DIPEPTIDYL PEPTIDASE 4 (PTHR11731:SF128)	serine protease
P30301	MIP	Lens fiber major intrinsic protein MIP ortholog	LENS FIBER MAJOR INTRINSIC PROTEIN (PTHR19139:SF39)	transporter
Q9P2Y5	UVRAG	UV radiation resistance-associated gene protein UVRAG ortholog	UV RADIATION RESISTANCE-ASSOCIATED GENE PROTEIN (PTHR15157:SF5)	-
P25440	BRD2	Bromodomain-containing protein 2 BRD2 ortholog	BROMODOMAIN-CONTAINING PROTEIN 2 (PTHR22880:SF225)	-
P10747	CD28	T-cell-specific surface glycoprotein CD28 CD28 ortholog	T-CELL-SPECIFIC SURFACE GLYCOPROTEIN CD28 (PTHR11494:SF7)	immunoglobulin receptor superfamily
P55072	VCP	Transitional endoplasmic reticulum ATPase VCP ortholog	TRANSITIONAL ENDOPLASMIC RETICULUM ATPASE (PTHR23077:SF69)	-
P26010	ITGB7	Integrin beta-7 ITGB7 ortholog	INTEGRIN BETA-7 (PTHR10082:SF36)	cell adhesion molecule
P02774	DBP	Vitamin D-binding protein GC ortholog	VITAMIN D-BINDING PROTEIN (PTHR11385:SF11)	transfer/carrier protein

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 March 2020 doi:10.20944/preprints202003.0440.v1

Q92973	MIP	Transportin-1 TNPO1 ortholog	TRANSPORTIN-1 (PTHR10527:SF21)	transporter
P06396	GSN	Gelsolin GSN ortholog	GELSOLIN-RELATED (PTHR11977:SF29)	non-motor actin binding protein
P01579	IFNG	Interferon gamma IFNG ortholog	INTERFERON GAMMA (PTHR11419:SF0)	-
Q9NNX6	CD209	CD209 antigen CD209 ortholog	CD209 ANTIGEN (PTHR22802:SF400)	membrane traffic protein
Q16653	MOG	Myelin-oligodendrocyte glycoprotein MOG ortholog	MYELIN-OLIGODENDROCYTE GLYCOPROTEIN (PTHR24100:SF71)	immunoglobulin receptor superfamily
Q13263	TRIM28	Transcription intermediary factor 1-beta TRIM28 ortholog	TRANSCRIPTION INTERMEDIARY FACTOR 1-BETA (PTHR25462:SF274)	-
Q9C035	TRIM5	Tripartite motif-containing protein 5 TRIM5 ortholog	TRIPARTITE MOTIF-CONTAINING PROTEIN 5 (PTHR24103:SF642)	ubiquitin-protein ligase
P02778	CXCL10	C-X-C motif chemokine 10 CXCL10 ortholog	C-X-C MOTIF CHEMOKINE 10 (PTHR10179:SF47)	chemokine
Q96PU5	NEDD4L	E3 ubiquitin-protein ligase NEDD4-like NEDD4L ortholog	E3 UBIQUITIN-PROTEIN LIGASE NEDD4-LIKE (PTHR11254:SF310)	ubiquitin-protein ligase
Q9P253	VPS18	Vacuolar protein sorting-associated protein 18 homolog VPS18 ortholog	VACUOLAR PROTEIN SORTING-ASSOCIATED PROTEIN 18 HOMOLOG (PTHR23323:SF26)	membrane trafficking regulatory protein
P20339	RAB5A	Ras-related protein Rab-5A RAB5A ortholog	RAS-RELATED PROTEIN RAB-5A (PTHR24073:SF1129)	-
O75531	BANF1	Barrier-to-autointegration factor BANF1 ortholog	BARRIER-TO-AUTOINTEGRATION FACTOR (PTHR12912:SF10)	chromatin/chromatin-binding, or -regulatory protein
Q9Y6K5	OAS3	2'-5'-oligoadenylate synthase 3 OAS3 ortholog	2'-5'-OLIGOADENYLATE SYNTHASE 3 (PTHR11258:SF4)	nucleotidyltransferase
Q14653	IRF3	Interferon regulatory factor 3 IRF3 ortholog	INTERFERON REGULATORY FACTOR 3 (PTHR11949:SF1)	winged helix/forkhead transcription factor
P63172	DYNLT1	Dynein light chain Tctex-type 1 DYNLT1 ortholog	DYNEIN LIGHT CHAIN TCTEX-TYPE 1 (PTHR21255:SF19)	microtubule or microtubule-binding cytoskeletal protein
P00973	OAS1	2'-5'-oligoadenylate synthase 1 OAS1 ortholog	2'-5'-OLIGOADENYLATE SYNTHASE 1 (PTHR11258:SF13)	nucleotidyltransferase
Q9UID6	ZNF639	Zinc finger protein 639 ZNF639 ortholog	ZINC FINGER PROTEIN 639 (PTHR24404:SF35)	C2H2 zinc finger transcription factor
P11940	PABPC1	Polyadenylate-binding protein 1 PABPC1 ortholog	POLYADENYLATE-BINDING PROTEIN 1 (PTHR24012:SF409)	-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 March 2020 doi:10.20944/preprints202003.0440.v1

Q5D1E8	ZC3H12A	Endoribonuclease ZC3H12A ZC3H12A ortholog	ENDORIBONUCLEASE ZC3H12A (PTHR12876:SF10)	endoribonuclease
O15304	SIVA1	Apoptosis regulatory protein Siva SIVA1 ortholog	APOPTOSIS REGULATORY PROTEIN SIVA (PTHR14365:SF1)	-
O95484	CLDN9	Claudin-9 CLDN9 ortholog	CLAUDIN-9 (PTHR12002:SF42)	tight junction
O15393	TMPRSS2	Transmembrane protease serine 2 TMPRSS2 ortholog	TRANSMEMBRANE PROTEASE SERINE 2 (PTHR24253:SF89)	serine protease
Q96F44	TRIM11	E3 ubiquitin-protein ligase TRIM11 TRIM11 ortholog	E3 UBIQUITIN-PROTEIN LIGASE TRIM11 (PTHR24103:SF648)	ubiquitin-protein ligase
P38567	HYAL3	Hyaluronidase PH-20 SPAM1 ortholog	HYALURONIDASE PH-20 (PTHR11769:SF20)	glycosidase
Q10586	DBP	D site-binding protein DBP ortholog	D SITE-BINDING PROTEIN (PTHR11988:SF7)	basic leucine zipper transcription factor
P05161	ISG15	Ubiquitin-like protein ISG15 ISG15 ortholog	UBIQUITIN-LIKE PROTEIN ISG15 (PTHR10666:SF267)	-
Q676U5	ATG16L1	Autophagy-related protein 16-1 ATG16L1 ortholog	AUTOPHAGY-RELATED PROTEIN 16-1 (PTHR19878:SF6)	-
P29728	OAS2	2'-5'-oligoadenylate synthase 2 OAS2 ortholog	2'-5'-OLIGOADENYLATE SYNTHASE 2 (PTHR11258:SF3)	nucleotidyltransferase
Q9BRG2	SH2D3A	SH2 domain-containing protein 3A SH2D3A ortholog	SH2 DOMAIN-CONTAINING PROTEIN 3A (PTHR14247:SF11)	-
P42566	EPS15	Epidermal growth factor receptor substrate 15 EPS15 ortholog	EPIDERMAL GROWTH FACTOR RECEPTOR SUBSTRATE 15 (PTHR11216:SF54)	membrane traffic protein
P26022	PTX3	Pentraxin-related protein PTX3 PTX3 ortholog	PENTRAXIN-RELATED PROTEIN PTX3 (PTHR46943:SF1)	-
O00308	WWP2	NEDD4-like E3 ubiquitin-protein ligase WWP2 WWP2 ortholog	NEDD4-LIKE E3 UBIQUITIN-PROTEIN LIGASE WWP2 (PTHR11254:SF396)	ubiquitin-protein ligase
Q05823	RNASEL	2-5A-dependent ribonuclease RNASEL ortholog	2-5A-DEPENDENT RIBONUCLEASE (PTHR24141:SF1)	-
P49790	NUP153	Nuclear pore complex protein Nup153 NUP153 ortholog	NUCLEAR PORE COMPLEX PROTEIN NUP153 (PTHR23193:SF23)	transporter
P12821	ACE	Angiotensin-converting enzyme ACE ortholog	ANGIOTENSIN-CONVERTING ENZYME (PTHR10514:SF25)	metalloprotease
Q15768	EFNB3	Ephrin-B3 EFNB3 ortholog	EPHRIN-B3 (PTHR11304:SF34)	membrane-bound signaling molecule

