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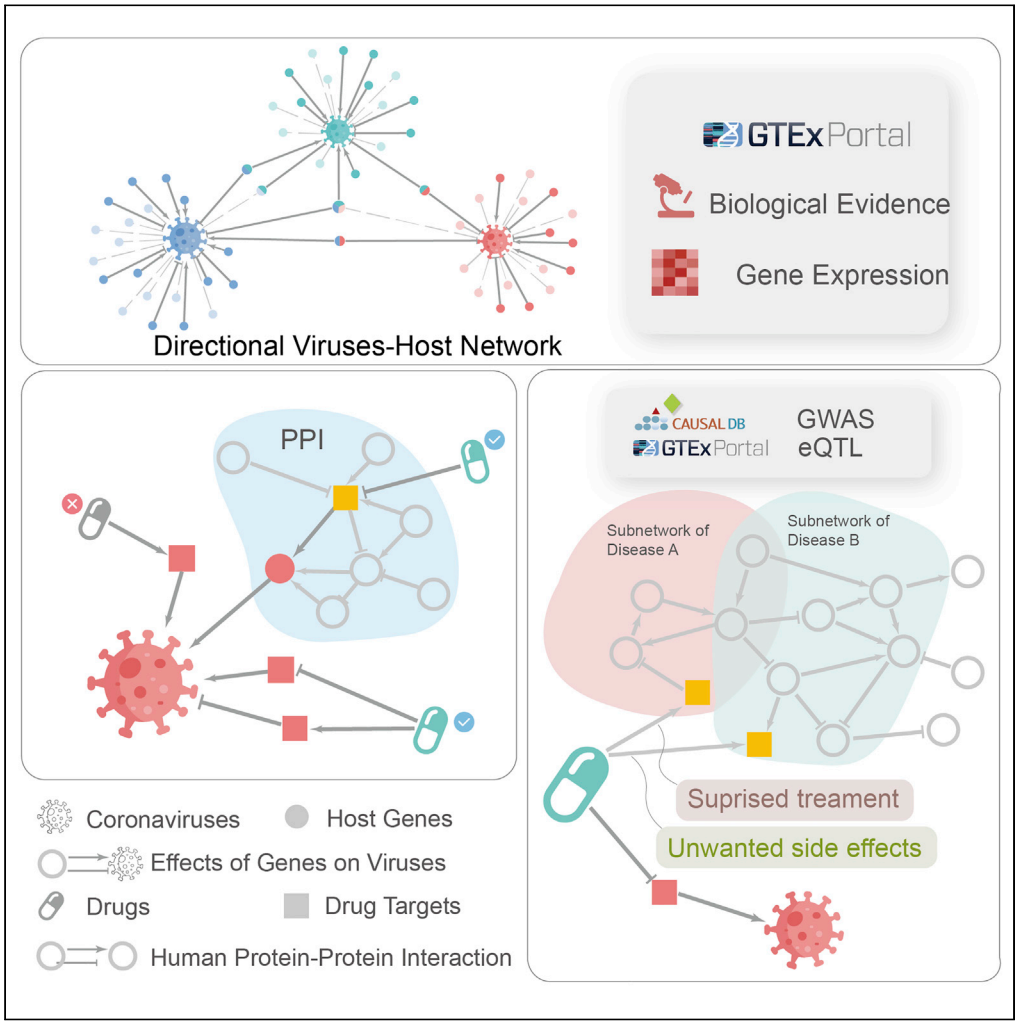

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Highlights

A catalog of host genes associated with three CoVs from multi-omics

Drug repositioning utilized the direction information in the network

Drug prioritization considered the side/beneficial effects on comorbidities

Seven of twenty-nine prioritized approved drugs are in clinical trials for COVID-19

Wang et al., iScience 25, 105348
November 18, 2022
https://doi.org/10.1016/j.isci.2022.105348

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Rational drug repositioning for coronavirus-associated diseases using directional mapping and side-effect inference

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SUMMARY

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen of coronavirus disease 2019 (COVID-19), has infected hundreds of millions of people and caused millions of deaths. Looking for valid druggable targets with minimal side effects for the treatment of COVID-19 remains critical. After discovering host genes from multiscale omics data, we developed an end-to-end network method to investigate drug-host gene(s)-coronavirus (CoV) paths and the mechanism of action between the drug and the host factor in a directional network. We also inspected the potential side effect of the candidate drug on several common comorbidities. We established a catalog of host genes associated with three CoVs. Rule-based prioritization yielded 29 Food and Drug Administration (FDA)-approved drugs via accounting for the effects of drugs on CoVs, comorbidities, and drug-target confidence information. Seven drugs are currently undergoing clinical trials as COVID-19 treatment. This catalog of druggable host genes associated with CoVs and the prioritized repurposed drugs will provide a new sight in therapeutics discovery for severe COVID-19 patients.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is currently spreading around the world rapidly (Del Rio and Malani, 2020). This coronavirus (CoV) has infected more than half a billion people and caused over 5 million deaths, implying a global health threat. Despite prevention strategies such as social distancing and vaccines (Wiersinga et al., 2020), the most common treatments for infected patients are supportive care and respiratory support because there are no effective antiviral drugs. As the development of a new drug takes years to a decade, drug repositioning can significantly accelerate the development cycle of therapies for COVID-19.

The key to drug repositioning of COVID-19 is to identify critical targets for the CoV replication cycle. Current candidates that have been tested in clinical trials can be divided into two groups according to their mechanism of action (MoA): virus-based and host-based treatment options. The former targets the virus components involved in the CoV replication cycle. For example, approved nucleoside analogues (favipiravir and ribavirin) and experimental nucleoside analogues (remdesivir and galidesivir) may have potential against SARS-CoV-2 (Elfiky, 2020; Malin et al., 2020; Ozlusen et al., 2021; Tong et al., 2020). Two oral antiviral treatments, Molnupiravir and Paxlovid, were recently authorized by the Food and Drug Adminstration (FDA). Molnupiravir has relatively low efficacy and may have potentially serious adverse effects, such as mutagenicity and congenital disabilities (Borio et al., 2022). Paxlovid is an oral protease inhibitor that appears to be more effective than existing protease inhibitors with fewer safety concerns (Borio et al., 2022). The host-based approaches are less straightforward than the virus-based approaches. They target the key host factors utilized by CoV for viral replication or stimulate innate antiviral responses in hosts. It was quickly discovered that SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and leverages the serine protease TMPRSS2 for S protein initiation (Hoffmann et al., 2020). ACE2 regulates the renin-angiotensin system (RAS) in several diseases and expresses in the lungs and the kidney, small intestine, testis, and heart (Donoghue et al., 2000; Gordon et al., 2020). TMPRSS2 activates the virus-membrane fusion on the cell surface by cleaving the S protein. In addition to ACE2 and TMPRSS2, several candidate receptors can aid SARS-CoV-2 infection, such as the cell-surface proteins tyrosine-protein kinase receptor UFO (Axl), low-density

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https://doi.org/10.1016/j.isci.2022.105348

lipoprotein receptor class A domain-containing protein 3 (LDLRAD3), and C-type lectin domain family 4 member G (CLEC4G) (Wang et al., 2021b; Zhu et al., 2021a). Moreover, members of pathways that mediate membrane fusion and lipid metabolism, such as PI3K type 3 (PIK3C3) and PI3K regulatory subunit 4 (PIK3R4) from phosphatidylinositol 3-kinase (PI3K) pathway and sterol regulatory element-binding protein 1 and 2 (SREBF1 and SREBF2), are also crucial for infection (Baggen et al., 2021b). Several efforts have been made to identify drugs that inhibit SARS-CoV-2 by targeting host proteins. An *in vitro* study demonstrates that the inhibition of the protease activity of TMPRSS2 partially prevents the entry of SARS-CoV-2 into the lung epithelial cells (Bottcher et al., 2006). *In vitro* studies suggest that both chloroquine and hydroxychloroquine may prevent the transport of SARS-CoV-2 from the early endosome to the endolysosome. In addition to treating malaria, chloroquine and hydroxychloroquine also have immunomodulatory effects. (Liu et al., 2020). However, none of these options was confirmed to have an anti-SARS-CoV-2 effect, which motivates the discoveries of other uncovered but practical host factors.

