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, thalidom, 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
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 interferon 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
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)
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 473 genes. 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).
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
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).
**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
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-
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).

*Thalidomide (0.980)*

Thalidomide 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).
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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References:

1. Sci AS-IJCRM, 2020 undefined. Coronavirus: A mini-review. academia.edu [Internet]. [cited 2020 Mar 24]; Available from: http://www.academia.edu/download/62221295/corona_virus.pdf

2. Perlman S. Another Decade, Another Coronavirus. New England Journal of Medicine [Internet]. 2020 [cited 2020 Feb 2];NEJMe2001126. Available from: http://www.nejm.org/doi/10.1056/NEJMe2001126

3. Lim YX, Ng YL, Tam JP, Liu DX. Human Coronaviruses: A Review of Virus-Host Interactions. Wiley Online Library [Internet]. [cited 2020 Mar 24]; Available from: www.mdpi.com/journal/diseases

4. Andersen K, Rambaut A, Lipkin W, Medicine EH-N, 2020 undefined. The proximal origin of SARS-CoV-2. nature.com [Internet]. [cited 2020 Mar 24]; Available from: https://www.nature.com/articles/s41591-020-0820-9

5. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance [Internet]. 2020 [cited 2020 Feb 2];25(3):2000045. Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.3.2000045

6. Zhu W, Shen X. An Overall Picture of SARS Coronavirus (SARS-CoV) Genome-Encoded Major Proteins: Structures, Functions and Drug Development. 2006 [cited 2020 Feb 2]; Available from: http://www.who.int/csr/sars/country/

7. Poon LLM, Chu DKW, Chan KH, Wong OK, Ellis TM, Leung YHC, et al. Identification of a Novel Coronavirus in Bats. JOURNAL OF VIROLOGY [Internet]. 2005 [cited 2020 Feb 2];79(4):2001–9. Available from: http://jvi.asm.org/

8. Hu B, Ge X, Wang LF, Shi Z. Bat origin of human coronaviruses Coronaviruses: Emerging and re-emerging pathogens in humans and animals Susanna Lau Positive-strand RNA viruses. Vol. 12, Virology Journal. BioMed Central Ltd.; 2015.

9. Hu B, Ge X, Wang L, journal ZS-V, 2015 undefined. Bat origin of human coronaviruses. virology.ji.biomedcentral.com [Internet]. [cited 2020 Feb 2]; Available from: https://virology.ji.biomedcentral.com/articles/10.1186/s12985-015-0422-1

10. Ge X, Li J, Yang X, Chmura A, Zhu G, Nature JE-, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. nature.com [Internet]. [cited 2020 Feb 2]; Available from: https://www.nature.com/articles/nature12711

11. Banerjee A, Kulcsar K, Misra V, Frieman M, Mossman K, contributed equally K. viruses Bats and Coronaviruses. mdpi.com [Internet]. [cited 2020 Mar 24]; Available from: www.mdpi.com/journal/viruses

12. Parry J. China coronavirus: cases surge as official admits human to human transmission. 2020 [cited 2020 Feb 2]; Available from: https://www.bmj.com/content/368/bmj.m236.long

13. Pillaiyar T, Manickam M, Namavigayam V, Hayashi Y, Jung SH. An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: Peptidomimetics and small molecule chemotherapy. Vol. 59, Journal of Medicinal Chemistry. American Chemical Society; 2016. p. 6595–628.
14. On the origin and continuing evolution of SARS-CoV-2 | National Science Review | Oxford Academic [Internet]. [cited 2020 Mar 24]. Available from: https://academic.oup.com/nsr/advance-article/doi/10.1093/nsr/nwaa036/5775463

15. Zhang T, Wu Q, Zhang Z. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. CelPress. 2020;

16. Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. Journal of Medical Virology. 2020 Mar 11;

17. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annual Review of Virology. 2016;

18. Li F, Li W, Farzan M, Harrison SC. Structural biology: Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science. 2005;

19. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses. 2012.

20. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. jstage.jst.go.jp [Internet]. [cited 2020 Mar 24]; Available from: www.biosciencetrends.com

21. Yao T, Qian J, Zhu W, Wang Y, Wang G. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus—A possible reference for coronavirus disease-19 treatment option. Journal of Medical Virology. 2020 Mar 12;

22. Li G, Leuven KU. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). 2020 [cited 2020 Mar 24]; Available from: https://doi.org/10.1038/s41422-020-0282-0

23. Kumar S. Drug and Vaccine Design against Novel Coronavirus (2019-nCoV) Spike Protein through Computational Approach. Preprints (www.preprints.org) [Internet]. 2020;(February). Available from: https://www.preprints.org/manuscript/202002.0071/v1

24. Dhama K, Sharan K, Tiwari R, Dadar M, Malik YS, Singh KP, et al. COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Human vaccines & immunotherapeutics [Internet]. 2020 Mar 18 [cited 2020 Mar 24];1–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32186952

25. Hu B. Clinical course and outcome of novel coronavirus COVID-19 infection in 107 patients discharged from the Wuhan hospital. Preprint. 2020;1–23.

26. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Elsevier [Internet]. [cited 2020 Mar 24]; Available from: https://www.sciencedirect.com/science/article/pii/S0140673620305663

27. Al-Tawfiq J, Hospital ZM-J of, 2020 undefined. Diagnosis of SARS-CoV-2 Infection based on CT scan vs. RT-PCR: Reflecting on Experience from MERS-CoV. journalofhospitalinfection.com [Internet]. [cited 2020 Mar 24]; Available from: https://www.journalofhospitalinfection.com/article/S0195-6701(20)30100-6/abstract
28. Liu X, Wang Y, Kang H, Tong Z. Combination of RT-qPCR Testing and Clinical Features For Diagnosis of COVID-19 facilitates management of SARS-CoV-2 Outbreak. Wiley Online Library [Internet]. 2020 [cited 2020 Mar 24]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25721

29. Guo L, Huang Y, Tu M, Wang S, Chen S, Long W. Confusion and Thinking on the Diagnosis and Treatment of Patients with Negative RT-PCR Results for SARS-CoV-2. 2020 [cited 2020 Mar 24]; Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3551322

30. Talevi A, Bellera C. Challenges and opportunities with drug repurposing: finding strategies to find alternative uses of therapeutics. 2020 [cited 2020 Mar 24]; Available from: https://www.tandfonline.com/doi/full/10.1080/17460441.2020.1704729

31. Pushpakom S, Iorio F, Eyers P, … KE-N reviews D, 2019 undefined. Drug repurposing: progress, challenges and recommendations. nature.com [Internet]. [cited 2020 Mar 24]; Available from: https://www.nature.com/nrd/journal/v18/n1/full/nrd.2018.168.html

32. Lötsch J, Kringle D. Use of Computational Functional Genomics in Drug Discovery and Repurposing for Analgesic Indications. Clinical Pharmacology and Therapeutics. 2018 Jun 1;103(6):975–8.

33. Piñero J, Ramírez-Anguita JM, Saüch-Pitarch J, Ronzano F, Centeno E, Sanz F, et al. The DisGeNET knowledge platform for disease genomics: 2019 update. Nucleic Acids Research. 2019 Nov;

34. Davis A, Grondin C, … RJ-N acids, 2019 undefined. The comparative toxicogenomics database: update 2019. academic.oup.com [Internet]. [cited 2020 Mar 24]; Available from: https://academic.oup.com/nar/article-abstract/47/D1/D419/5106145

35. Mi H, Muruganujan A, Ebert D, … XH-N acids, 2019 undefined. PANTHER version 14: more genomes, a new PANTHER GO-slim and improvements in enrichment analysis tools. academic.oup.com [Internet]. [cited 2020 Mar 24]; Available from: https://academic.oup.com/nar/article-abstract/47/D1/D419/5165346

36. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, et al. STRING v11: Protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Research. 2019 Jan;47(D1):D607–13.

37. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: A software Environment for integrated models of biomolecular interaction networks. Genome Research. 2003 Nov;13(11):2498–504.

38. Chin CH, Chen SH, Wu HH, Ho CW, Ko MT, Lin CY. cytoHubba: Identifying hub objects and sub-networks from complex interactome. BMC Systems Biology. 2014 Dec;8(4).

39. Griffith M, Griffith OL, Coffman AC, Weible J V., Mcmichael JF, Spies NC, et al. DGIdb: Mining the druggable genome. Nature Methods. 2013 Dec;10(12):1209–10.

40. Szklarczyk D, Santos A, … C von M-N acids, 2016 undefined. STITCH 5: augmenting protein–chemical interaction networks with tissue and affinity data.
41. Foulger RE, Osumi-Sutherland D, McIntosh BK, Hulo C, Masson P, Poux S, et al. Representing virus-host interactions and other multi-organism processes in the Gene Ontology. BMC Microbiology. 2015 Jul 28;15(1).

42. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. Journal of clinical oncology: official journal of the American Society of Clinical Oncology [Internet]. 2005 Feb 10 [cited 2020 Mar 24];23(5):1011–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15585754

43. Herbein G, O’Brien WA. Tumor necrosis factor (TNF)-α and TNF receptors in viral pathogenesis. Vol. 223, Proceedings of the Society for Experimental Biology and Medicine. 2000. p. 241–57.

44. Haga S, Yamamoto N, Nakai-Murakami C, Osawa Y, Tokunaga K, Sata T, et al. Modulation of TNF-α-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-α production and facilitates viral entry. Proceedings of the National Academy of Sciences of the United States of America. 2008 Jun 3;105(22):7809–14.

45. Frei K, Malipiero U V., Leist TP, Zinkernagel RM, Schwab ME, Fontana A. On the cellular source and function of interleukin 6 produced in the central nervous system in viral diseases. European Journal of Immunology [Internet]. 1989 Apr 1 [cited 2020 Mar 24];19(4):689–94. Available from: http://doi.wiley.com/10.1002/eji.1830190418

46. Mukaida N. Pathophysiological roles of interleukin-8/CXCL8 in pulmonary diseases. Vol. 284, American Journal of Physiology - Lung Cellular and Molecular Physiology. American Physiological SocietyBethesda, MD ; 2003.

47. Brooks DG, Trifilo MJ, Edelmann KH, Teyton L, McGavern DB, Oldstone MBA. Interleukin-10 determines viral clearance or persistence in vivo. Nature Medicine. 2006 Nov 15;12(11):1301–9.

48. Sabbatucci M, Covino AA, Purificato C, Mallano A, Federico M, Lu J, et al. Endogenous CCL2 neutralization restricts HIV-1 replication in primary human macrophages by inhibiting viral DNA accumulation. Retrovirology. 2015 Jan 22;12(1).

49. Ansari AW, Heiken H, Meyer-Olson D, Schmidt RE. CCL2: A potential prognostic marker and target of anti-inflammatory strategy in HIV/AIDS pathogenesis. European Journal of Immunology. 2011 Dec;41(12):3412–8.

50. Angela Covino D, Sabbatucci M, Fantuzzi L. The CCL2/CCR2 Axis in the Pathogenesis of HIV-1 Infection: A New Cellular Target for Therapy? Current Drug Targets. 2015 Dec 22;17(1):76–110.

51. Kim KS, Jung H, Shin IK, Choi BR, Kim DH. Induction of interleukin-1 beta (IL-1β) is a critical component of lung inflammation during influenza A (H1N1) virus infection. Journal of Medical Virology. 2015 Jul 1;87(7):1104–12.

52. Liu Y, Li S, Zhang G, Nie G, Meng Z, Mao D, et al. Genetic variants in IL1A and IL1B contribute to the susceptibility to 2009 pandemic H1N1 influenza A virus. BMC Immunology. 2013 Aug 8;14(1):37.

53. Olejnik J, Hume AJ, Mühlberger E. Toll-like receptor 4 in acute viral infection: Too
much of a good thing. Vol. 14, PLoS Pathogens. Public Library of Science; 2018.

54. Okumura A, Pitha PM, Yoshimura A, Harty RN. Interaction between Ebola Virus Glycoprotein and Host Toll-Like Receptor 4 Leads to Induction of Proinflammatory Cytokines and SOCS1. Journal of Virology. 2010 Jan 1;84(1):27–33.

55. Othumpangat S, Noti JD, McMillen CM, Beezhold DH. ICAM-1 Regulates the survival of influenza virus in lung epithelial cells during the early stages of infection. Virology. 2016 Jan 1;487:85–94.

56. BOUNOU S, GIGUÈRE J-F, CANTIN R, GILBERT C, IMBEAULT M, MARTIN G, et al. The importance of virus-associated host ICAM-1 in human immunodeficiency virus type 1 dissemination depends on the cellular context. The FASEB Journal. 2004 Aug 18;18(11):1294–6.

57. Dabo AJ, Cummins N, Eden E, Geraghty P. Matrix metalloproteinase 9 exerts antiviral activity against respiratory syncytial virus. PLoS ONE. 2015 Aug 18;10(8).

58. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the Eye of the Cytokine Storm. Microbiology and Molecular Biology Reviews. 2012 Mar 1;76(1):16–32.

59. Ďelia R V., Harrison K, Oyston PC, Lukaszewski RA, Clark GC. Targeting the “Cytokine Storm” for Therapeutic Benefit. Vol. 20, Clinical and Vaccine Immunology. American Society for Microbiology; 2013. p. 319–27.

60. Proinflammatory Cytokine Responses in Extra-Respiratory Tissues During Severe Influenza - PubMed [Internet]. [cited 2020 Mar 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/28973159/

61. Aguiar ACC, Murce E, Cortopassi WA, Pimentel AS, Almeida MMFS, Barros DCS, et al. Chloroquine analogs as antimalarial candidates with potent in vitro and in vivo activity. International Journal for Parasitology: Drugs and Drug Resistance. 2018 Dec 1;8(3):459–64.

62. Gupta SK, Dubé MP, Stein JH, Clauss MA, Liu Z. A pilot trial of pentoxifylline on endothelial function and inflammation in HIV-infected patients initiating antiretroviral therapy. Vol. 30, AIDS. Lippincott Williams and Wilkins; 2016. p. 2139–42.

63. Fazely F, Dezube B, Allen-Ryan J, Pardee A, Ruprecht R. Pentoxifylline (Trental) decreases the replication of the human immunodeficiency virus type 1 in human peripheral blood mononuclear cells and in cultured T cells [see comments]. Blood [Internet]. 1991 Apr 15 [cited 2020 Mar 25];77(8):1653–6. Available from: https://ashpublications.org/blood/article/77/8/1653/168632/Pentoxifylline-Trental-decreases-the-replication

64. Vignesh R, Shankar EM. Thalidomide as a Potential HIV Latency Reversal Agent: Is It the Right Time to Forget the Ancestral Sins? Vol. 24, EBioMedicine. Elsevier B.V.; 2017. p. 20–1.

65. Cheong J, Cho H, Kim J, Kim S, Kyaw Y, Win A. Sorafenib suppresses hepatitis B virus gene expression via inhibiting JNK pathway. Hepatoma Research. 2015;1(2):97.