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 March 2020 doi:10.20944/preprints202003.0440.v1

Q16666	IFI16	Gamma-interferon-inducible protein 16 IFI16 ortholog	GAMMA-INTERFERON-INDUCIBLE PROTEIN 16 (PTHR12200:SF5)	DNA-binding transcription factor
Q99816	TSG101	Tumor susceptibility gene 101 protein TSG101 ortholog	TUMOR SUSCEPTIBILITY GENE 101 PROTEIN (PTHR23306:SF17)	ubiquitin-protein ligase
Q9Y624	F11R	Junctional adhesion molecule A F11R ortholog	JUNCTIONAL ADHESION MOLECULE A (PTHR45113:SF1)	-
P17844	DDX5	Probable ATP-dependent RNA helicase DDX5 DDX5 ortholog	ATP-DEPENDENT RNA HELICASE DDX5-RELATED (PTHR47958:SF90)	-
P52948	NUP98	Nuclear pore complex protein Nup98-Nup96 NUP98 ortholog	NUCLEAR PORE COMPLEX PROTEIN NUP98-NUP96 (PTHR23198:SF17)	transporter
P20591	MX1	Interferon-induced GTP-binding protein Mx1 MX1 ortholog	INTERFERON-INDUCED GTP-BINDING PROTEIN MX1 (PTHR11566:SF51)	membrane traffic protein
Q13114	TRAF3	TNF receptor-associated factor 3 TRAF3 ortholog	TNF RECEPTOR-ASSOCIATED FACTOR 3 (PTHR10131:SF76)	scaffold/adaptor protein
P28223	HTR2A	5-hydroxytryptamine receptor 2A HTR2A ortholog	5-HYDROXYTRYPTAMINE RECEPTOR 2A (PTHR24247:SF30)	G-protein coupled receptor
Q8IUH3	RBM45	RNA-binding protein 45 RBM45 ortholog	RNA-BINDING PROTEIN 45 (PTHR24012:SF812)	-
Q9NV58	RNF19A	E3 ubiquitin-protein ligase RNF19A RNF19A ortholog	E3 UBIQUITIN-PROTEIN LIGASE RNF19A (PTHR11685:SF111)	ubiquitin-protein ligase
Q15223	NECTIN1	Nectin-1 NECTIN1 ortholog	NECTIN-1 (PTHR23277:SF69)	-
Q31612	HLA-B	HLA class I histocompatibility antigen, B-73 alpha chain HLA-B ortholog	HLA CLASS I HISTOCOMPATIBILITY ANTIGEN, B-73 ALPHA CHAIN (PTHR16675:SF186)	-
Q01628	IFITM3	Interferon-induced transmembrane protein 3 IFITM3 ortholog	INTERFERON-INDUCED TRANSMEMBRANE PROTEIN 3 (PTHR13999:SF4)	-
P52799	EFNB2	Ephrin-B2 EFNB2 ortholog	EPHRIN-B2 (PTHR11304:SF18)	membrane-bound signaling molecule
P08174	CD55	Complement decay-accelerating factor CD55 ortholog	COMPLEMENT DECAY-ACCELERATING FACTOR (PTHR19325:SF317)	-
P51681	CCR5	C-C chemokine receptor type 5 CCR5 ortholog	C-C CHEMOKINE RECEPTOR TYPE 5 (PTHR10489:SF686)	-
P78362	SRPK2	SRSF protein kinase 2 SRPK2	SRSF PROTEIN KINASE 2 (PTHR24055:SF102)	non-receptor serine/threonine protein

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 March 2020 doi:10.20944/preprints202003.0440.v1

		ortholog		kinase
Q9H0U4	RAB1B	Ras-related protein Rab-1B RAB1B ortholog	RAS-RELATED PROTEIN RAB-1B (PTHR24073:SF1096)	-
P37198	NUP62	Nuclear pore glycoprotein p62 NUP62 ortholog	NUCLEAR PORE GLYCOPROTEIN P62 (PTHR12084:SF12)	transporter
P42701	IL12RB1	Interleukin-12 receptor subunit beta-1 IL12RB1 ortholog	INTERLEUKIN-12 RECEPTOR SUBUNIT BETA-1 (PTHR23036:SF51)	cytokine
P0DMV8	HSPA1A	Heat shock 70 kDa protein 1A HSPA1A ortholog	HEAT SHOCK 70 KDA PROTEIN 1A-RELATED (PTHR19375:SF223)	-
P01375	TNF	Tumor necrosis factor TNF ortholog	TUMOR NECROSIS FACTOR (PTHR11471:SF23)	-
Q12899	TRIM26	Tripartite motif-containing protein 26 TRIM26 ortholog	TRIPARTITE MOTIF-CONTAINING PROTEIN 26 (PTHR24103:SF369)	ubiquitin-protein ligase
P00533	EGFR	Epidermal growth factor receptor EGFR ortholog	EPIDERMAL GROWTH FACTOR RECEPTOR (PTHR24416:SF91)	-
Q07817	BCL2L1	Bcl-2-like protein 1 BCL2L1 ortholog	BCL-2-LIKE PROTEIN 1 (PTHR11256:SF12)	-
P80075	CCL8	C-C motif chemokine 8 CCL8 ortholog	C-C MOTIF CHEMOKINE 8 (PTHR12015:SF168)	cytokine
O95832	CLDN1	Claudin-1 CLDN1 ortholog	CLAUDIN-1 (PTHR12002:SF92)	tight junction
P07858	CTSB	Cathepsin B CTSB ortholog	CATHEPSIN B (PTHR12411:SF714)	cysteine protease
O00602	FCN1	Ficolin-1 FCN1 ortholog	FICOLIN-1-RELATED (PTHR19143:SF346)	intercellular signal molecule
Q9NWF4	SLC52A1	Solute carrier family 52, riboflavin transporter, member 1 SLC52A1 ortholog	SOLUTE CARRIER FAMILY 52, RIBOFLAVIN TRANSPORTER, MEMBER 1 (PTHR12929:SF1)	secondary carrier transporter
Q9HAB3	SLC52A2	Solute carrier family 52, riboflavin transporter, member 2 SLC52A2 ortholog	SOLUTE CARRIER FAMILY 52, RIBOFLAVIN TRANSPORTER, MEMBER 2 (PTHR12929:SF17)	secondary carrier transporter
O00592	PC	Podocalyxin PODXL ortholog	PODOCALYXIN (PTHR12067:SF5)	cell adhesion molecule
P25098	GRK2	Beta-adrenergic receptor kinase 1 GRK2 ortholog	BETA-ADRENERGIC RECEPTOR KINASE 1 (PTHR24355:SF22)	non-receptor serine/threonine protein kinase
P20023	CR2	Complement receptor type 2 CR2 ortholog	COMPLEMENT RECEPTOR TYPE 2 (PTHR19325:SF391)	-
P14735	IDE	Insulin-degrading enzyme IDE ortholog	INSULIN-DEGRADING ENZYME-RELATED (PTHR43690:SF18)	metalloprotease