Fortunately, more comprehensive approaches have been applied to identify host factors, such as affinity purification mass spectrometry (AP-MS) and CRISPR screening (Schneider et al., 2021; Stukalov et al., 2021). By systematically collecting and collating the results of these data, more host genes can be discovered. Thus, our goal is to find drug candidates that can target these host genes. Existing computational drug-repositioning methods can be classified into structure-based and network-based methods (Dotolo et al., 2021). The network-based methodology combines the virus-host interactome and drug targets in the human protein-protein interaction (PPI) network as a systems pharmacology-based network medicine platform, which is vital and widely used in drug repositioning for COVID-19 (Dotolo et al., 2021; Fiscon et al., 2021; Ge et al., 2021; Li et al., 2021; Morselli Gysi et al., 2021; Zhou et al., 2020a, 2020b, 2020b). These methods can be divided into three categories: clustering, propagation, and deep learning. They measure the similarity of sub-networks from the network, the proximity of drugs to the host network, or predicted interactions. Some even predict combinations of drugs (Siminea et al., 2022). Network pharmacology can choose drugs combined in lower doses but targeting the causal disease mechanism, may solve the one symptom–one target–one drug problem caused by traditional combination therapy (Casas et al., 2019; Nogales et al., 2022). However, these methods ignore that most of the applied PPI networks are all directional, which initializes the incorporation of this type of information in our analysis. For example, we should consider inhibitors of proviral genes rather than stimulators, even though both classes of drug-based networks show a similar pattern with the host network. Furthermore, a drug may target multiple host genes through the network. If the drug stimulates some genes and inhibits others, its effect on the virus needs to be reassessed. Importantly, current methods barely avoid the potential side effect of repurposed drugs for COVID-19 patients with chronic underlying diseases, such as diabetes mellitus, cardiovascular disease, chronic pulmonary disease, and cancers.

In this study, to identify the potential antiviral agents, we applied an end-to-end computational method to search drug-gene(s)-coronavirus (CoV) paths in a directional network and inferred the effect of drugs on CoV. We constructed the integrative network by aggregating three networks with direction information, including a virus-host interactome, a human PPI network, and a drug-target network. By leveraging the edge direction in the networks, we can determine whether a drug is reachable to the virus and the MoA between the drug and the virus protein, i.e., inhibition or stimulation. Considering that patients with specific comorbidities are more susceptible to COVID-19 infection, we inspected the side effect of the drug candidate on several common comorbidities based on the genetic information of several complex diseases. We reported 29 FDA-approved drugs (7 currently in clinical trials as COVID-19 treatment) by a scoring strategy accounting for the effects of drugs on CoVs and comorbidities and other auxiliary information. We also compared the prediction performances with the connectivity map (CMAP) method. Together, we established a precise host-based antiviral drug repositioning strategy by incorporating directional information and minimizing side effects, which will provide a new sight in therapy discovery for the pandemic.

RESULTS

Strategy overview for the compilation of directional effect of host genes and COVID-19 drug repositioning

The analytical workflow for our drug repositioning is shown in Figure 1. The whole analysis process is mainly divided into four steps. We first comprehensively collected candidate host genes from three major domains for mechanistic research of CoV infection: genetic risk genes, physical interaction genes, and biological regulation genes (Figure 1A). The source of genetic risk genes was mainly collected from the GWASs of

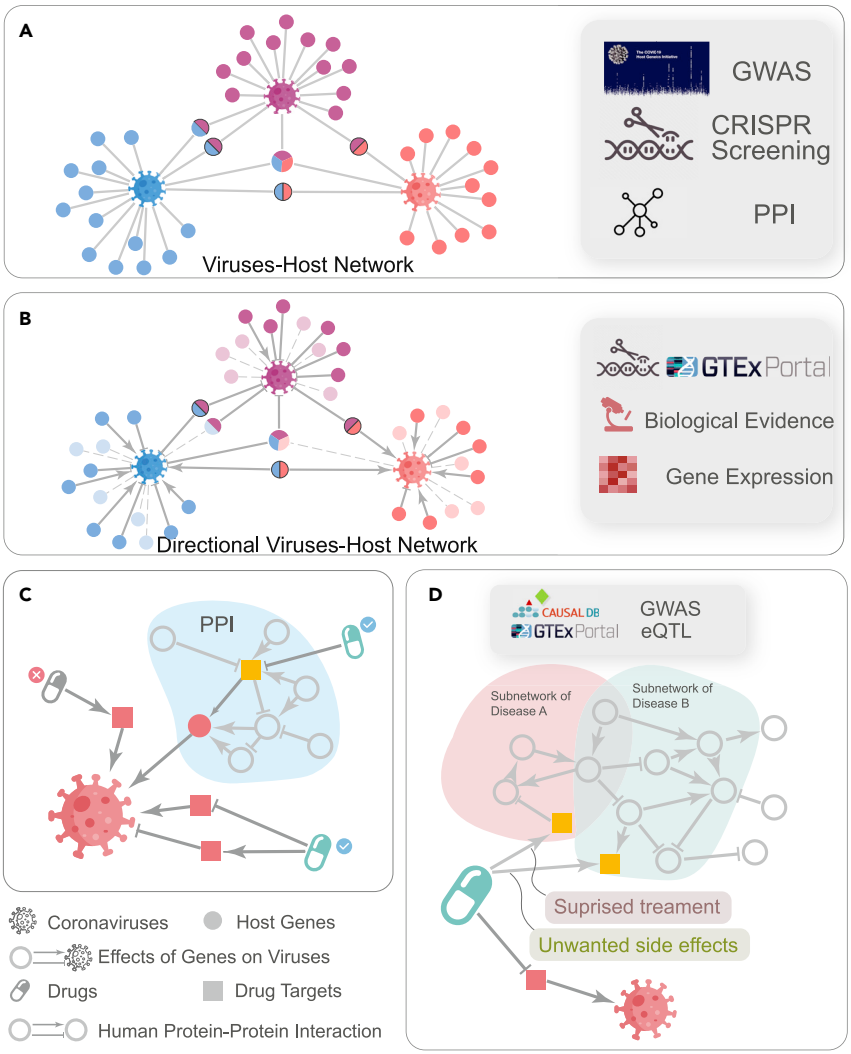

Figure 1. Overview of host-based drug repositioning framework

(A) We collected host genes from three aspects, which are genetic risk genes, physical interaction genes, and biological regulation genes.