66. Lundberg L, Brahms A, Hooper I, Carey B, Lin SC, Dahal B, et al. Repurposed FDA-Approved drug sorafenib reduces replication of Venezuelan equine encephalitis virus and other alphaviruses. Antiviral Research. 2018 Sep 1;157:57–67.
67. Ryang J, Yan Y, Song Y, Liu F, Ng TB. Anti-HIV, antitumor and immunomodulatory activities of paclitaxel from fermentation broth using molecular imprinting technique. AMB Express [Internet]. 2019 Dec 1 [cited 2020 Mar 25];9(1):194. Available from: https://amb-express.springeropen.com/articles/10.1186/s13568-019-0915-1

68. Shi G, Ozog S, Torbett BE, Compton AA. MTOR inhibitors lower an intrinsic barrier to virus infection mediated by IFITM3. Proceedings of the National Academy of Sciences of the United States of America. 2018 Oct 23;115(43):E10069–78.

69. Yu WC, Hui DSC, Chan-Yeung M. Antiviral agents and corticosteroids in the treatment of severe acute respiratory syndrome (SARS). Vol. 59, Thorax. BMJ Publishing Group Ltd; 2004. p. 643–5.

70. España E, Nam JH, Song EJ, Song D, Lee CK, Kim JK. Lipophilic statins inhibit Zika virus production in Vero cells. Scientific Reports. 2019 Dec 1;9(1):1–11.

71. Boyd AR, Mortensen EM. Are statins beneficial for viral pneumonia? Vol. 41, European Respiratory Journal. European Respiratory Society; 2013. p. 1010–1.
**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 degree 19.5 by 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
**Retriving of disease-gene association of COVID-19 from DisGeNet and CTD**

**DisGeNET**
- 28 gene-sets of disease-gene association of COVID-19 related symptoms, clinical outcomes, high-risk, gene ontology term, viral entry, viral replication

**CTD**
- The Comparative Toxicogenomics Database (CTD) - Curated COVID-19 gene-set

**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

**Panther GO-Slim Biological Process**
- Total # Genes: 229
- Total # processes hits: 620

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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
| 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-acetylgalcosamine--dolichyl-phosphate N-acetylgalcosaminophosphotransferase DPAGT1 ortholog | UDP-N-ACETYLGLUCOSAMINE--DOLICHYL-PHOSPHATE N-ACETYLGLUCOSAMINOPHOSPHOTRANSFERASE (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 25 (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 (PTHR19143:SF373) | - |
| 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 | - |
| Accession  | Description                                                                 | Description in Human (NCBI) | Type |
|------------|------------------------------------------------------------------------------|------------------------------|------|
| P05231     | IL6 ortholog                                                                 | INTERLEUKIN-6 ortholog       |      |
| Q15025     | TNIP1 ortholog                                                               | TNFAIP3-INTERACTING PROTEIN 1 ortholog |      |
| P11498     | PC ortholog                                                                  | PYRUVATE CARBOXYLASE, MITOCHONDRIAL ligase |      |
| Q96D42     | HAVCR1 ortholog                                                              | HEPATITIS A VIRUS CELLULAR RECEPTOR 1 ortholog |      |
| P10145     | CXCL8 ortholog                                                               | INTERLEUKIN-8 ortholog       |      |
| P21549     | AGT ortholog                                                                 | SERINE--PYRUVATE AMINOTRANSFERASE ortholog |      |
| Q9NY35     | CLDN1 ortholog                                                               | CLAUDIN DOMAIN-CONTAINING PROTEIN 1 ortholog |      |
| P60033     | CD81 ortholog                                                                | CD81 ANTIGEN ortholog       |      |
| P13501     | CCL5 ortholog                                                                | C-C MOTIF CHEMOKINE 5 ortholog |      |
| P04406     | GAPDH ortholog                                                               | GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE ortholog |      |
| P46531     | NOTCH1 ortholog                                                              | NEUROGENIC LOCUS NOTCH HOMOLOG PROTEIN 1 ortholog |      |
| P08865     | RPSA ortholog                                                                | 40S RIBOSOMAL PROTEIN SA ortholog |      |
| P17301     | ITGA2 ortholog                                                               | INTEGRIN ALPHA-2 ortholog  |      |
| P17927     | CR1 ortholog                                                                 | COMPLEMENT RECEPTOR TYPE 1 ortholog |      |
| P13164     | IFTM1 ortholog                                                               | INTERFERON-INDUCED TRANSMEMBRANE PROTEIN 1 ortholog |      |
| Q96SB4     | SRPK1 ortholog                                                               | SRSF PROTEIN KINASE 1 ortholog |      |
| P0DMV9     | HSPA1B ortholog                                                               | HEAT SHOCK 70 KDA PROTEIN 1A-RELATED ortholog |      |
| 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 HOMEBOX 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 ITCH 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 TPO ortholog | THROMBOPOIETIN (PTHR10560:SF60) | - |
| 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 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 |
| Accession | Gene | Description | Protein Name | Type of Protein |
|-----------|------|-------------|--------------|----------------|
| Q92973    | MIP  | Transportin-1 | TRANSPORTIN-1 | transporter |
| P06396    | GSN  | Gelsolin     | GELSOLIN-RELATED | non-motor actin binding protein |
| P01579    | IFNG | Interferon gamma | INTERFERON GAMMA | - |
| Q9NNX6    | CD209 | CD209 antigen | CD209 ANTIGEN | membrane traffic protein |
| Q16653    | MOG  | Myelin-oligodendrocyte glycoprotein | MYELIN-OLIGODENDROCYTE GLYCOPROTEIN | immunoglobulin receptor superfamily |
| Q13263    | TRIM28 | Transcription intermediary factor 1-beta | TRANSCRIPTION INTERMEDIARY FACTOR 1-BETA | - |
| Q9C035    | TRIM5 | Tripartite motif-containing protein 5 | TRIPARTITE MOTIF-CONTAINING PROTEIN 5 | ubiquitin-protein ligase |
| P02778    | CXCL10 | C-X-C motif chemokine 10 | C-X-C MOTIF CHEMOKINE 10 | chemokine |
| Q96PU5    | NEDD4L | E3 ubiquitin-protein ligase | E3 UBIQUITIN-PROTEIN LIGASE NEDD4-LIKE | ubiquitin-protein ligase |
| Q9P253    | VPS18 | Vacuolar protein sorting-associated protein 18 homolog | VACUOLAR PROTEIN SORTING-ASSOCIATED PROTEIN 18 HOMOLOG | membrane trafficking regulatory protein |
| P20339    | RAB5A | Ras-related protein Rab-5A | RAS-RELATED PROTEIN RAB-5A | - |
| O75531    | BANF1 | Barrier-to-autointegration factor | BARRIER-TO-AUTOINTEGRATION FACTOR | chromatin/chromatin-binding, or -regulatory protein |
| Q9Y6K5    | OAS3 | 2'-5'-oligoadenylate synthase 3 | 2'-5'-OLIGOADENYLATE SYNTHASE 3 | nucleotidyltransferase |
| Q14653    | IRF3 | Interferon regulatory factor 3 | INTERFERON REGULATORY FACTOR 3 | winged helix/forkhead transcription factor |
| P63172    | DYNLT1 | Dynemin light chain Tctex-type 1 | DYNEIN LIGHT CHAIN TCTEX-TYPE 1 | microtubule or microtubule-binding cytoskeletal protein |
| P00973    | OAS1 | 2'-5'-oligoadenylate synthase 1 | 2'-5'-OLIGOADENYLATE SYNTHASE 1 | nucleotidyltransferase |
| Q9UID6    | ZNF639 | Zinc finger protein 639 | ZINC FINGER PROTEIN 639 | C2H2 zinc finger transcription factor |
| P11940    | PABPC1 | Polyadenylate-binding protein 1 | POLYADENYLATE-BINDING PROTEIN 1 | - |
| ID     | Gene    | Description                                                                 | Ortholog ID               | Domain                                                                 |
|--------|---------|-----------------------------------------------------------------------------|---------------------------|------------------------------------------------------------------------|
| Q5D1E8 | ZC3H12A | Endoribonuclease ZC3H12A ortholog                                           | ENDORIBONUCLEASE ZC3H12A (PTHR12876:SF10) | endoribonuclease                                                       |
| O15304 | SIVA1   | Apoptosis regulatory protein Siva ortholog                                  | APOPTOSIS REGULATORY PROTEIN SIVA (PTHR14365:SF1) | -                                                                     |
| O95484 | CLDN9   | Claudin-9 ortholog                                                          | CLAUDIN-9 (PTHR12002:SF42) | tight junction                                                          |
| O15393 | TMPRS2  | Transmembrane protease serine 2 ortholog                                    | TRANSMEMBRANE PROTEASE SERINE 2 (PTHR24253:SF89) | serine protease                                                        |
| Q96F44 | TRIM11  | E3 ubiquitin-protein ligase TRIM11 ortholog                                  | E3 UBQUITIN-PROTEIN LIGASE TRIM11 (PTHR24103:SF648) | ubiquitin-protein ligase                                               |
| P38567 | HYAL3   | Hyaluronidase PH-20 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 ortholog                                       | UBIQUITIN-LIKE PROTEIN ISG15 (PTHR10666:SF267) | -                                                                     |
| Q676U5 | ATG16L1 | Autophagy-related protein 16-1 ortholog                                      | AUTOPHAGY-RELATED PROTEIN 16-1 (PTHR19878:SF6) | -                                                                     |
| P29728 | OAS2    | 2'-5'-oligoadenylate synthase 2 ortholog                                    | 2'-5'-OLIGOADENYLATE SYNTHASE 2 (PTHR11258:SF3) | nucleotidyltransferase                                                 |
| Q9BRG2 | SH2D3A  | SH2 domain-containing protein 3A ortholog                                   | SH2 DOMAIN-CONTAINING PROTEIN 3A (PTHR14247:SF11) | -                                                                     |
| P42566 | EPS15   | Epidermal growth factor receptor substrate 15 ortholog                      | EPIDERMAL GROWTH FACTOR RECEPTOR SUBSTRATE 15 (PTHR11216:SF54) | membrane traffic protein                                               |
| P26022 | PTX3    | Pentraxin-related protein PTX3 ortholog                                     | PENTRAXIN-RELATED PROTEIN PTX3 (PTHR46943:SF1) | -                                                                     |
| O00308 | WWP2    | NEDD4-like E3 ubiquitin-protein ligase WWP2 ortholog                        | NEDD4-LIKE E3 UBQUITIN-PROTEIN LIGASE WWP2 (PTHR11254:SF396) | ubiquitin-protein ligase                                               |
| Q05823 | RNASEL  | 2-5A-dependent ribonuclease ortholog                                       | 2-5A-DEPENDENT RIBONUCLEASE (PTHR24141:SF1) | -                                                                     |
| P49790 | NUP153  | Nuclear pore complex protein Nup153 ortholog                                | NUCLEAR PORE COMPLEX PROTEIN NUP153 (PTHR23193:SF23) | transporter                                                            |
| P12821 | ACE     | Angiotensin-converting enzyme ortholog                                      | ANGIOTENSIN-CONVERTING ENZYME (PTHR10514:SF25) | metalloprotease                                                        |
| Q15768 | EFNB3   | Ephrin-B3 ortholog                                                          | EPHRIN-B3 (PTHR11304:SF34) | membrane-bound signaling molecule                                       |
| Accession | Protein | Description | Ortholog | Function |
|-----------|---------|-------------|----------|----------|
| 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 (PTHR11666: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 ortholog | SRSF PROTEIN KINASE 2 (PTHR24055:SF102) | non-receptor serine/threonine protein |
| ortholog          | kinase                                      |
|-------------------|---------------------------------------------|
| Q9H0U4 RAB1B      | Ras-related protein Rab-1B                 |
| P37198 NUP62      | Nuclear pore glycoprotein p62               |
| P42701 IL12RB1    | Interleukin-12 receptor subunit beta-1      |
| P0DMV8 HSPA1A     | Heat shock 70 kDa protein 1A                |
| P01375 TNF        | Tumor necrosis factor                       |
| Q12899 TRIM26     | Tripartite motif-containing protein 26       |
| P00533 EGFR       | Epidermal growth factor receptor            |
| Q07817 BCL2L1     | Bcl-2-like protein 1                        |
| P80075 CCL8       | C-C motif chemokine 8                       |
| O95832 CLDN1      | Claudin-1                                   |
| P07858 CTSB       | Cathepsin B                                 |
| O00602 FCN1       | Ficolin-1                                   |
| Q9NWF4 SLC52A1    | Solute carrier family 52, riboflavin transporter, member 1 |
| Q9HAB3 SLC52A2    | Solute carrier family 52, riboflavin transporter, member 2 |
| O00592 PC         | Podocalyxin                                 |
| P25098 GRK2       | Beta-adrenergic receptor kinase              |
| P20023 CR2        | Complement receptor type 2                  |
| P14735 IDE        | Insulin-degrading enzyme                    |