O43820	HYAL3	Hyaluronidase-3 HYAL3 ortholog	HYALURONIDASE-3 (PTHR11769:SF19)	glycosidase
O00574	CXCR6	C-X-C chemokine receptor type 6 CXCR6 ortholog	C-X-C CHEMOKINE RECEPTOR TYPE 6 (PTHR10489:SF705)	-
P09914	IFIT1	Interferon-induced protein with tetratricopeptide repeats 1 IFIT1 ortholog	INTERFERON-INDUCED PROTEIN WITH TETRATRICOPEPTIDE REPEATS 1 (PTHR10271:SF30)	-
P30411	BDKRB2	B2 bradykinin receptor BDKRB2 ortholog	B2 BRADYKININ RECEPTOR (PTHR24228:SF25)	G-protein coupled receptor
P02810	PA	Salivary acidic proline-rich phosphoprotein 1/2 PRH2 ortholog	SALIVARY ACIDIC PROLINE-RICH PHOSPHOPROTEIN 1/2 (PTHR23203:SF16)	antimicrobial response protein
Q99549	MPHOSPH8	M-phase phosphoprotein 8 MPHOSPH8 ortholog	M-PHASE PHOSPHOPROTEIN 8 (PTHR24166:SF47)	-
P61073	CXCR4	C-X-C chemokine receptor type 4 CXCR4 ortholog	C-X-C CHEMOKINE RECEPTOR TYPE 4 (PTHR10489:SF594)	-
P01574	IFNB1	Interferon beta IFNB1 ortholog	INTERFERON BETA (PTHR11691:SF68)	-
P07711	CTSL	Cathepsin L1 CTSL ortholog	CATHEPSIN L1 (PTHR12411:SF57)	cysteine protease
Q9H0M0	WWP1	NEDD4-like E3 ubiquitin-protein ligase WWP1 WWP1 ortholog	NEDD4-LIKE E3 UBIQUITIN-PROTEIN LIGASE WWP1 (PTHR11254:SF299)	ubiquitin-protein ligase
Q08357	SLC20A2	Sodium-dependent phosphate transporter 2 SLC20A2 ortholog	SODIUM-DEPENDENT PHOSPHATE TRANSPORTER 2 (PTHR11101:SF83)	transporter
Q15758	SLC1A5	Neutral amino acid transporter B(0) SLC1A5 ortholog	NEUTRAL AMINO ACID TRANSPORTER B(0) (PTHR11958:SF19)	primary active transporter
P62820	RAB1A	Ras-related protein Rab-1A RAB1A ortholog	RAS-RELATED PROTEIN RAB-1A (PTHR24073:SF963)	-
Q9P2K8	EIF2AK4	eIF-2-alpha kinase GCN2 EIF2AK4 ortholog	EIF-2-ALPHA KINASE GCN2 (PTHR11042:SF164)	non-receptor serine/threonine protein kinase
P02649	APOE	Apolipoprotein E APOE ortholog	APOLIPOPROTEIN E (PTHR18976:SF2)	-
P60953	CDC42	Cell division control protein 42 homolog CDC42 ortholog	CELL DIVISION CONTROL PROTEIN 42 HOMOLOG (PTHR24072:SF136)	small GTPase
O00482	NR5A2	Nuclear receptor subfamily 5 group A member 2 NR5A2 ortholog	NUCLEAR RECEPTOR SUBFAMILY 5 GROUP A MEMBER 2 (PTHR24086:SF18)	C4 zinc finger nuclear receptor
O00187	MASP2	Mannan-binding lectin serine	MANNAN-BINDING LECTIN	serine protease

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 March 2020 doi:10.20944/preprints202003.0440.v1

		protease 2 MASP2 ortholog	SERINE PROTEASE 2 (PTHR24255:SF10)	
P01730	CD4	T-cell surface glycoprotein CD4 CD4 ortholog	T-CELL SURFACE GLYCOPROTEIN CD4 (PTHR11422:SF0)	-
P04233	CD74	HLA class II histocompatibility antigen gamma chain CD74 ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN GAMMA CHAIN (PTHR14093:SF17)	scaffold/adaptor protein
Q9BYF1	ACE2	Angiotensin-converting enzyme 2 ACE2 ortholog	ANGIOTENSIN-CONVERTING ENZYME 2 (PTHR10514:SF24)	metalloprotease
P57740	NUP107	Nuclear pore complex protein Nup107 NUP107 ortholog	NUCLEAR PORE COMPLEX PROTEIN NUP107 (PTHR13003:SF2)	transporter
Q03135	CAV1	Caveolin-1 CAV1 ortholog	CAVEOLIN-1 (PTHR10844:SF18)	scaffold/adaptor protein
O00635	TRIM38	E3 ubiquitin-protein ligase TRIM38 TRIM38 ortholog	E3 UBIQUITIN-PROTEIN LIGASE TRIM38 (PTHR24103:SF47)	ubiquitin-protein ligase
P03973	SLPI	Antileukoproteinase SLPI ortholog	ANTILEUKOPROTEINASE (PTHR19441:SF44)	protease inhibitor
P02743	APCS	Serum amyloid P-component APCS ortholog	SERUM AMYLOID P-COMPONENT (PTHR45869:SF5)	-
Q15075	EEA1	Early endosome antigen 1 EEA1 ortholog	EARLY ENDOSOME ANTIGEN 1 (PTHR23164:SF17)	membrane trafficking regulatory protein
Q9Y2S7	POLDIP2	Polymerase delta-interacting protein 2 POLDIP2 ortholog	POLYMERASE DELTA-INTERACTING PROTEIN 2 (PTHR14289:SF16)	-
Q14973	SLC10A1	Sodium/bile acid cotransporter SLC10A1 ortholog	SODIUM/BILE ACID COTRANSPORTER (PTHR10361:SF40)	primary active transporter
P10415	BCL2	Apoptosis regulator Bcl-2 BCL2 ortholog	APOPTOSIS REGULATOR BCL-2 (PTHR11256:SF11)	-
Q9UL45	PA	Biogenesis of lysosome-related organelles complex 1 subunit 6 BLOC1S6 ortholog	BIOGENESIS OF LYSOSOME-RELATED ORGANELLES COMPLEX 1 SUBUNIT 6 (PTHR31328:SF2)	-
Q86U86	PB1	Protein polybromo-1 PBRM1 ortholog	PROTEIN POLYBROMO-1 (PTHR16062:SF15)	-
P02786	TFRC	Transferrin receptor protein 1 TFRC ortholog	TRANSFERRIN RECEPTOR PROTEIN 1 (PTHR10404:SF26)	metalloprotease
Q06418	TYRO3	Tyrosine-protein kinase receptor TYRO3 TYRO3 ortholog	TYROSINE-PROTEIN KINASE RECEPTOR TYRO3 (PTHR24416:SF279)	-
P51636	CAV2	Caveolin-2 CAV2	CAVEOLIN-2 (PTHR10844:SF3)	scaffold/adaptor protein