(B) We then determined the direction of the effect of viral infection while collecting host genes. Genes with negative direction have inhibitory effects to the infection of viruses.

(C) By combining three directional networks, we constructed a virus-host-drug interactome with orientation information. We applied the random walk with restart algorithm to the seek shortest paths from the drugs to the viruses. Then we inspected the accessibility of each drug to host genes and assembled directional drug-gene(s)-Co-Vs paths.

(D) We checked the putative effects of repositioned drugs on common diseases using the similar strategy in (C). The disease-related genes and their directions were inferred by GWAS and eQTL data.

COVID-19. Physically interacting genes were obtained from the literature, PPI databases, and AP-MS experiments. The biological regulation genes were collected from the results of the CRISPR screen of CoV-infected cells. To select drugs with the correct mechanisms of action (MoA), we also determined the direction of the effect of viral infection while collecting host genes (Figure 1B, STAR Methods). We determined the direction of genetic risk genes by GWAS and variant annotation. We used the up- and downregulation of physically interacting genes in viral infection expression profiles as their direction. The direction of biological regulation genes was derived from their effect on the screening results. We then collected data on human protein interactions, their direction of action, and the effects of drugs and drug targets. Thus, we constructed a directed multicomponent network including CoV, host genes, human genes, drug targets, and drugs. We then searched for drug-gene(s)-CoVs paths in this network and used

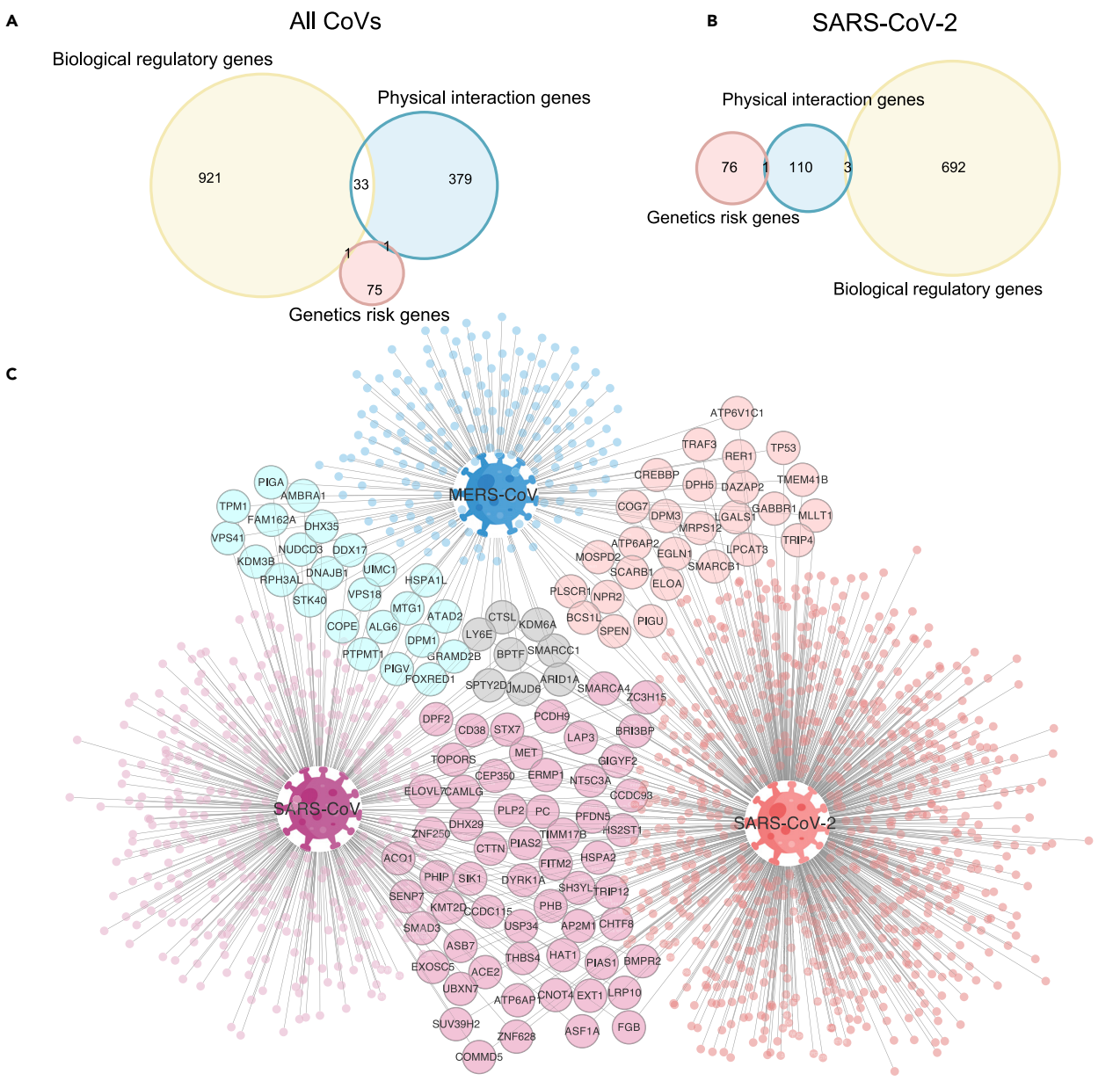
A
All CoVs
Biological regulatory genes
Physical interaction genes
921
33
379
1
1
75
Genetics risk genes
B
SARS-CoV-2
Physical interaction genes
76
1
110
3
692
Genetics risk genes
Biological regulatory genes
C
MERS-CoV
SARS-CoV
SARS-CoV-2
D
Terpenoid backbone biosynthesis
Inflammatory bowel disease
Leishmaniasis
GPI-anchor biosynthesis
Th17 cell differentiation
Toxoplasmosis
Measles
Hepatitis C
Influenza A
Cytokine-cytokine receptor interaction
Gene Ratio
P.adj
Count
E
Collecting duct acid secretion
Glycosaminoglycan biosynthesis
Vibrio cholerae infection
Bacterial invasion of epithelial cells
Epithelial cell signaling in Helicobacter pylori infection
Synaptic vesicle cycle
Rheumatoid arthritis
Salmonella infection
Phagosome
Human papillomavirus infection
Gene Ratio
P.adj
Count

Figure 2. Integration of host genes and enrichment analysis

(A and B) Venn plot shows the overlap between all (A) and SARS-CoV-2 (B) host genes curated in three categories.

(C) All host genes with direction. Labeled purple nodes are genes shared by SARS-CoV and SARS-CoV-2.

(D and E) Labeled pink nodes are genes shared by SARS-CoV-2 and MERS-CoV. Labeled bright cyan nodes are genes shared by SARS-CoV and MERS-CoV. In the middle gray are genes shared by the three viruses. KEGG pathway enrichment analysis of antiviral genes (D) and proviral genes (E).

the direction information to screen out drugs with suitable MoAs (Figure 2C). To investigate the impact of drug candidates on the underlying disease in patients with COVID-19, we also identified genetic risk genes for common complex diseases and their direction to disease from genetic data. Finally, drugs with a potential inhibitory effect on the disease were prioritized based on a combined score, and conversely, drugs that promote disease were filtered out (Figure 1D, STAR Methods).