- Ras-related protein Rab-1B ortholog
- Nuclear pore glycoprotein p62 ortholog
- Interleukin-12 receptor subunit beta-1 ortholog
- Heat shock 70 kDa protein 1A ortholog
- Tumor necrosis factor ortholog
- Tripartite motif-containing protein 26 ortholog
- Epidermal growth factor receptor ortholog
- Bcl-2-like protein 1 ortholog
- C-C motif chemokine 8 ortholog
- Claudin-1 ortholog
- Cathepsin B ortholog
- Ficolin-1 ortholog
- Podocalyxin ortholog
- Beta-adrenergic receptor kinase ortholog
- Complement receptor type 2 ortholog
- Insulin-degrading enzyme ortholog

- RAS-RELATED PROTEIN RAB-1B (PTHR24073:SF1096)
- NUCLEAR PORE GLYCOPROTEIN P62 (PTHR12084:SF12)
- INTERLEUKIN-12 RECEPTOR SUBUNIT ETA-1 (PTHR23036:SF51)
- HEAT SHOCK 70 KDA PROTEIN 1A-RELATED (PTHR19375:SF223)
- TUMOR NECROSIS FACTOR (PTHR11471:SF23)
- TRIPARTITE MOTIF-CONTAINING PROTEIN 26 (PTHR24103:SF369)
- EPIDERMAL GROWTH FACTOR RECEPTOR (PTHR24416:SF91)
- BCL-2-LIKE PROTEIN 1 (PTHR11256:SF12)
- C-C MOTIF CHEMOKINE 8 (PTHR12015:SF168)
- CLAUDIN-1 (PTHR12002:SF92)
- CATHEPSIN B (PTHR12411:SF714)
- FICOLIN-1-RELATED (PTHR19143:SF346)
- SOLUTE CARRIER FAMILY 52, RIBOFLAVIN TRANSPORTER, MEMBER 1 (PTHR12929:SF17)
- SOLUTE CARRIER FAMILY 52, RIBOFLAVIN TRANSPORTER, MEMBER 2 (PTHR12929:SF17)
- PODOCALYXIN (PTHR12067:SF5)
- BETA-ADRENERGIC RECEPTOR KINASE 1 (PTHR24355:SF22)
- COMPLEMENT RECEPTOR TYPE 2 (PTHR19325:SF391)
- INSULIN-DEGRADING ENZYME-RELATED (PTHR43690:SF18)