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		ortholog		
Q96QI5	HS3ST5	Heparan sulfate glucosamine 3-O-sulfotransferase 6 HS3ST6 ortholog	HEPARAN SULFATE GLUCOSAMINE 3-O-SULFOTRANSFERASE 6 (PTHR10605:SF62)	-
P26196	DDX6	Probable ATP-dependent RNA helicase DDX6 DDX6 ortholog	ATP-DEPENDENT RNA HELICASE DDX6-RELATED (PTHR47960:SF2)	-
Q92786	PROX1	Prospero homeobox protein 1 PROX1 ortholog	PROSPERO HOMEOBOX PROTEIN 1 (PTHR12198:SF6)	homeodomain transcription factor
Q13155	AIMP2	Aminoacyl tRNA synthase complex-interacting multifunctional protein 2 AIMP2 ortholog	AMINOACYL TRNA SYNTHASE COMPLEX-INTERACTING MULTIFUNCTIONAL PROTEIN 2 (PTHR13438:SF2)	scaffold/adaptor protein
P01130	LDLR	Low-density lipoprotein receptor LDLR ortholog	LOW-DENSITY LIPOPROTEIN RECEPTOR (PTHR24270:SF21)	apolipoprotein
Q12906	ILF3	Interleukin enhancer-binding factor 3 ILF3 ortholog	INTERLEUKIN ENHANCER-BINDING FACTOR 3 (PTHR45762:SF4)	RNA binding protein
Q9UQF0	ERVW-1	Syncytin-1 ERVW-1 ortholog	SYNCYTIN-1 (PTHR10424:SF48)	-
P11279	LAMP1	Lysosome-associated membrane glycoprotein 1 LAMP1 ortholog	LYSOSOME-ASSOCIATED MEMBRANE GLYCOPROTEIN 1 (PTHR11506:SF27)	membrane trafficking regulatory protein
O95433	AHSA1	Activator of 90 kDa heat shock protein ATPase homolog 1 AHSA1 ortholog	ACTIVATOR OF 90 KDA HEAT SHOCK PROTEIN ATPASE HOMOLOG 1 (PTHR13009:SF7)	chaperone
P06493	CDK1	Cyclin-dependent kinase 1 CDK1 ortholog	CYCLIN-DEPENDENT KINASE 1 (PTHR24056:SF334)	non-receptor serine/threonine protein kinase
Q8WZ33	MIP	MaFF-interacting protein MAFIP ortholog	MAFF-INTERACTING PROTEIN-RELATED (PTHR19960:SF12)	non-motor microtubule binding protein
P13500	CCL2	C-C motif chemokine 2 CCL2 ortholog	C-C MOTIF CHEMOKINE 2 (PTHR12015:SF98)	cytokine
Q96AZ6	ISG20	Interferon-stimulated gene 20 kDa protein ISG20 ortholog	INTERFERON-STIMULATED GENE 20 KDA PROTEIN (PTHR12801:SF59)	exoribonuclease
P02765	AHSG	Alpha-2-HS-glycoprotein AHSG ortholog	ALPHA-2-HS-GLYCOPROTEIN (PTHR13814:SF6)	protease inhibitor
Q96NY8	NECTIN4	Nectin-4 NECTIN4 ortholog	NECTIN-4 (PTHR23277:SF11)	-
Q6UWE0	LRSAM1	E3 ubiquitin-protein ligase LRSAM1 LRSAM1 ortholog	E3 UBIQUITIN-PROTEIN LIGASE LRSAM1 (PTHR16083:SF5)	-
P15144	ANPEP	Aminopeptidase N	AMINOPEPTIDASE N	metalloprotease

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 March 2020 doi:10.20944/preprints202003.0440.v1

		ANPEP ortholog	(PTHR11533:SF172)	
Q92956	TNFRSF14	Tumor necrosis factor receptor superfamily member 14 TNFRSF14 ortholog	TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY MEMBER 14 (PTHR46838:SF1)	-
Q9BVG3	TRIM62	E3 ubiquitin-protein ligase TRIM62 TRIM62 ortholog	E3 UBIQUITIN-PROTEIN LIGASE TRIM62 (PTHR24103:SF573)	ubiquitin-protein ligase
P35659	DEK	Protein DEK DEK ortholog	PROTEIN DEK (PTHR13468:SF1)	chromatin/chromatin-binding, or -regulatory protein
Q6UXB4	CLEC4G	C-type lectin domain family 4 member G CLEC4G ortholog	C-TYPE LECTIN DOMAIN FAMILY 4 MEMBER G (PTHR22802:SF245)	membrane traffic protein
P35568	IRS1	Insulin receptor substrate 1 IRS1 ortholog	INSULIN RECEPTOR SUBSTRATE 1 (PTHR10614:SF11)	-
P62937	PPIA	Peptidyl-prolyl cis-trans isomerase A PPIA ortholog	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE A (PTHR11071:SF490)	-
Q02880	TOP2B	DNA topoisomerase 2-beta TOP2B ortholog	DNA TOPOISOMERASE 2-BETA (PTHR10169:SF36)	-
P19525	EIF2AK2	Interferon-induced, double-stranded RNA-activated protein kinase EIF2AK2 ortholog	INTERFERON-INDUCED, DOUBLE-STRANDED RNA-ACTIVATED PROTEIN KINASE (PTHR11042:SF163)	non-receptor serine/threonine protein kinase
Q9UBH6	XPR1	Xenotropic and polytropic retrovirus receptor 1 XPR1 ortholog	XENOTROPIC AND POLYTROPIC RETROVIRUS RECEPTOR 1 (PTHR10783:SF4)	secondary carrier transporter
P22301	IL10	Interleukin-10 IL10 ortholog	-	-
P56747	CLDN6	Claudin-6 CLDN6 ortholog	CLAUDIN-6 (PTHR12002:SF41)	tight junction
Q9H2E6	SEMA6A	Semaphorin-6A SEMA6A ortholog	SEMAPHORIN-6A (PTHR11036:SF12)	membrane-bound signaling molecule
O95292	VAPB	Vesicle-associated membrane protein-associated protein B/C VAPB ortholog	VESICLE-ASSOCIATED MEMBRANE PROTEIN-ASSOCIATED PROTEIN B/C (PTHR10809:SF12)	membrane trafficking regulatory protein
Q92824	PCSK5	Proprotein convertase subtilisin/kexin type 5 PCSK5 ortholog	PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 5 (PTHR42884:SF7)	serine protease
P00491	NP	Purine nucleoside phosphorylase PNP ortholog	PURINE NUCLEOSIDE PHOSPHORYLASE (PTHR11904:SF12)	nucleotide kinase
P02788	LTF	Lactotransferrin LTF ortholog	LACTOTRANSFERRIN (PTHR11485:SF33)	transfer/carrier protein