Comprehensive integration of CoV host genes and their pathogenic direction

Phylogenetic analysis of human CoVs shows that SARS-CoV-2, SARS-CoV, and MERS-CoV have a high conservative genome (Figure S1). Specifically, the envelope and nucleocapsid proteins of SARS-CoV-2 are two evolutionarily conserved regions, having high sequence identities between SARS-CoV and MERS-CoV (Zhou et al., 2020a). Therefore, these three viruses may share infectious mechanisms through common host genes, and the therapeutic drugs could be overlapped. We systematically integrated candidate host genes from three different angles: (1) to identify genetic risk genes of COVID-19, we first got significant risk variants (p-value<5×10^{-8}) of 517 COVID-19 GWASs from GRASP (https://grasp.nhlbi.nih.gov/Covid19GWASResults.aspx) (Table S1), yielding 2,618 risk variants significantly associated with COVID-19 (Table S2). If the risk variant is an expression quantitative trait locus (eQTL) of whole blood or lung, we retrieved the eGene of the eQTL as the risk gene and inferred the direction of the risk gene to the virus by matching the effect size of the GWAS and the effect size of the eQTL. We identified 77 genetic risk genes (Table S3), including innate antiviral defenses, which are critical early in infection (IFNAR2, OAS1, and OAS3). OAS3 encodes for the oligoadenylate synthase family of proteins that degrades viral RNA and activates antiviral responses, and its expression was predicted to be significantly associated with the disease (Pairo-Castineira et al., 2021; Schmiedel et al., 2020). The association on chromosome 19p13.12 colocalizes an eQTL of TYK2, the target of JAK inhibitors, whose high expression is associated with COVID-19 (Schmiedel et al., 2020). (2) To collect the high confidence proteins interacting with CoVs, we gathered data from PPI databases, public literature, and affinity AP-MS analyses. We used up- and downregulation of genes in the CoV infection process as gene-to-virus direction. Expression profiling data were obtained from publicly available tissue from virus-infected and normal samples. We identified 435 genes that interact with viral proteins and their direction of action (Table S4). Among them, 16 genes interacted with both SARS-CoV and SARS-CoV-2 and were significantly differentially expressed in the expression profiles of the two viruses (Figure S2). Aconitase1 (ACO1) is overexpressed in COVID-19 and underexpressed in non-COVID-19 viral infections. Interestingly, ACO1 is involved in iron metabolism, and heme appears to be interlinked with COVID-19 pathophysiology (Thair et al., 2021). PCDH9, one of the downregulated genes, interacts with multiple proteins of CoVs, including M, NSP6, ORF6, ORF7a, ORF7b, and S proteins. PCDH9 protocadherin is essential in epithelial cell-cell adhesion and the integrity of endothelial barrier function (Bass et al., 2021). The disruption of cadherin proteins by viral protein ORF7b could contribute to several symptoms of COVID-19 infection, including multiorgan failure (Troyanovsky et al., 2007). (3) Genome-wide screens have been widely used to identify host factors for various viruses, including CoVs (Flint et al., 2019; Li et al., 2020; Wang et al., 2021a). Genome-wide perturbations can identify genes in human cells that play a key role in viral infection and the body's response. We selected the top-ranked genes from six genome-wide CRISPR screens (Table S5) and determined their direction based on the perturbation pattern and the effect size. We identified 958 genes from the CRISPR screen data (Table S6). It is worth noting that seven genes were selected in the screening of all three viruses, including CTSL, which encodes the Cathepsin L protease. CTSL can functionally cleave the SARS-CoV-2 spike protein and enhance virus entry (Zhao et al., 2021). Studies have shown that inhibitors of CSTL can effectively prevent human CoVs infection (Zhou et al., 2016).

By combining the genes from the three sources, we identified 1,410 host genes (Table S7). Remarkably, no genes were collected from all three sources simultaneously, and the overlap between the three sources is also relatively small, suggesting current biological assays or genetic methods may capture complementary patterns of CoV-host crosstalk. For example, only 1 out of the 77 genetic risk genes is derived from the CRISPR screen and physical interaction, respectively (Figure 2A). For SARS-CoV-2, we revealed 882 candidate host genes (Figure 2B). Among them, BMPR2 is not only a genetic risk gene but also interacts with

SARS-CoV-2 ORF3 protein. Heterozygous mutations in BMPR2 can cause hereditary pulmonary hypertension (Rhodes et al., 2019). Drugs targeting BMPR2 may affect the prognosis of patients with pulmonary hypertension based on genetic evidence. SARS-CoV-2 and SARS-CoV share 67 host genes (Figure 2C), including ACE2, the primary cell entry receptor for SARS-CoV-2, whereas 35 genes, including TMEM41B, were identified as host genes of both SARS-CoV-2 and MERS-CoV. TMEM41B, an essential host factor for HCoV-229E, can promote lipid localization in infected cells (Trimarco et al., 2021). We divided these genes into antiviral and proviral genes according to their effect on the CoVs. There are 654 antiviral genes and 756 proviral genes. Antiviral genes were enriched in viral-infection-related pathways such as influenza A and hepatitis C and inflammation-related pathways such as cytokine-cytokine receptor interaction and Th17 cell differentiation (Figure 2D). Proviral genes were also enriched in some infection-related pathways, such as human papillomavirus infection, Salmonella infection, and *Vibrio cholerae* infection (Figure 2E). Both proviral and antiviral genes were also enriched in autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease.

Drug repositioning and prioritization for COVID-19 treatment using directional network propagation and side-effect inference

The catalog of host genes associated with CoVs and the directional information can provide mechanistic insight for drug target selection. As the development of a new drug takes a long time and huge cost, we believe our integrated resource could be alternatively suitable for improving drug repositioning opportunities on COVID-19. We developed an end-to-end network approach to search for potential drug repurposing. We first constructed a directional informative human PPI network by fusing STRING, KEGG, and reactome data (Jassal et al., 2020; Kanehisa et al., 2019; Szklarczyk et al., 2019). The directional human interactome used in this study contains 11,126 proteins and 167,776 interactions. We also collected drug and drug-target interactions with a clear direction of action from DGIdb (Freshour et al., 2021). Together, 23,306 directional drug-target interactions of 9,540 drugs were used in this study. We merged drug-target interactions, human protein interactions, and virus-host interactions into a whole drug-gene-CoV network. Then we used the random walk with restart (RWR) algorithm to find drug-gene(s)-CoVs paths in the network and inferred the direction of the drug to the CoVs (see STAR Methods). Totally, 6,234 drugs with inhibitory effects on CoVs were inferred. Older age and comorbidities play essential roles in influencing the severity of COVID-19. We applied a genetics-based method to predict the impact of repurposed drugs on comorbidities, including diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic liver disease, chronic kidney injury, autoimmune disease, and cancers. According to our previous strategy, we filtered and prioritized potential drugs by inspecting their impact on these complex diseases (Cui et al., 2020). We collected 10,557 variants in 17 diseases and mapped these variants to 536 genes (Table S8). Finally, we identified 246 drugs with possible side effects and 269 with potential comorbidity treatments.