ubiquitin-protein ligase
non-receptor serine/threonine protein kinase
metalloprotease
| Accession | Symbol | Description | PDB ID | Function |
|-----------|--------|-------------|--------|----------|
| O43820    | HYAL3  | Hyaluronidase-3 ortholog | HYALURONIDASE-3 (PTHR11769:SF19) | glycosidase |
| O00574    | CXCR6  | C-X-C chemokine receptor type 6 ortholog | C-X-C CHEMOKINE RECEPTOR TYPE 6 (PTHR10489:SF705) | - |
| P09914    | IFIT1  | Interferon-induced protein with tetra-tripeptide repeats 1 ortholog | INTERFERON-INDUCED PROTEIN WITH TETRA-TRIPETIDE REPEATS 1 (PTHR10271:SF30) | - |
| P30411    | BDKRB2 | B2 bradykinin receptor ortholog | B2 BRADYKININ RECEPTOR (PTHR24228:SF25) | G-protein coupled receptor |
| P02810    | PA     | Salivary acidic proline-rich phosphoprotein 1/2 ortholog | SALIVARY ACIDIC PROLINE-RICH PHOSPHOPROTEIN 1/2 (PTHR23203:SF16) | antimicrobial response protein |
| Q99549    | MPHOSPH8 | M-phase phosphoprotein 8 ortholog | M-PHASE PHOSPHOPROTEIN 8 (PTHR24166:SF47) | - |
| P61073    | CXCR4  | C-X-C chemokine receptor type 4 ortholog | C-X-C CHEMOKINE RECEPTOR TYPE 4 (PTHR10489:SF594) | - |
| P01574    | IFNB1  | Interferon beta ortholog | INTERFERON BETA (PTHR11691:SF68) | - |
| P07711    | CTSL   | Cathepsin L1 ortholog | CATHEPSIN L1 (PTHR12411:SF57) | cysteine protease |
| Q9H0M0    | WWP1   | NEDD4-like E3 ubiquitin-protein ligase WWP1 ortholog | NEDD4-LIKE E3 UBQUITIN-PROTEIN LIGASE WWP1 (PTHR11254:SF299) | ubiquitin-protein ligase |
| Q08357    | SLC20A2 | Sodium-dependent phosphate transporter 2 ortholog | SODIUM-DEPENDENT PHOSPHATE TRANSPORTER 2 (PTHR11101:SF83) | transporter |
| Q15758    | SLC1A5 | Neutral amino acid transporter B(0) ortholog | NEUTRAL AMINO ACID TRANSPORTER B(0) (PTHR11958:SF19) | primary active transporter |
| P62820    | RAB1A  | Ras-related protein Rab-1A ortholog | RAS-RELATED PROTEIN RAB-1A (PTHR24073:SF963) | - |
| Q9P2K8    | EIF2AK4 | eIF-2-alpha kinase GCN2 ortholog | EIF-2-ALPHA KINASE GCN2 (PTHR11042:SF164) | non-receptor serine/threonine protein kinase |
| P02649    | APOE   | Apolipoprotein E ortholog | APOLIPOPROTEIN E (PTHR18976:SF2) | - |
| P60953    | CDC42  | Cell division control protein 42 ortholog | CELL DIVISION CONTROL PROTEIN 42 HOMOLOG (PTHR24072:SF136) | small GTPase |
| O00482    | NR5A2  | Nuclear receptor subfamily 5 group A member 2 ortholog | NUCLEAR RECEPTOR SUBFAMILY 5 GROUP A MEMBER 2 (PTHR24086:SF18) | C4 zinc finger nuclear receptor |
| O00187    | MASP2  | Mannan-binding lectin serine ortholog | MANNAN-BINDING LECTIN | serine protease |
| Gene ID | Gene Name | Description | Protein Name | Ortholog ID |
|---------|-----------|-------------|--------------|-------------|
| P01730  | CD4       | T-cell surface glycoprotein CD4 | T-CELL SURFACE GLYCOPROTEIN CD4 | (PTHR11422:SF0) |
| P04233  | CD74      | HLA class II histocompatibility antigen gamma chain | HLA CLASS II HISTOCOMPATIBILITY ANTIGEN GAMMA CHAIN | (PTHR14093:SF17) |
| Q9BYF1  | ACE2      | Angiotensin-converting enzyme 2 | ANGIOTENSIN-CONVERTING ENZYME 2 | (PTHR10514:SF24) |
| P57740  | NUP107    | Nuclear pore complex protein | NUCLEAR PORE COMPLEX PROTEIN NUP107 | (PTHR13003:SF2) |
| Q03135  | CAV1      | Caveolin-1 | CAVEOLIN-1 | (PTHR10844:SF18) |
| O00635  | TRIM38    | E3 ubiquitin-protein ligase | E3 UBIQUITIN-PROTEIN LIGASE TRIM38 | (PTHR24103:SF47) |
| P03973  | SLPI      | Antileukoproteinase | ANTILEUKOPROTEINASE | (PTHR19441:SF44) |
| P02743  | APCS      | Serum amyloid P-component | SERUM AMYLOID P-COMPONENT | (PTHR45869:SF5) |
| Q15075  | EEA1      | Early endosome antigen 1 | EARLY ENDOSONE ANTIGEN 1 | (PTHR23164:SF17) |
| Q9Y2S7  | POLDIP2   | Polymerase delta-interacting protein 2 | POLYMERASE DELTA-INTERACTING PROTEIN 2 | (PTHR14289:SF16) |
| Q14973  | SLC10A1   | Sodium/bile acid cotransporter | SODIUM/BILE ACID COTRANSPORTER | (PTHR10361:SF40) |
| P10415  | BCL2      | Apoptosis regulator Bcl-2 | APOPTOSIS REGULATOR BCL-2 | (PTHR11256:SF11) |
| Q9UL45  | PA        | Biogenesis of lysosome-related organelles complex 1 subunit 6 | BIOGENESIS OF LYSOSOME-RELATED ORGANELLES COMPLEX 1 SUBUNIT 6 | (PTHR31328:SF2) |
| Q86U86  | PB1       | Protein polybromo-1 | PROTEIN POLYBROMO-1 | (PTHR16062:SF15) |
| P02786  | TFRC      | Transferrin receptor protein 1 | TRANSFERRIN RECEPTOR PROTEIN 1 | (PTHR10404:SF26) |
| Q06418  | TYRO3     | Tyrosine-protein kinase receptor | TYROSINE-PROTEIN KINASE RECEPTOR TYRO3 | (PTHR24416:SF279) |
| P51636  | CAV2      | Caveolin-2 | CAVEOLIN-2 | (PTHR10844:SF3) |
| Gene ID  | Ortholog           | Description                                                                                           |
|----------|---------------------|--------------------------------------------------------------------------------------------------------|
| Q96Q15  | HS3ST5              | Heparan sulfate glucosamine 3-O-sulfotransferase 6 (ortholog)                                        |
| P26196  | DDX6               | Probable ATP-dependent RNA helicase DDX6 (ortholog)                                                  |
| Q92786  | PROX1              | Prospero homeobox protein 1 (ortholog)                                                               |
| Q13155  | AIMP2              | Aminoacyl tRNA synthase complex-interacting multifunctional protein 2 (ortholog)                       |
| P01130  | LDLR               | Low-density lipoprotein receptor (ortholog)                                                           |
| Q12906  | ILF3               | Interleukin enhancer-binding factor 3 (ortholog)                                                      |
| Q9UQF0  | ERWV-1             | Syncytin-1 (ERWV-1 ortholog)                                                                         |
| P11279  | LAMP1              | Lysosome-associated membrane glycoprotein 1 (ortholog)                                                |
| Q95433  | AHS1               | Activator of 90 kDa heat shock protein ATPase homolog 1 (ortholog)                                   |
| P06493  | CDK1               | Cyclin-dependent kinase 1 (ortholog)                                                                  |
| Q8WZ33  | MIP                | MaFF-interacting protein (ortholog)                                                                  |
| P13500  | CCL2               | C-C motif chemokine 2 (ortholog)                                                                      |
| Q96AZ6  | ISG20              | Interferon-stimulated gene 20 kDa protein (ortholog)                                                  |
| P02765  | AHSG               | Alpha-2-HS-glycoprotein (ortholog)                                                                   |
| Q96NY8  | NECTIN4            | Nectin-4 (ortholog)                                                                                  |
| Q6UWE0  | LRSAM1             | E3 ubiquitin-protein ligase (ortholog)                                                                |
| P15144  | ANPEP              | Aminopeptidase N (ortholog)                                                                          |