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 March 2020 doi:10.20944/preprints202003.0440.v1

Q9BV40	VAMP8	Vesicle-associated membrane protein 8 VAMP8 ortholog	VESICLE-ASSOCIATED MEMBRANE PROTEIN 8 (PTHR45701:SF7)	-
Q7Z2W4	ZC3HAV1	Zinc finger CCCH-type antiviral protein 1 ZC3HAV1 ortholog	ZINC FINGER CCCH-TYPE ANTIVIRAL PROTEIN 1 (PTHR45740:SF8)	-
O75791	GRAP2	GRB2-related adapter protein 2 GRAP2 ortholog	GRB2-RELATED ADAPTER PROTEIN 2 (PTHR46037:SF3)	-
P04746	PA	Pancreatic alpha-amylase AMY2A ortholog	ALPHA-AMYLASE 1-RELATED (PTHR43447:SF27)	amylase
P01891	HLA-A	HLA class I histocompatibility antigen, A-68 alpha chain HLA-A ortholog	HLA CLASS I HISTOCOMPATIBILITY ANTIGEN, A-68 ALPHA CHAIN (PTHR16675:SF229)	-
Q14393	GAS6	Growth arrest-specific protein 6 GAS6 ortholog	GROWTH ARREST-SPECIFIC PROTEIN 6 (PTHR24035:SF104)	extracellular matrix protein
O60260	PRKN	E3 ubiquitin-protein ligase parkin PRKN ortholog	E3 UBIQUITIN-PROTEIN LIGASE PARKIN (PTHR11685:SF212)	ubiquitin-protein ligase
Q8WTV0	SCARB1	Scavenger receptor class B member 1 SCARB1 ortholog	SCAVENGER RECEPTOR CLASS B MEMBER 1 (PTHR11923:SF96)	membrane trafficking regulatory protein
P13591	NCAM1	Neural cell adhesion molecule 1 NCAM1 ortholog	NEURAL CELL ADHESION MOLECULE 1 (PTHR12231:SF239)	-
P46108	CRK	Adapter molecule crk CRK ortholog	ADAPTER MOLECULE CRK (PTHR19969:SF8)	-
O75116	ROCK2	Rho-associated protein kinase 2 ROCK2 ortholog	RHO-ASSOCIATED PROTEIN KINASE 2 (PTHR22988:SF28)	non-receptor serine/threonine protein kinase
Q9BVP2	NS	Guanine nucleotide-binding protein-like 3 GNL3 ortholog	GUANINE NUCLEOTIDE-BINDING PROTEIN-LIKE 3 (PTHR11089:SF11)	-
P01024	C3	Complement C3 C3 ortholog	COMPLEMENT C3 (PTHR11412:SF81)	protease inhibitor
P19838	NFKB1	Nuclear factor NF-kappa-B p105 subunit NFKB1 ortholog	NUCLEAR FACTOR NF-KAPPA-B P105 SUBUNIT (PTHR24169:SF9)	Rel homology transcription factor
=Q15365	PCBP1	Poly(rC)-binding protein 1 PCBP1 ortholog	POLY(RC)-BINDING PROTEIN 1 (PTHR10288:SF96)	RNA binding protein
P19474	TRIM21	E3 ubiquitin-protein ligase TRIM21 TRIM21 ortholog	E3 UBIQUITIN-PROTEIN LIGASE TRIM21 (PTHR24103:SF46)	ubiquitin-protein ligase
Q16539	MAPK14	Mitogen-activated protein kinase 14 MAPK14 ortholog	MITOGEN-ACTIVATED PROTEIN KINASE 14 (PTHR24055:SF110)	non-receptor serine/threonine protein kinase

Q01629	IFITM2	Interferon-induced transmembrane protein 2 IFITM2 ortholog	INTERFERON-INDUCED TRANSMEMBRANE PROTEIN 2 (PTHR13999:SF8)	-
P09382	LGALS1	Galectin-1 LGALS1 ortholog	GALECTIN-1 (PTHR11346:SF97)	extracellular matrix protein
P28482	MAPK1	Mitogen-activated protein kinase 1 MAPK1 ortholog	MITOGEN-ACTIVATED PROTEIN KINASE 1 (PTHR24055:SF203)	non-receptor serine/threonine protein kinase
Q6ZTQ4	CDHR3	Cadherin-related family member 3 CDHR3 ortholog	CADHERIN-24-RELATED (PTHR24027:SF272)	-
P54296	MYOM2	Myomesin-2 MYOM2 ortholog	MYOMESIN-2 (PTHR13817:SF22)	-
Q06787	FMR1	Synaptic functional regulator FMR1 FMR1 ortholog	SYNAPTIC FUNCTIONAL REGULATOR FMR1 (PTHR10603:SF4)	translation factor
P49685	GPR15	G-protein coupled receptor 15 GPR15 ortholog	G-PROTEIN COUPLED RECEPTOR 15 (PTHR24228:SF10)	G-protein coupled receptor
Q9NRG9	AAAS	Aladin AAAS ortholog	ALADIN (PTHR14494:SF0)	-
O95817	BAG3	BAG family molecular chaperone regulator 3 BAG3 ortholog	BAG FAMILY MOLECULAR CHAPERONE REGULATOR 3 (PTHR12329:SF12)	-
P04004	VTN	Vitronectin VTN ortholog	VITRONECTIN (PTHR22917:SF3)	-
P61769	B2M	Beta-2-microglobulin B2M ortholog	BETA-2-MICROGLOBULIN (PTHR19944:SF62)	major histocompatibility complex protein
Q12891	HYAL2	Hyaluronidase-2 HYAL2 ortholog	HYALURONIDASE-2 (PTHR11769:SF6)	glycosidase
O15118	NPC1	NPC intracellular cholesterol transporter 1 NPC1 ortholog	NPC INTRACELLULAR CHOLESTEROL TRANSPORTER 1 (PTHR45727:SF2)	-
Q8IZT8	HS3ST5	Heparan sulfate glucosamine 3-O-sulfotransferase 5 HS3ST5 ortholog	HEPARAN SULFATE GLUCOSAMINE 3-O-SULFOTRANSFERASE 5 (PTHR10605:SF46)	-
Q9BZY9	TRIM31	E3 ubiquitin-protein ligase TRIM31 TRIM31 ortholog	E3 UBIQUITIN-PROTEIN LIGASE TRIM31 (PTHR24103:SF87)	ubiquitin-protein ligase
Q9UDY6	TRIM10	Tripartite motif-containing protein 10 TRIM10 ortholog	TRIPARTITE MOTIF-CONTAINING PROTEIN 10 (PTHR24103:SF329)	ubiquitin-protein ligase
Q08752	PPID	Peptidyl-prolyl cis-trans isomerase D	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE D-	-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 March 2020 doi:10.20944/preprints202003.0440.v1