To select the optimal drugs, we utilized the properties of drug-gene(s)-CoVs path (including drug-target interaction, network mapping, and source of host genes) for each drug to derive a combined score and used it to prioritize drug candidates (see STAR Methods). We found that 29 of the top 100 drugs are FDA approved (Figure 3A, Table 1), and seven of these are in clinical trials for the treatment of COVID-19. We collected 397 drugs in clinical trials for COVID-19 from Clinicaltrials.gov and overlapped with the top 100 drugs. None of the drugs in clinical trials prior to phase 3 have been found in clinical trials for COVID-19, and there are nine drugs in phase 3/4 clinical trials for COVID-19 (Figure 3B); this may be because most of the COVID-19 clinical trial drugs are in clinical phase 3 or FDA approved. We identified well-studied drugs with clinical trials, such as aspirin and chlorpromazine. Chlorpromazine is an antipsychotic drug that has recently been proposed to have antiviral activity against SARS-CoV-2 (Stip, 2020). The MoA of chlorpromazine is either via inhibition of clathrin-mediated endocytosis and/or at later stages of virus assembly and egress (Stip et al., 2020). We also identified drugs with no clinical trials evidence but showed potential, such as bosutinib. Bosutinib is a treatment for chronic myeloid leukemia by inhibiting the Abelson kinase signaling pathway. In addition, experimental data suggest that bosutinib is a powerful anti-inflammatory agent (Ma et al., 2017; Tiribelli et al., 2019). Recently, bosutinib was found to strongly inhibit SARS-CoV-2 *in vitro* with low toxicity (Yang et al., 2021). Recently, it was reported that pseudoephedrine can antagonize COVID-19 virus by blocking virus expansion (Yu et al., 2021). Another example is that ponatinib is a potent inhibitor of SARS-CoV2-induced cytokine storm (Chan et al., 2021), whereas epinephrine may be considered an intervention to minimize the severity of COVID-19 (Derakhshan et al., 2020).

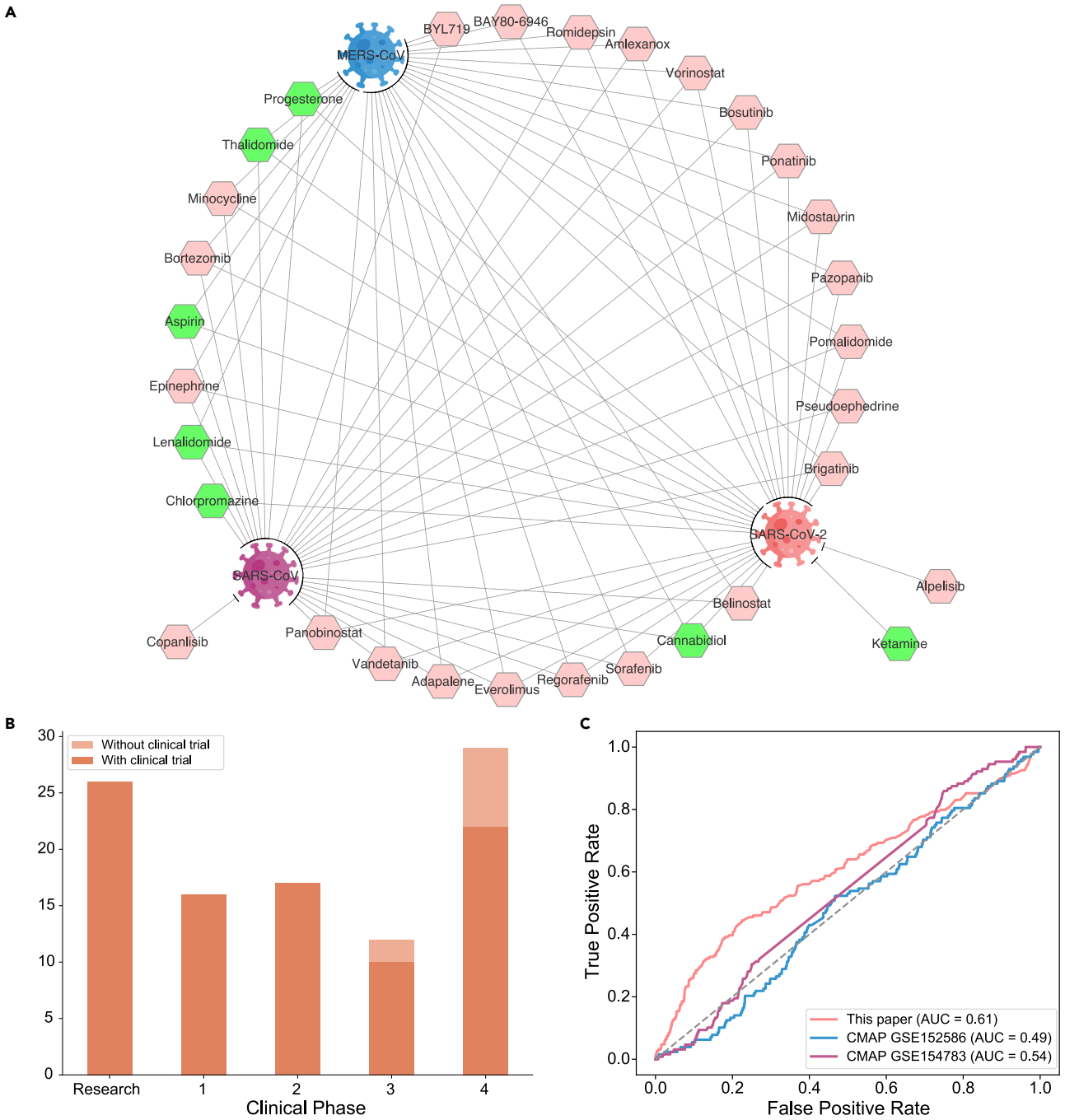

Figure 3. Network-based drug repositioning and prioritization

(A) FDA-approved drugs in our top 100 prioritized drugs. Green nodes are drugs in clinical trials for COVID-19 treatment.

(B) The overlap of the top 100 drugs and clinical trials.

(C) Performance comparison between our strategy and CMAP. We used the top 50 genes that were up-regulated and down-regulated in the expression profiles of SARS-CoV-2-infected samples and controls as input to CMAP. We used data from two types of cells, alveolar type II cells (GSE152586) and green monkey kidney cells (GSE154783).

Moreover, we compared our method with the CMAP method based on similarity analysis of expression profiles, which was frequently used in drug repositioning (Subramanian et al., 2017). CMAP contains the cellular gene expression profiles under the perturbation of 2,428 drugs. We measured the associations of gene expression patterns between CoV-infected patients and the reference-compound-perturbed cells (STAR

Table 1. 29 FDA-approved drugs and related evidence in our top 100 prioritized drugs