**Table Notes:**
- **Q96Q15**: HEPARAN SULFATE GLUCOSAMINE 3-O-SULFOTRANSFERASE 6 (ortholog)
- **P26196**: ATP-DEPENDENT RNA HELICASE DDX6-RELATED (ortholog)
- **Q92786**: PROSPERO HOMEOBOX PROTEIN 1 (ortholog)
- **Q13155**: AMINOACYL TRNA SYNTHASE COMPLEX-INTERACTING MULTIFUNCTIONAL PROTEIN 2 (ortholog)
- **P01130**: LOW-DENSITY LIPOPROTEIN RECEPTOR (ortholog)
- **Q12906**: INTERLEUKIN ENHANCER-BINDING FACTOR 3 (ortholog)
- **Q9UQF0**: SYNCTIN-1 (ortholog)
- **P11279**: LYSOSOME-ASSOCIATED MEMBRANE GLYCOPROTEIN 1 (ortholog)
- **O95433**: ACTIVATOR OF 90 KDA HEAT SHOCK PROTEIN ATPASE HOMOLOG 1 (ortholog)
- **P06493**: CYCLIN-DEPENDENT KINASE 1 (ortholog)
- **Q8WZ33**: MAFF-INTERACTING PROTEIN-RELATED (ortholog)
- **P13500**: C-C MOTIF CHEMOKINE 2 (ortholog)
- **Q96AZ6**: INTERFERON-STIMULATED GENE 20 KDA PROTEIN (ortholog)
- **P02765**: ALPHA-2-HS-GLYCOPROTEIN (ortholog)
- **Q96NY8**: NECTIN-4 (ortholog)
- **Q6UWE0**: E3 UBQUITIN-PROTEIN LIGASE (ortholog)
- **P15144**: AMINOPEPTIDASE N (ortholog)
| Accession | Description | Ortholog Description | Protein Type |
|-----------|-------------|----------------------|--------------|
| Q92956    | TNFRSF14    | Tumor necrosis factor receptor superfamily member 14 (PTHR46838:SF1) | - |
| Q9BVG3    | TRIM62     | E3 ubiquitin-protein ligase (PTHR24103:SF573) | ubiquitin-protein ligase |
| P35659    | DEK        | Protein DEK (PTHR13468:SF1) | chromatin/chromatin-binding, or -regulatory protein |
| Q6UXB4    | CLEC4G     | C-type lectin domain family 4 member G (PTHR22802:SF245) | membrane traffic protein |
| P35568    | IRS1       | Insulin receptor substrate 1 (PTHR10614:SF11) | - |
| P62937    | PPIA       | Peptidyl-prolyl cis-trans isomerase A (PTHR11071:SF490) | - |
| Q02880    | TOP2B      | DNA topoisomerase 2-beta (PTHR10169:SF36) | - |
| P19525    | EIF2AK2    | Interferon-induced, double-stranded RNA-activated protein kinase (PTHR11042:SF163) | non-receptor serine/threonine protein kinase |
| Q9UBH6    | XPR1       | Xenotropic and polytropic retrovirus receptor 1 (PTHR10169:SF36) | secondary carrier transporter |
| P22301    | IL10       | Interleukin-10 (PTHR12002:SF41) | - |
| P56747    | CLDN6      | Claudin-6 (PTHR11036:SF12) | tight junction |
| Q9H2E6    | SEMA6A     | Semaphorin-6A (PTHR11036:SF12) | membrane-bound signaling molecule |
| O95292    | VAPB       | Vesicle-associated membrane protein-associated protein B/C (PTHR10809:SF12) | membrane trafficking regulatory protein |
| Q92824    | PCSK5      | Proprotein convertase subtilisin/kexin type 5 (PTHR42884:SF7) | serine protease |
| P00491    | NP         | Purine nucleoside phosphorylase (PTHR11904:SF12) | nucleotide kinase |
| P02788    | LTF        | Lactotransferrin (PTHR111485:SF33) | transfer/carryer protein |
| Accession | Protein Name | Description | Ortholog | Notes |
|-----------|--------------|-------------|-----------|-------|
| Q9BV40    | VAMP8        | Vesicle-associated membrane protein 8 | VESICLE-ASSOCIATED MEMBRANE PROTEIN 8 (PTHR45701:SF7) | - |
| Q7Z2W4    | ZC3HAV1      | Zinc finger CCCH-type antiviral protein 1 | ZINC FINGER CCCH-TYPE ANTIVIRAL PROTEIN 1 (PTHR45740:SF8) | - |
| O75791    | GRAP2        | GRB2-related adapter protein 2 | GRB2-RELATED ADAPTER PROTEIN 2 (PTHR46037:SF3) | - |
| P04746    | PA           | Pancreatic alpha-amylase | ALPHA-AMYLASE 1-RELATED (PTHR43447:SF27) | amylase |
| P01891    | HLA-A        | HLA class I histocompatibility antigen, A-68 alpha chain | HLA CLASS I HISTOCOMPATIBILITY ANTIGEN, A-68 ALPHA CHAIN (PTHR16675:SF229) | - |
| Q14393    | GAS6         | Growth arrest-specific protein 6 | GROWTH ARREST-SPECIFIC PROTEIN 6 (PTHR24035:SF104) | extracellular matrix protein |
| O60260    | PRKN         | E3 ubiquitin-protein ligase parkin | E3 UBIQUITIN-PROTEIN LIGASE PARKIN (PTHR111685:SF212) | ubiquitin-protein ligase |
| Q8WTV0    | SCARB1       | Scavenger receptor class B member 1 | SCAVENGER RECEPTOR CLASS B MEMBER 1 (PTHR11923:SF96) | membrane trafficking regulatory protein |
| P13591    | NCAM1        | Neural cell adhesion molecule 1 | NEURAL CELL ADHESION MOLECULE 1 (PTHR12231:SF239) | - |
| P46108    | CRK          | Adapter molecule crk | ADAPTER MOLECULE CRK (PTHR19969:SF8) | - |
| O75116    | ROCK2        | Rho-associated protein kinase 2 | RHO-ASSOCIATED PROTEIN KINASE 2 (PTHR22988:SF28) | non-receptor serine/threonine protein kinase |
| Q9BVP2    | NS           | Guanine nucleotide-binding protein-like 3 | GUANINE NUCLEOTIDE-BINDING PROTEIN-LIKE 3 (PTHR11089:SF11) | - |
| P01024    | C3           | Complement C3 | COMPLEMENT C3 (PTHR11412:SF81) | protease inhibitor |
| P19838    | NFKB1        | Nuclear factor NF-kappa-B p105 subunit | NUCLEAR FACTOR NF-KAPPA-B P105 SUBUNIT (PTHR24169:SF9) | Rel homology transcription factor |
| =Q15365   | PCBP1        | Poly(rC)-binding protein 1 | POLY(RC)-BINDING PROTEIN 1 (PTHR10288:SF96) | RNA binding protein |
| P19474    | TRIM21       | E3 ubiquitin-protein ligase | E3 UBIQUITIN-PROTEIN LIGASE TRIM21 (PTHR24103:SF46) | ubiquitin-protein ligase |
| Q16539    | MAPK14       | Mitogen-activated protein kinase 14 | MITOGEN-ACTIVATED PROTEIN KINASE 14 (PTHR24055:SF110) | non-receptor serine/threonine protein kinase |
| Accession | Gene Symbol | Description | Ortholog Accession | Function |
|-----------|-------------|-------------|--------------------|----------|
| Q01629    | IFITM2      | Interferon-induced transmembrane protein 2 | INTERFERON-INDUCED TRANSMEMBRANE PROTEIN 2 (PTHR13999:SF8) | -        |
| P09382    | LGALS1      | Galectin-1 | GALECTIN-1 (PTHR11346:SF97) | extracellular matrix protein |
| P28482    | MAPK1       | Mitogen-activated kinase 1 | MITOGEN-ACTIVATED PROTEIN KINASE 1 (PTHR24055:SF203) | non-receptor serine/threonine protein kinase |
| Q6ZTQ4    | CDHR3       | Cadherin-related family member 3 | CADHERIN-24-RELATED (PTHR24027:SF272) | -        |
| P54296    | MYOM2       | Myomesin-2 | MYOMESIN-2 (PTHR13817:SF22) | -        |
| Q06787    | FMR1        | Synaptic functional regulator | SYNAPTIC FUNCTIONAL REGULATOR FMR1 (PTHR10603:SF4) | translation factor |
| P49685    | GPR15       | G-protein coupled receptor 15 | G-PROTEIN COUPLED RECEPTOR 15 (PTHR24228:SF10) | G-protein coupled receptor |
| Q9NRC9    | AAAS        | Aladin | ALADIN (PTHR14494:SF0) | -        |
| O95817    | BAG3        | BAG family molecular chaperone regulator 3 | BAG FAMILY MOLECULAR CHAPERONE REGULATOR 3 (PTHR12329:SF12) | -        |
| P04004    | VTN         | Vitronectin | VITRONECTIN (PTHR22917:SF3) | -        |
| P61769    | B2M         | Beta-2-microglobulin | BETA-2-MICROGLOBULIN (PTHR19944:SF62) | major histocompatibility complex protein |
| Q12891    | HYAL2       | Hyaluronidase-2 | HYALURONIDASE-2 (PTHR11769:SF6) | glycosidase |
| O15118    | NPC1        | NPC intracellular cholesterol transporter 1 | NPC INTRACELLULAR CHOLESTEROL TRANSPORTER 1 (PTHR45727:SF2) | -        |
| Q8IZT8    | HS3ST5      | Heparan sulfate glucosamine 3-O-sulfotransferase 5 | HEPARAN SULFATE GLUCOSAMINE 3-O-SULFOTRANSFERASE 5 (PTHR10605:SF46) | -        |
| Q9BZY9    | TRIM31      | E3 ubiquitin-protein ligase | E3 UBIQUITIN-PROTEIN LIGASE TRIM31 (PTHR24103:SF87) | ubiquitin-protein ligase |
| Q9UDY6    | TRIM10      | Tripartite motif-containing protein 10 | TRIPARTITE MOTIF-CONTAINING PROTEIN 10 (PTHR24103:SF329) | ubiquitin-protein ligase |
| Q08752    | PPID        | Peptidyl-prolyl cis-trans isomerase D | PEPTIDYL-PROLYL CIS-TRANS ISOMERASE D- | -        |
| PPID     | ortholog                                      | RELATED (PTHR11071:SF380) | membrane trafficking regulatory protein |