		PPID ortholog	RELATED (PTHR11071:SF380)	
Q9H1Y0	ATG5	Autophagy protein 5 ATG5 ortholog	AUTOPHAGY PROTEIN 5 (PTHR13040:SF2)	membrane trafficking regulatory protein
Q9UQG0	ERVK-11	Endogenous retrovirus group K member 11 Pol protein ERVK-11 ortholog	ENDOGENOUS RETROVIRUS GROUP K MEMBER 10 POL PROTEIN-RELATED (PTHR41694:SF3)	-
P78536	ADAM17	Disintegrin and metalloproteinase domain-containing protein 17 ADAM17 ortholog	DISINTEGRIN AND METALLOPROTEINASE DOMAIN-CONTAINING PROTEIN 17 (PTHR45702:SF6)	-
Q9UGI6	K3	Small conductance calcium-activated potassium channel protein 3 KCNN3 ortholog	SMALL CONDUCTANCE CALCIUM-ACTIVATED POTASSIUM CHANNEL PROTEIN 3 (PTHR10153:SF40)	voltage-gated ion channel
P05556	ITGB1	Integrin beta-1 ITGB1 ortholog	INTEGRIN BETA-1 (PTHR10082:SF28)	cell adhesion molecule
P24298	GPT	Alanine aminotransferase 1 GPT ortholog	ALANINE AMINOTRANSFERASE 1 (PTHR11751:SF308)	transaminase
O43504	LAMTOR 5	Ragulator complex protein LAMTOR5 LAMTOR5 ortholog	RAGULATOR COMPLEX PROTEIN LAMTOR5 (PTHR13342:SF4)	-
Q9NPH2	ISYNA1	Inositol-3-phosphate synthase 1 ISYNA1 ortholog	INOSITOL-3-PHOSPHATE SYNTHASE 1 (PTHR11510:SF5)	isomerase
Q15517	CDSN	Corneodesmosin CDSN ortholog	CORNEODESMOSIN (PTHR23207:SF2)	-
P56545	CTBP2	C-terminal-binding protein 2 CTBP2 ortholog	C-TERMINAL-BINDING PROTEIN 2 (PTHR46029:SF3)	transcription cofactor
O00571	DDX3X	ATP-dependent RNA helicase DDX3X DDX3X ortholog	ATP-DEPENDENT RNA HELICASE DDX3X (PTHR47958:SF4)	-
P15151	PVR	Poliovirus receptor PVR ortholog	POLIOVIRUS RECEPTOR (PTHR23277:SF109)	-
P60568	IL2	Interleukin-2 IL2 ortholog	-	-
Q9H2X3	CLEC4M	C-type lectin domain family 4 member M CLEC4M ortholog	C-TYPE LECTIN DOMAIN FAMILY 4 MEMBER M (PTHR22802:SF197)	membrane traffic protein
Q9NY25	CLEC5A	C-type lectin domain family 5 member A CLEC5A ortholog	C-TYPE LECTIN DOMAIN FAMILY 5 MEMBER A (PTHR47536:SF1)	-
P05362	ICAM1	Intercellular adhesion molecule 1 ICAM1 ortholog	INTERCELLULAR ADHESION MOLECULE 1 (PTHR13771:SF9)	-
Q92692	NECTIN2	Nectin-2	NECTIN-2 (PTHR47387:SF1)	-

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		NECTIN2 ortholog		
P02751	FN1	Fibronectin FN1 ortholog	FIBRONECTIN (PTHR19143:SF267)	intercellular signal molecule
Q12824	SMARCB1	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 SMARCB1 ortholog	SWI/SNF-RELATED MATRIX-ASSOCIATED ACTIN-DEPENDENT REGULATOR OF CHROMATIN SUBFAMILY B MEMBER 1 (PTHR10019:SF5)	DNA binding protein
Q7Z6L0	PRRT2	Proline-rich transmembrane protein 2 PRRT2 ortholog	PROLINE-RICH TRANSMEMBRANE PROTEIN 2 (PTHR14948:SF20)	-
P09341	CXCL1	Growth-regulated alpha protein CXCL1 ortholog	GROWTH-REGULATED ALPHA PROTEIN (PTHR10179:SF69)	chemokine
P07202	TPO	Thyroid peroxidase TPO ortholog	THYROID PEROXIDASE (PTHR11475:SF60)	peroxidase
P01562	IFNA13 IFNA1	Interferon alpha-1/13 IFNA13 ortholog	INTERFERON ALPHA-1/13 (PTHR11691:SF64)	-
Q14242	SELPLG	P-selectin glycoprotein ligand 1 SELPLG ortholog	P-SELECTIN GLYCOPROTEIN LIGAND 1 (PTHR17384:SF7)	-
P02724	GYPA	Glycophorin-A GYPA ortholog	GLYCOPHORIN-A (PTHR13813:SF3)	-
O00182	LGALS9	Galectin-9 LGALS9 ortholog	GALECTIN-9 (PTHR11346:SF80)	extracellular matrix protein
O60493	SNX3	Sorting nexin-3 SNX3 ortholog	SORTING NEXIN-3 (PTHR45963:SF1)	-
Q13049	TRIM32	E3 ubiquitin-protein ligase TRIM32 TRIM32 ortholog	E3 UBIQUITIN-PROTEIN LIGASE TRIM32 (PTHR25464:SF3)	-
P29508	SERPINB3	Serpin B3 SERPINB3 ortholog	SERPIN B3 (PTHR11461:SF320)	protease inhibitor
P15529	CD46	Membrane cofactor protein CD46 ortholog	MEMBRANE COFACTOR PROTEIN (PTHR19325:SF521)	-
P06756	ITGAV	Integrin alpha-V ITGAV ortholog	INTEGRIN ALPHA-V (PTHR23220:SF4)	-
Q13291	SLAMF1	Signaling lymphocytic activation molecule SLAMF1 ortholog	SIGNALING LYMPHOCYTIC ACTIVATION MOLECULE (PTHR12080:SF49)	immunoglobulin receptor superfamily
P55265	ADAR	Double-stranded RNA-specific adenosine deaminase ADAR ortholog	DOUBLE-STRANDED RNA-SPECIFIC ADENOSINE DEAMINASE (PTHR10910:SF107)	RNA binding protein
Q9UQV4	LAMP3	Lysosome-associated membrane glycoprotein 3	LYSOSOME-ASSOCIATED MEMBRANE GLYCOPROTEIN	membrane trafficking regulatory protein

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		LAMP3 ortholog	3 (PTHR11506:SF30)	
Q9BZR9	TRIM8	E3 ubiquitin-protein ligase TRIM8 TRIM8 ortholog	E3 UBIQUITIN-PROTEIN LIGASE TRIM8 (PTHR25465:SF19)	-
C9JQL5	C9JQL5	Putative dispanin subfamily A member 2d unassigned ortholog	DISPANIN SUBFAMILY A MEMBER 2D-RELATED (PTHR13999:SF23)	-
Q12794	HYAL1	Hyaluronidase-1 HYAL1 ortholog	HYALURONIDASE-1 (PTHR11769:SF23)	glycosidase

Table 1 : The 279 enriched gene based on gene ontology (GO Slim) – Biological process selected based on criteria P-Value less than 0.05