D2V Score	Drug	CHEMBL ID	Clinical Trial	N of Drug-gene-CoV paths	Original indication
29.375	Bosutinib	CHEMBL288441	None	92	Chronic Myelogenous Leukemia
28.083	Thalidomide	CHEMBL468	NCT04273581, NCT04273529	82	Erythema Nodosum Leprosum
27.833	Aspirin	CHEMBL25	NCT04333407, NCT04498273, NCT04343001, NCT04410328, NCT04365309, NCT04381936, NCT04363840, NCT02735707, NCT04324463, NCT04425863	92	Nonsteroidal Anti-Inflammatory Drug (NSAID)
24.750	Midostaurin	CHEMBL608533	None	75	Acute Myeloid Leukemia
24.917	Regorafenib	CHEMBL1946170	None	74	Metastatic Colorectal Cancer
23.708	Pseudoephedrine	CHEMBL1590	None	70	Decongestant
24.583	Ponatinib	CHEMBL1171837	None	77	Chronic Myeloid Leukemia
21.833	Cannabidiol	CHEMBL190461	NCT04731116, NCT04615949, NCT04467918, NCT04504877	72	Epilepsy
23.167	Adapalene	CHEMBL1265	None	69	Acne Vulgaris
23.167	Panobinostat	CHEMBL483254	None	73	Multiple Myeloma
23.000	Romidepsin	CHEMBL343448	None	73	Cutaneous T cell Lymphoma
22.625	Vorinostat	CHEMBL98	None	73	Cutaneous T cell Lymphoma
22.625	Belinostat	CHEMBL408513	None	73	Peripheral T cell Lymphoma
22.417	Bortezomib	CHEMBL325041	None	63	Multiple Myeloma
21.833	BYl719	CHEMBL2396661	None	70	Breast Cancer
21.500	BAY80-6946	CHEMBL3218576	None	70	Follicular Lymphoma
21.417	Pomalidomide	CHEMBL43452	None	65	Multiple Myeloma
20.917	Lenalidomide	CHEMBL848	NCT04361643	66	Transfusion-Dependent Anemia
20.708	Amlexanox	CHEMBL1096	None	68	Aphthous Ulcers
20.208	Sorafenib	CHEMBL1336	None	62	Renal Cell Carcinoma
18.917	Everolimus	CHEMBL1908360	None	54	Breast Cancer
14.417	Pazopanib	CHEMBL477772	None	46	Renal Cell Carcinoma
18.417	Minocycline	CHEMBL1434	None	54	Bacterial Infections
17.583	Brigatinib	CHEMBL3545311	None	55	Non-Small Cell Lung Cancer
17.333	Progesterone	CHEMBL103	NCT04365127, NCT04865029	54	Amenorrhea
17.333	Vandetanib	CHEMBL24828	None	55	Thyroid Cancer
16.208	Epinephrine	CHEMBL679	None	46	Allergic Reactions (Type I)
17.083	Chlorpromazine	CHEMBL71	NCT04366739, NCT04354805	54	Schizophrenia
17.042	Ketamine	CHEMBL742	NCT04366739, NCT04354805	57	Anesthetic Agent

Methods). COVID-19 clinical trial drugs are used as ground truth. Our method has the highest area under the curve (AUC) of 0.61 compared with the results calculated by CMAP using two SARS-CoV-2 infection expression profiles (Figure 3C).

Rational interpretation of several drug repositioning opportunities for the treatment of COVID-19

Network analysis methods such as deep learning, network diffusion, and network proximity can evaluate the accessibility of drugs to SARS-CoV-2 in the background network (Ge et al., 2021; Morselli Gysi et al., 2021; Zhou et al., 2020a). However, given a proviral host gene, we should choose its inhibitor/antagonist as therapeutics instead of its activator/agonist, even if the activator/agonist shows higher proximity to this host gene in the network. For example, SIGMAR1, the target of the NSP6 SARS-CoV-2 protein (Morselli Gysi et al., 2021), is identified as a proviral gene in our study. Although which class of drugs, i.e., agonists or antagonists of SIGMAR1, is responsible for the replication activity of SARS-CoV-2 remains to be verified by more experiments (Hashimoto, 2021), the latest evidence revealed that knockout or knockdown of SIGMAR1 could cause significant reductions in SARS-CoV-2 replication (Morselli Gysi et al., 2021). Furthermore, a clinical trial demonstrated that the antidepressant fluvoxamine, an antagonist of SIGMAR1, could prevent clinical deterioration in adult outpatients infected with SARS-CoV-2 (Figure 4A) (Lenze et al., 2020). However, there are network-based approaches to select SIGMAR1 agonists, such as amitriptyline, as a potential treatment for COVID-19 (Morselli Gysi et al., 2021), implying confliction and limitation may largely exist among current methods.

Drugs with multiple targets may have implications for other diseases in the fight against viral infections. Just as we can predict the antiviral properties of existing drugs, we can also predict whether these drugs will influence preexisting conditions in patients with viral infections. For instance, cannabidiol (CBD), a member of the cannabinoid class of natural products, is an FDA-approved drug for epilepsy treatment. There are four clinical trials of CBD for the treatment of COVID-19. Studies have shown that CBD can inhibit the cell entry and replication of SARS-CoV-2 (Nguyen et al., 2022; van Breemen et al., 2022). In our analysis, CBD, ranked at 23rd, directly or indirectly targeted 87 host genes. Our comorbidity treatment analysis found that CBD is also an agonist of PPARG and GPX1. Since 1997, a group of PPARG agonists, thiazolidinediones, has been used to treat type 2 diabetes by alleviating insulin resistance (Larsen et al., 2003). In theory, cannabis has desirable effects on hyperglycemia through its anti-inflammatory and antioxidant properties (Mattes et al., 2021). GPX1 has been shown to exert a protective effect against the presence of coronary artery disease (CAD) (Tang et al., 2008). Its activity was a useful marker for monitoring cardiovascular disease (Wickremasinghe et al., 2016). There is now a growing body of evidence that CBD is also beneficial for the cardiovascular system (Kicman and Toczek, 2020; Stanley et al., 2013). The anti-inflammatory and antioxidant effects of CBD may make it a treatment for coronary heart disease and diabetes, together with COVID-19 (Figure 4B). Estradiol cypionate (EC) is an estrogen medication used in hormone therapy for menopausal symptoms and low estrogen levels in *cis* women. The analysis of electronic health records of over 68,000 COVID-19 patients revealed that estrogen therapy is associated with more than 50% reduction in mortality (Seeland et al., 2020). EC was repositioned as COVID-19 treatment in other studies and is now in phase 2 clinical trial (Siminea et al., 2022). In our analysis, EC can indirectly target HK2 and PLCB4 through ESR2, identified as a risk factor for atrial fibrillation. Furthermore, estrogen may increase the risk of myocardial infarction in transgender women by promoting thrombosis (Dutra et al., 2019). Therefore, EC, despite its potential antiviral effect, could be excluded due to its possible cardiovascular side effects (Figure 4C). Together, our new drug repositioning strategy utilizes the direction information in the network to screen the MoA of the candidate drugs and, from a genetic perspective, considers the potential unwanted side effects of many complex diseases.