|----------|-----------------------------------------------|---------------------------|----------------------------------------|
| Q9H1Y0   | ATG5 Autophagy protein 5                      | AUTOPHAGY PROTEIN 5       |                                       |
|          | ATG5 ortholog                                 | (PTHR13040:SF2)           |                                       |
| 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) | -                                       |
| P78356   | 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                         | INTEGRIN BETA-1           | cell adhesion molecule                 |
|          | ITGB1 ortholog                                | (PTHR10082:SF28)          |                                        |
| P24298   | GPT Alanine aminotransferase 1 GPT ortholog   | ALANINE AMINOTRANSFERASE 1 | transaminase                           |
|          | (PTHR11751:SF308)                             |                           |                                        |
| O43504   | LAMTOR5 Regulator complex protein LAMTOR5     | RAGULATOR COMPLEX PROTEIN LAMTOR5 | -                                      |
|          | LAMTOR5 ortholog                              | (PTHR13342:SF4)           |                                        |
| Q9NPH2   | ISYNA1 Inositol-3-phosphate synthase 1 ISYNA1 ortholog | INOSITOL-3-PHOSPHATE SYNTHASE 1 | isomerase                              |
|          | ISYNA1 ortholog                               | (PTHR11510:SF5)           |                                        |
| Q15517   | CDSN Corneodesmosin CDSN ortholog             | CORNEODESMOSIN            | -                                      |
|          | (PTHR23207:SF2)                               |                           |                                        |
| P56545   | CTBP2 C-terminal-binding protein 2 CTBP2 ortholog | C-TERMINAL-BINDING PROTEIN 2 | transcription cofactor                |
|          | CTBP2 ortholog                                | (PTHR46029:SF3)           |                                        |
| O00571   | DDX3X ATP-dependent RNA helicase DDX3X        | ATP-DEPENDENT RNA HELICASE DDX3X | -                                      |
|          | DDX3X ortholog                                | (PTHR47958:SF4)           |                                        |
| P15151   | PVR Poliovirus receptor PVR ortholog          | POLIOVIRUS RECEPTOR       | -                                      |
|          | PVR ortholog                                  | (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 | membrane traffic protein             |
| Q9NY25   | CLEC5A C-type lectin domain family 5 member A CLEC5A ortholog | C-TYPE LECTIN DOMAIN FAMILY 5 MEMBER A | -                                      |
| P05362   | ICAM1 Intercellular adhesion molecule 1 ICAM1 ortholog | INTERCELLULAR ADHESION MOLECULE 1 | -                                      |
| Q92692   | NECTIN2 Nectin-2                             | NECTIN-2 (PTHR47387:SF1)  | -                                      |
| Accession | Gene Abbreviation | Gene Symbol | Protein Description | Interpreted Function |
|-----------|------------------|-------------|---------------------|----------------------|
| P02751    | FN1              | NECTIN2     | ortholog            | intercellular signal molecule |
| Q12824    | SMARCB1          | FIBRONECTIN | (PTHR19143:SF267)   | DNA binding protein   |
| Q7Z6L0    | PRRT2            | P09341      | FN1 ortholog         | chemokine             |
| P07202    | TPO              | P01562      | IFNA13 ortholog      | peroxidase            |
| P09341    | CXCL1            | P07202      | IFNA13 ortholog      | chemokine             |
| Q14242    | SELPLG           | P02724      | GYP A ortholog       | protease inhibitor     |
| O00182    | LGALS9           | O60493      | SNX3 ortholog        | extracellular matrix protein |
| Q13049    | TRIM32           | Q13291      | SLAMF1 ortholog      | immunoglobulin receptor superfamily |
| P29508    | SERPINB3         | P15529      | CD46 ortholog        | -                     |
| P06756    | ITGAV            | P06756      | ITGAV ortholog       | -                     |
| Q13291    | SLAMF1           | Q13291      | SLAMF1 ortholog      | -                     |
| P55265    | ADAR             | P55265      | ADAR ortholog        | RNA binding protein   |
| Q9UQV4    | LAMP3            | Q9UQV4      | LAMP3 ortholog       | membrane trafficking regulatory protein |
| ID     | Gene/Ortholog                                                                 | Description                                                                 | Other Description                                                                 |
|--------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Q9BZR9 | TRIM8, LAMP3 ortholog                                                        | E3 ubiquitin-protein ligase 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, HYAL1 ortholog                                                        | 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
| SNO | Gene | Symptoms | STICH prediction of FDA approved for repurposing | DGIdb2.0 prediction of FDA approved Drugs for repurposing |
|-----|------|----------|-----------------------------------------------|-------------------------------------------------------|
| 1   | VEGFA | Fever, Pneumonia, Heart Disease, Kidney Disease, Lung Disease, Diabetes, Hypertension, Cancer, Sepsis, Acute Kidney Injury | carvedilol 0.816  
cilostazol 0.818  
fenofibrate 0.822  
gliclazide 0.800  
pegaptanib sod. 0.457  
pyroglutamate 0.814  
sorafenib 0.909 | Drug | Interaction Type | Score |
|     |      |          |                                               | Ranibizumab inhibitor 14 | Bevacizumab antibody, inhibitor 10 | Aflibercept binder, antibody, inhibitor 7 |
|     |      |          |                                               | Gliclazide n/a 5 | Carvedilol other 5 | Pyrogulatamic acid n/a 4 |
|     |      |          |                                               | Dalteparin sodium inhibitor 4 | Pentosan polysulfate sodium n/a 2 | Fenofibrate n/a 2 |
|     |      |          |                                               | Phenytoin n/a 2 | Cilostazol n/a 2 | Gentamicin n/a 2 |
|     |      |          |                                               | Sorafenib n/a 1 | Sorafenib tosylate inhibitor 1 | Pegaptanib sodium antagonist 1 |
|     |      |          |                                               | Lenalidomide n/a 1 | Vandetanib inhibitor 1 |                  |
| 2 | TNF | Fever, Pneumonia, Heart Disease, Kidney Disease, Lung Disease, Diabetes, Hypertension, Cancer, Sepsis, Acute Kidney Injury, Neutrophilia, Lymphopenia, 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 |
| 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 |
| Condition | Drug | Interaction Type | Score |
|-----------|------|------------------|-------|
| Cancer, Sepsis, Acute Kidney Injury, Neutrophilia, Thrombocytopenia, SARS-CoV | aspirin | 0.450 |       |
| | fentanyl | 0.826 |       |
| | omeprazole | 0.819 |       |
| | paclitaxel | 0.947 |       |
| | quinol | 0.700 |       |
| | retinoic acid | 0.949 |       |
| | 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     |
| 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 |       |
| | 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     |
| Drug                | Interaction Type | Score |
|---------------------|------------------|-------|
| acetate             |                  |       |
| 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     |