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<table>
<tr><th>SNO</th><th>Gene</th><th>Symptoms</th><th>STICH prediction of FDA approved for repurposing</th><th>DGIdb2.0 prediction of FDA approved Drugs for repurposing</th></tr>
<tr>
<td>1</td>
<td>VEGFA</td>
<td>Fever, Pneumonia, Heart Disease, Kidney Disease, Lung Disease, Diabetes, Hypertension, Cancer, Sepsis, Acute Kidney Injury</td>
<td>
<table>
<tr><td>carvedilol</td><td>0.816</td></tr>
<tr><td>cilostazol</td><td>0.818</td></tr>
<tr><td>fenofibrate</td><td>0.822</td></tr>
<tr><td>gliclazide</td><td>0.800</td></tr>
<tr><td>pegaptanib sod.</td><td>0.457</td></tr>
<tr><td>pyroglutamate</td><td>0.814</td></tr>
<tr><td>sorafenib</td><td>0.909</td></tr>
</table>
</td>
<td>
<table>
<tr><th>Drug</th><th>Interaction Type</th><th>Score</th></tr>
<tr><td>Ranibizumab</td><td>inhibitor</td><td>14</td></tr>
<tr><td>Bevacizumab</td><td>antibody, inhibitor</td><td>10</td></tr>
<tr><td>Aflibercept</td><td>binder, antibody, inhibitor</td><td>7</td></tr>
<tr><td>Gliclazide</td><td>n/a</td><td>5</td></tr>
<tr><td>Carvedilol</td><td>other</td><td>5</td></tr>
<tr><td>Tromethamine</td><td>n/a</td><td>4</td></tr>
<tr><td>Pyroglutamic acid</td><td>n/a</td><td>4</td></tr>
<tr><td>Dalteparin sodium</td><td>inhibitor</td><td>4</td></tr>
<tr><td>Pentosan polysulfate sodium</td><td>n/a</td><td>2</td></tr>
<tr><td>Fenofibrate</td><td>n/a</td><td>2</td></tr>
<tr><td>Phenytoin</td><td>n/a</td><td>2</td></tr>
<tr><td>Cilostazol</td><td>n/a</td><td>2</td></tr>
<tr><td>Gentamicin</td><td>n/a</td><td>2</td></tr>
<tr><td>Sorafenib</td><td>n/a</td><td>1</td></tr>
<tr><td>Sorafenib tosylate</td><td>inhibitor</td><td>1</td></tr>
<tr><td>Pegaptanib sodium</td><td>antagonist</td><td>1</td></tr>
<tr><td>Lenalidomide</td><td>n/a</td><td>1</td></tr>
<tr><td>Vandetanib</td><td>inhibitor</td><td>1</td></tr>
</table>
</td>
</tr>
</table>

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2	TNF	Fever, Pneumonia, Heart Disease, Kidney Disease, Lung Disease, Diabetes, Hypertension, Cancer, Sepsis, Acute Kidney Injury, Neutrophilia, Lymphophenia, Thrombocytopenia, Multiple Organ Failure, SARS-CoV, Viral Life Cycle	amrinone 0.800 anti-D 0.851 **chloroquine** 0.969 clenbuterol 0.819 gentamicin 0.400 lenalidomide 0.940 **penicillin** 0.933 **pentoxifylline** 0.990 pirfenidone 0.816 pomalidomide 0.800 sulphate 0.495 **thalidomide** 0.980 timolol 0.647	**Drug** / **Interaction Type** / **Score** Infliximab / antibody, inhibitor / 17 Adalimumab / antibody, inhibitor / 12 Etanercept / antibody, inhibitor / 12 Thalidomide / inhibitor / 11 **Chloroquine** / n/a / 6 Certolizumab pegol / neutralizer, antibody, inhibitor / 6 Inamrinone / inhibitor / 6 Clenbuterol / n/a / 6 Golimumab / antibody, inhibitor / 6 Glucosamine / n/a / 6 Risperidone / n/a / 3 Carbamazepine / n/a / 3 Cefotaxime / n/a / 3 Folic acid / n/a / 2 Rabeprazole / n/a / 2 Timolol maleate / n/a / 2 Pomalidomide / inhibitor / 2 **Penicillin** g sodium / n/a / 2 Omeprazole / n/a / 2 Didanosine / n/a / 2 Midazolam / n/a / 2 Miltefosine / n/a / 2 Methimazole / n/a / 2

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				Glimepiride	n/a	2
				Fluocinolone acetonide	n/a	2
				Hydroxychloroquine	n/a	2
				Cromolyn sodium	n/a	2
				Pyridoxine	n/a	2
				Prazosin hydrochloride	n/a	2
				Gentamicin	n/a	2
				Meropenem	n/a	2
				Lactulose hydrate	n/a	2
				Nordihydroguaiaretic acid	n/a	2
				Propylthiouracil	n/a	2
				Bupivacaine	n/a	2
				Magnesium sulfate	n/a	2
				Spironolactone	n/a	2
				Procarbazine	n/a	2
				Lenalidomide	inhibitor	2
				Abacavir	n/a	1
				Apremilast	n/a	1
				Pentoxifylline	antibody	1
				Pirfenidone	inhibitor	1
3	IL6	Fever, Pneumonia, Heart Disease, Kidney Disease, Lung Disease, Diabetes, Hypertension,	-	**Drug**	**Interaction Type**	**Score**
				Siltuximab	antagonist, antibody, inhibitor	4
				Gemfibrozil	n/a	2
				Linezolid	n/a	2
				Levofloxacin	n/a	2

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		Cancer, Sepsis, Acute Kidney Injury, Neutrophilia, Thrombocytopenia, SARS-CoV		Ifosfamide n/a 2 Arsenic trioxide n/a 2 Metronidazole n/a 2 Vitamin k n/a 2 Fentanyl n/a 2 Saquinavir n/a 2 Interferon alfa-2b n/a 2 Nelfinavir n/a 2 Gallium nitrate n/a 2
4	CXCL8	Cough, Fever, Dyspnea, Pneumonia, Kidney Disease, Lung Disease, Diabetes, Hypertension, Cancer, Sepsis, Neutrophilia, Leukocytosis, Thrombocytopenia, SARS-CoV, Viral Life Cycle	aspirin 0.450 fentanyl 0.826 omeprazole 0.819 **paclitaxel** 0.947 quinol 0.700 retinoic acid 0.949	**Drug** **Interaction Type** **Score** Cetuximab n/a 4 Naproxen n/a 2 Cidofovir n/a 2 Paclitaxel n/a 2 Aspirin n/a 2 Omeprazole n/a 2 Leflunomide n/a 2 Dipyridamole n/a 2 Danazol n/a 2 Midazolam n/a 2 Foscarnet n/a 2 Clarithromycin n/a 2 Acetaminophen n/a 2 Methimazole n/a 2 Tocopherol acetate n/a 2 Ceftriaxone n/a 2 Fentanyl n/a 2 Medroxyprogesterone n/a 2