DISCUSSION

The key step in host-based drug repurposing for the treatment of infectious diseases is identifying the true host gene. An increasing number of studies are looking for host genes on a genome-wide scale by different means, such as GWAS, CRISPR screening, and AP-MS. These large-scale and complementary screens require systematic integrative analysis to discover more accurate host genes. Moreover, current host-based drug repositioning strategies generally utilize network proximity, network diffusion, and deep learning approaches to identify potential repurposing candidates (Belyaeva et al., 2021; Morselli Gysi et al., 2021; Siminea et al., 2022). The main goal of these approaches is to find drugs that can directly or indirectly control as many host genes as possible. However, the networks used in these analyses are

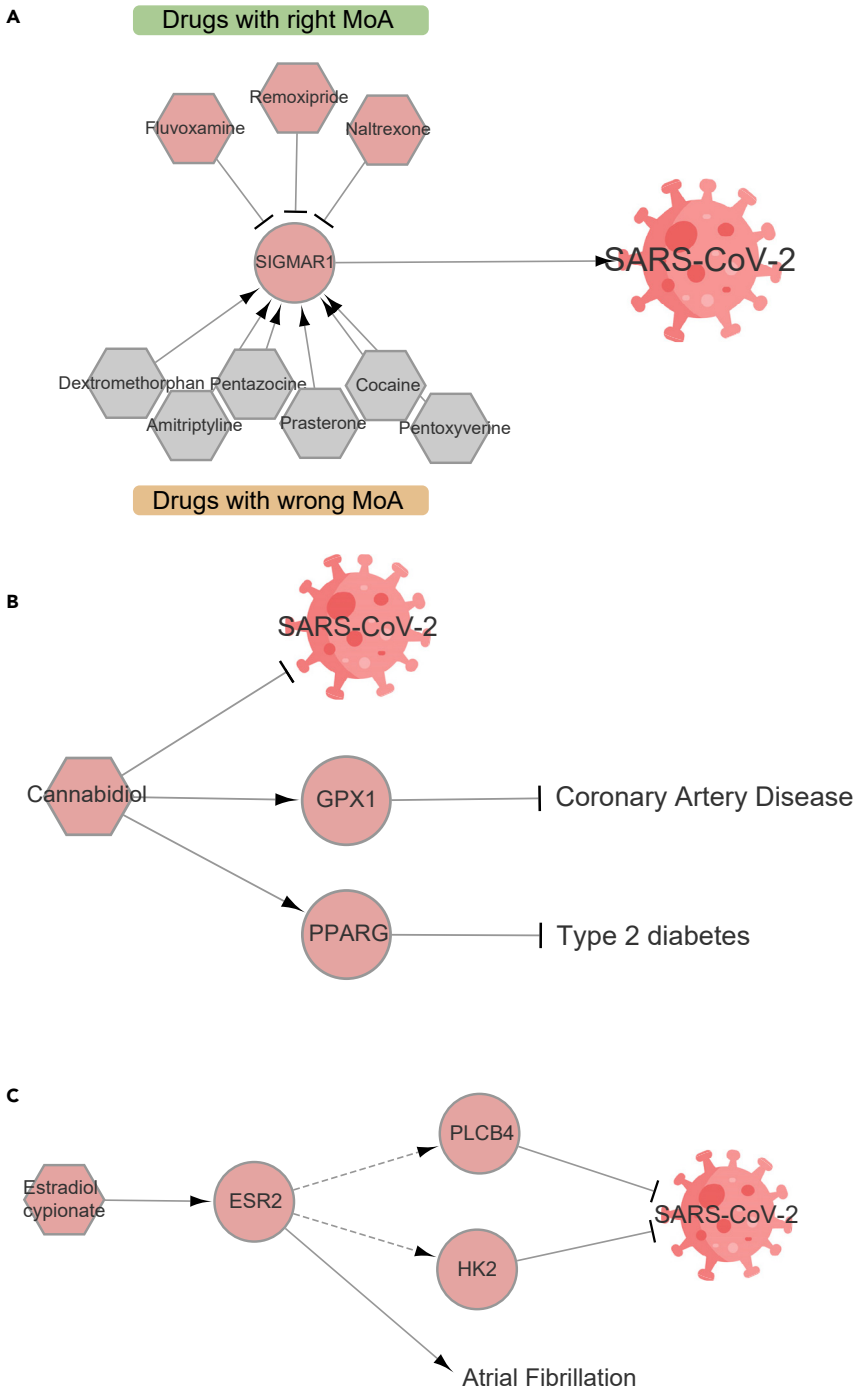

Figure 4. Examples of our drug repositioning candidates

(A) Three inhibitors of SIGMAR1 have the potential to treat COVID-19, while other activators such as amitriptyline were filtered because of the wrong MoA.

(B) Cannabidiol has potential anti-coronavirus effects. Moreover, it acts as an agonist of GPX1 and PPARG to prevent coronary heart disease and type 2 diabetes.

(C) Estradiol cypionate indirectly targets two antiviral genes, HK2 and PLCB4, by stimulating ESR2. However, ESR2 is also an atrial fibrillation risk gene, which means estradiol cypionate increase the risk of cardiovascular disease.

undirected graphs. In other words, some protein interactions are activating and some inhibiting. Although some host genes are proviral and some are antiviral, drugs targeting the same target sometimes contain antagonists and agonists. Thus, it is necessary to search for drugs with correct MoA in directed networks.

To this end, we comprehensively identified host genes and their directions to CoVs by systematically integrating multi-omics data from mass spectrometry, CRISPR screening, and GWAS. We identified 964 host genes for SARS-CoV-2, 477 host genes for SARS-CoV, 236 host genes for MERS-CoV, and 1,410 unique genes. These genes include genetic risk genes such as TYK2, physical interaction genes such as ACO1, and biological regulation genes such as CTSL. The host genes from the three sources overlapped little, indicating that high-throughput biological assays are complementary. There are more overlapping genes between SARS-CoV-2 and SARS-CoV than between SARS-CoV-2 and MERS-CoV; this may be because the genome and structure of SARS-CoV-2 are more similar to SARS-CoV. We also used multi-omics data to determine the direction of host genes to viruses, that is, their effects on viral infection. We identified 654 antiviral genes and 756 proviral genes. Functional enrichment analysis showed that the pathways enriched in both proviral and antiviral genes were involved in infection- and immune-related pathways. To apply the catalog of host genes to drug repositioning, we constructed a background network by fusing three directed networks, including a virus-host network, a human PPI network, and a drug-target network. We screened 6,234 drug candidates and designed a scoring system to rank them. Twenty-nine of the top 100 prioritized drugs are FDA approved, including seven in clinical trials for COVID-19. In comparison with the results of CMAP, the AUC of our method is larger. In this scoring system, besides adding drug-target interaction scoring and host gene scoring, we also considered the effects of drugs on comorbidities. We found that CBD not only inhibits SARS-CoV-2 but may also act as a therapeutic drug for coronary heart disease and diabetes. EC also has antiviral potential, but we found that it may increase the risk of cardiovascular disease. Overall, we first comprehensively characterized the host genes of CoVs and their role in viral infection. In drug relocation prediction, unlike traditional network-based methods, our method focuses more on the directionality of the MoAs and the interaction networks of drugs to screen drugs with the correct MoA. In addition, we innovatively considered the potential impact of drug candidates on comorbidities.

Limitations of the study

There were still several limitations of our study. We collected as many host genes as possible. However, as more research data become available, we may discover more host genes to refine the virus-host interaction network. Our analysis removed host genes whose directions could not be determined. Perhaps their direction can be identified with other experimental data, such as transcriptome-wide association studies (TWAS) and Mendelian randomization (Gaziano et al., 2021; Huang et al., 2021; Ma et al., 2022; Pairo-Castineira et al., 2021). We used data such as eQTLs, expression profiles, and CRISPR effect sizes to determine the directions of host genes. However, the accuracy of directions identification in these ways is limited by statistical power and tissue specificity. The effects of these host genes we identified on CoV need to be validated in *in vivo* and *in vitro* experiments. Besides, many COVID-19 drug repositioning studies, including this study, have used clinical trial datasets as ground truth for performance evaluation. Not all drugs in clinical trials have significant antiviral effects. There is currently no good dataset to verify the robustness of our strategy and others without biases. Finally, to infer the direction of a drug to CoV in each drug-gene(s)-CoVs path, we used a random walk algorithm and then combined multiple drug paths for prioritization. We can apply some more complex algorithms and models to our network in the future.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2022.105348.