| 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     |

| Drug               | Interaction Type | Score |
|-------------------|------------------|-------|
| Danazol           | inhibitor        | 3     |
| fenofibrate       |                  | 0.815 |
| pioglitazone      |                  | 0.984 |
| Statins           |                  | 0.986 |

**5** IL10

Fever, Pneumonia, Kidney Disease, Lung Disease, Diabetes, Hypertension, Cancer, Sepsis, Acute Kidney Injury, Lymphopenia, Multiple Organ Failure, SARS-CoV

**6** CCL2

Fever, Pneumonia, Kidney Disease, Lung Disease, Diabetes, Hypertension, Sepsis, SARS-CoV

**rapamycin** 0.985
| 7 | IL1B | Cough, Fever, Pneumonia, Heart Disease, Kidney Disease, Lung Disease, Diabetes, Hypertension, Cancer, Sepsis, Neutrophilia, Leukocytosis, Lymphophenia |
|---|---|---|
|  | gallium nitrate 0.800 | Drug | Interaction Type | Score |
|  | levofoxacin 0.800 | Canakinumab | binder, antibody, inhibitor | 7 |
|  | pentoxifylline 0.866 | Rilonacept | binder, inhibitor | 5 |
|  | diacerein 0.837 | Acitretin | n/a | 3 |
|  | cortisol 0.958 | Gallium nitrate | antagonist, inhibitor | 3 |
|  |  | Cytarabine | n/a | 2 |
|  |  | Thyroglobulin | n/a | 2 |
|  |  | Nicardipine | n/a | 2 |
|  |  | Ofloxacin | n/a | 2 |
|  |  | Hydrocortisone | n/a | 2 |
|  |  | Celcaflor | n/a | 2 |
|  |  | Fluticasone propionate | n/a | 2 |
|  |  | Raloxifene | n/a | 2 |
|  |  | Pentamidine | n/a | 2 |
|  |  | Verapamil | n/a | 2 |
|  |  | Lansoprazole | n/a | 2 |
|  |  | Erythromycin | n/a | 2 |
|  |  | Beclomethasone dipropionate | n/a | 2 |
|  |  | Pentoxifylline | n/a | 2 |
|  |  | Hydroquinone | n/a | 2 |
|  |  | Melatonin | n/a | 2 |
|  |  | Diacerein | n/a | 1 |

| 8 | TLR4 | Fever, Pneumonia, Kidney Disease, Lung Disease, Diabetes, |
|---|---|---|
|  | Ethanol 0.880 | Drug | Interaction Type | Score |
|  |  | Ritonavir | n/a | 2 |
|  |  | Saquinavir | n/a | 2 |
|   | Drug | Interaction Type | Score |
|---|------|------------------|-------|
| Alcohol | n/a | 2 |
| Infliximab | n/a | 2 |
| Nelfinavir | n/a | 2 |
| Folic acid | n/a | 1 |

|   | Drug | Interaction Type | Score |
|---|------|------------------|-------|
| Natalizumab | n/a | 2 |
| Lifitegrast | n/a | 1 |

|   | Drug | Interaction Type | Score |
|---|------|------------------|-------|
| Glucosamine | antagonist | 6 |
| **Captopril** | inhibitor | 5 |
| Bevacizumab | n/a | 2 |
| Methylldopa | 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
| 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        | CASP3                  | IL6      | TNF                    | CCL2          | MMP9                   | ALB         | IL10                   | PTGS2         | CXCL8                  | CASP3  | gentamicin 0.958       | IL6         |
|              | paclitaxel (0.972)     | IL6      | TNF                    | CCL2          | IL10                   | ICAM1       | IFNG                   | IL2           | FN1                   | CXCR4  | hydroxychloroquine 0.942 | TXC18       |
|              | retinoic acid (0.961)  | IL6      | TNF                    | CCL2          | MAPK1                  | ICAM1       | MAPK1                  | CCL5          | CXCR4                 | MAPK1  | sorafenib 0.948         | TXC18       |
|              | thalidomide (0.945)    | IL6      | TNF                    | CCL2          | EGFR                   | CCL5        | EGFR                   | CCL5          | CXCR4                 | EGFR   | sulindac 0.925          | TXC18       |
|              | IL10, VEGFA            | IL6      | TNF                    | CCL2          | MAPK1                  | ICAM1       | MAPK1                  | CCL5          | CXCR4                 | MAPK1  | thalidomide 0.45        | TXC18       |
|              | aspirin (0.954)        | IL6      | TNF                    | CCL2          | MAPK1                  | ICAM1       | MAPK1                  | CCL5          | CXCR4                 | MAPK1  | EGFR                   | TXC18       |
|              | rapamycin (0.985)      | IL6      | TNF                    | CCL2          | MAPK1                  | ICAM1       | MAPK1                  | CCL5          | CXCR4                 | MAPK1  | vandetanib 0.998        | TXC18       |
|              | retinoic acid (0.961)  | IL6      | TNF                    | CCL2          | MAPK1                  | ICAM1       | MAPK1                  | CCL5          | CXCR4                 | MAPK1  | IL6                    | TXC18       |

**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