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				acetate n/a 2 Verapamil n/a 2 Methylene blue n/a 2 Aluminum hydroxide n/a 2 Lansoprazole n/a 2 Talc n/a 2 Pentoxifylline n/a 2 Pamidronic acid n/a 2 Alprazolam n/a 2 Tretinoin n/a 2 Hydroquinone n/a 2 Bevacizumab n/a 1 Cyclophosphamide n/a 1
5	IL10	Fever, Pneumonia, Kidney Disease, Lung Disease, Diabetes, Hypertension, Cancer, Sepsis, Acute Kidney Injury, Lymphophenia, Multiple Organ Failure, SARS-CoV	**rapamycin** 0.985	**Drug** / **Interaction Type** / **Score** Mesalamine n/a 2 Rabeprazole n/a 2 Zidovudine n/a 2 Fluticasone propionate n/a 2 Clarithromycin n/a 2 Sirolimus n/a 2 Amoxicillin n/a 2 Acyclovir n/a 2 Tretinoin n/a 2
6	CCL2	Fever, Pneumonia, Kidney Disease, Lung Disease, Diabetes, Hypertension, Sepsis, SARS-	Statins 0.986 danazol 0.815 **fenofibrate** 0.984 **pioglitazone** 0.985	**Drug** / **Interaction Type** / **Score** Danazol inhibitor 3

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<table>
<tr><td></td><td></td><td>CoV, Viral Life Cycle</td><td></td><td></td></tr>
<tr><td>7</td><td>IL1B</td><td>Cough, Fever, Pneumonia, Heart Disease, Kidney Disease, Lung Disease, Diabetes, Hypertension, Cancer, Sepsis, Neutrophilia, Leukocytosis, Lymphophenia</td><td><table><tr><td>gallium nitrate</td><td>0.800</td></tr><tr><td>levofloxacin</td><td>0.800</td></tr><tr><td>pentoxifylline</td><td>0.866</td></tr><tr><td>diacerein</td><td>0.837</td></tr><tr><td>cortisol</td><td>0.958</td></tr></table></td><td><table><tr><th>Drug</th><th>Interaction Type</th><th>Score</th></tr><tr><td>Canakinumab</td><td>binder, antibody, inhibitor</td><td>7</td></tr><tr><td>Rilonacept</td><td>binder, inhibitor</td><td>5</td></tr><tr><td>Acitretin</td><td>n/a</td><td>3</td></tr><tr><td>Gallium nitrate</td><td>antagonist, inhibitor</td><td>3</td></tr><tr><td>Cytarabine</td><td>n/a</td><td>2</td></tr><tr><td>Thyroglobulin</td><td>n/a</td><td>2</td></tr><tr><td>Nicardipine</td><td>n/a</td><td>2</td></tr><tr><td>Ofloxacin</td><td>n/a</td><td>2</td></tr><tr><td>Hydrocortisone</td><td>n/a</td><td>2</td></tr><tr><td>Cefaclor</td><td>n/a</td><td>2</td></tr><tr><td>Fluticasone propionate</td><td>n/a</td><td>2</td></tr><tr><td>Raloxifene</td><td>n/a</td><td>2</td></tr><tr><td>Pentamidine</td><td>n/a</td><td>2</td></tr><tr><td>Verapamil</td><td>n/a</td><td>2</td></tr><tr><td>Lansoprazole</td><td>n/a</td><td>2</td></tr><tr><td>Erythromycin</td><td>n/a</td><td>2</td></tr><tr><td>Beclomethasone dipropionate</td><td>n/a</td><td>2</td></tr><tr><td>Pentoxifylline</td><td>n/a</td><td>2</td></tr><tr><td>Hydroquinone</td><td>n/a</td><td>2</td></tr><tr><td>Melatonin</td><td>n/a</td><td>2</td></tr><tr><td>Diacerein</td><td>n/a</td><td>1</td></tr></table></td></tr>
<tr><td>8</td><td>TLR4</td><td>Fever, Pneumonia, Kidney Disease, Lung Disease, Diabetes,</td><td><table><tr><td>Ethanol</td><td>0.880</td></tr></table></td><td><table><tr><th>Drug</th><th>Interaction Type</th><th>Score</th></tr><tr><td>Ritonavir</td><td>n/a</td><td>2</td></tr><tr><td>Saquinavir</td><td>n/a</td><td>2</td></tr></table></td></tr>
</table>

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		Hypertension, Cancer, Sepsis, Acute Kidney Injury, Neutrophilia, Thrombocytopenia		Alcohol n/a 2 Infliximab n/a 2 Nelfinavir n/a 2 Folic acid n/a 1
9	ICAM1	Fever, Pneumonia, Kidney Disease, Diabetes, Hypertension, Sepsis, Viral Entry, Viral Life Cycle	Statins 0.987 lifitegrast 0.766	**Drug** **Interaction Type** **Score** Natalizumab n/a 2 Lifitegrast n/a 1
10	MMP9	Cough, Fever, Pneumonia, Heart Disease, Kidney Disease, Lung Disease, Diabetes, Hypertension, Cancer, Sepsis, Neutrophilia, Leukocytosis, Multiple Organ Failure	**captopril 0.816**	**Drug** **Interaction Type** **Score** Glucosamine antagonist 6 **Captopril** inhibitor 5 Bevacizumab n/a 2 Methyldopa n/a 1 Nifedipine n/a 1

Table 2: Identified top 10 druggable genes, showing gene-disease association and predicted of STITCH &DGIdb2.0 of FDA drugs from drug-gene association

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Hypertension	STITCH Drug prediction	Diabetes	STITCH Drug prediction	Heart Disease	STITCH Drug prediction	Lung Disease	STITCH Drug prediction	Kidney Disease	STITCH Drug prediction	Cancer	STITCH Drug prediction	Asymptomatic
VEGFA IL6 TNF CCL2 MMP9 ALB IL10 PTGS2 CXCL8 CASP3	**CASP3** paclitaxel (0.972) retinoic acid (0.961) thalidomide (0.945) **IL10, VEGFA** aspirin (0.954) rapamycin (0.985) retinoic acid (0.961)	IL6 TNF CXCL8 IL10 CCL2 ICAM1 IFNG IL2 FN1 CXCR4	**CXCL12** Plerixafor 0.964 Quinine 0.915 **IFNG** pentoxifylline 0.914 IL10 aspirin 0.954 methylpredniso 0.930 Pentoxiflline 0.924 rapamycin 0.985 retonic acid 0.961	IL6 TNF CXCL8 CCL2 MAPK1 EGFR ICAM1 CCL5 CXCR4 AGT	**CXCR4** plerixafor 0.999 **EGFR** afatinib 0.999 eriotinib 0.999 gefitinib 0.999 lapatinib 0.999 paclitaxel 0.982 **IL6** Cortisol 0.976	IL6 TNF CXCL8 IFNG CCL5 IL10 CCL2 ICAM1 CXCL1 CXCR4	**CXCL12** Plerixafor 0.964	IL6 TNF CXCL8 CCL2 IL10 ICAM1 CCL5 FN1 EGFR CXCR4	**CXCR4** plerixafor 0.999 **EGFR** afatinib 0.999 bosutinib 0.909 erlotinib 0.999 lapatinib 0.981 vendetanib 0.998 **IL6** pentoxifylline 0.948 retinoic acid 0.968	VEGFA STAT3 IL6 TNF MAPK3 MAPK1 CASP3 MMP9 PTGS EGF	**CASP3** gentamicin 0.958 hydroxychloroquine 0.942 sorafenib 0.948 sulindac 0.925 thalidomide 0.45 **EGFR** erlotinib 0.999 vandetanib 0.998	IL6 TNF CXCL8 **IL1B** IL10 CCL2 ICAM1 IL2 **STAT3** CCL5

Table 3: Top 10 key genes of high risk with predicted FDA approved drug and asymptomatic group identified from Protein-Protein interaction network by using Cytohubba