ACKNOWLEDGMENTS

This work was supported by the following grants: Chinese National Key Research and Development Project [2021YFC2500403], National Natural Science Foundation of China [32070675, 31871327, 72104179]; Natural Science Foundation of Tianjin [19JCJQJC63600].

AUTHOR CONTRIBUTIONS

J.W. and M.J.L. designed the study. J.W. and J.L. performed the research and data analysis. J.W., J.L., and M.J.L. wrote the manuscript with contributions from all authors. D.Z. contributed on data analysis and interpretation. M.L., H.C., W.Z., and K.Z. collected data and reviewed the manuscript. H.D., F.S., K.C., and Y.Y. evaluated the computational tools and reviewed the manuscript. J.W., H.Y., and M.J.L. revised the manuscript. All authors approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

Received: June 3, 2022
Revised: September 2, 2022
Accepted: October 11, 2022
Published: November 18, 2022

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
COVID-19 GWAS	GRASP	https://grasp.nhlbi.nih.gov/Covid19GWASResults.aspx
whole blood and lung eQTL	GTEx (release v8)	http://gtexportal.org/home/index.html
Physical interaction genes	BioGRID, IntAct, STRING.Viruses, and APID	https://thebiogrid.org/, https://www.ebi.ac.uk/intact/, http://viruses.string-db.org, http://cicblade.dep.usal.es:8080/APID
AP-MS data	(Bojkova et al., 2020; Gordon et al., 2020; Stukalov et al., 2021)	N/A
PPI data	STRING, KEGG, Reactome	https://string-db.org/, https://www.genome.jp/kegg/, https://reactome.org
Virus infection differentially expressed genes	GEO: GSE122876, GSE33267, GSE152586	See Table S4 for details
CRISPR screening data	(Baggen et al., 2021a; Daniloski et al., 2021; Schneider et al., 2021; Wang et al., 2021a; Wei et al., 2021; Zhu et al., 2021b)	N/A
Drug-target information	DGIdb	http://www.dgidb.org
Credible sets of 17 complex diseases GWASs	CAUSALdb	http://mulinlab.tmu.edu.cn/causaldb, see Table S8 for details
Software and algorithms		
Python (v3.7)	The Python Language	https://www.python.org
VEP (release 96)	(McLaren et al., 2016)	https://www.ensembl.org/info/docs/tools/vep/script/index.html
B-SIFT	(Lee et al., 2009)	http://blocks.fhcrc.org/sift/SIFT.html
clusterProfiler (v4.4.4)	R package	https://bioconductor.org/packages/release/bioc/html/clusterProfiler.html
Cytoscape (v3.9.1)	(Shannon et al., 2003)	https://cytoscape.org
networkx	Python package	https://github.com/networkx/networkx
CMAP	(Subramanian et al., 2017)	https://clue.io/query
All code used in the manuscript	This manuscript	https://github.com/Jianhua-Wang/covid19-iscience-code

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Mulin Jun Li (mulinli@connect.hku.hk).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- This paper analyses existing, publicly available data. These accession numbers for the datasets are listed in the key resources table.
- All original code has been deposited at GitHub (https://github.com/Jianhua-Wang/covid19-iscience-code) and is publicly available as of the date of publication. It has been listed in the key resources table.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

This study analyses existing, publicly available data and does not contain wet lab experiments.

METHOD DETAILS

Comprehensive curation of host genes of three CoVs and determination of the directions between host genes and CoVs pathogenesis

Since the SARS-CoV-2 was most evolutionarily conserved with SARS-CoV and MERS-CoV, SARS-CoV-2 may share host genes or therapeutic targets with the other two CoVs. Thus, by fully utilizing the relevant information and shared mechanism of infection among these CoVs, we curated as many as host genes of these three CoVs from three categories: genetic risk genes, physical interaction genes, and biological regulatory genes.

Genetics risk genes

We first retrieved all risk SNP (p-value < 5e-8) in COVID-19 GWAS from GRASP COVID-19 data (https://grasp.nhlbi.nih.gov/Covid19GWASResults.aspx). Then, the risk SNPs were annotated as coding variants and non-coding variants by VEP (McLaren et al., 2016). For coding variants, the target gene is the gene where the mutation locates. We evaluated the effect of the gene by calculating the functional impact score of the risk allele using B-SIFT (Lee et al., 2009). We assigned the direction of effect as 1 for a B-SIFT score higher than 0.5 and −1 for a B-SIFT score lower than −0.95. For non-coding variants, we identified the target genes and directions by integrating significant expression quantitative trait locus (eQTL) data of whole blood and lung from GTEx (release v8) (Consortium et al., 2017). When a variant is both a COVID-19 risk variant and an eQTL, the associated expression gene is identified as the target gene of the variant. When the GWAS risk allele positively affects gene expression, the direction is 1; otherwise, it is −1.

Physical interaction genes

We collected host genes interacting with CoVs from four PPI databases, including BioGRID (Oughtred et al., 2019), IntAct (Orchard et al., 2014), STRING.Viruses (Cook et al., 2018), and APID (Alonso-Lopez et al., 2019). We also included high-confidence proteins that interacted with CoVs from three AP-MS experiments (Bojkova et al., 2020; Gordon et al., 2020; Stukalov et al., 2021). In addition, we also included the host genes of CoV collected by Zhou, Y. et al. (Zhou et al., 2020a). However, there is no information on the direction of host genes to CoV in these datasets. To determine the direction of each virus-protein interaction. We manually searched the name of the protein and matched the virus in the literature and inferred the direction according to the biological effect of protein on virus infection. The direction of a host protein on the virus is set as positive if the protein has a helpful role in the invasion and amplification of CoV. Moreover, we used gene expression profiles as complementary sources of directions. We got differentially expressed genes of all three CoVs by analyzing corresponding gene expression profiles from the NCBI Gene Expression Omnibus (Katsura et al., 2020; Sims et al., 2013; Yuan et al., 2019). Protein-coding genes with Adjust p-value $\leq$ 0.05 and |log2FoldChange| > 1 were included. The direction of a host protein can be regarded as the same as the sign of log2FoldChange if the protein gene is differentially expressed genes.

Biological regulatory genes

We also collected results from six genome-wide CRISPR perturbation screening assays (Baggen et al., 2021a; Daniloski et al., 2021; Schneider et al., 2021; Wang et al., 2021a; Wei et al., 2021; Zhu et al., 2021b). For every screen assay, the top 100 significant genes were included. We comprehensively consider the perturbation and the effect size of the gene to determine the direction of the gene to the virus. For example, a gene with a negative effector value in a CRISPR knockout screen will have a therapeutic effect on the virus.

Construction of the directional virus-host interactome

We construct a directed virus-host network by combining all gene-virus pairs from the three sources and their directions. Gene-virus pairs with conflicting directions between different sources were deleted. Non-protein-coding genes were removed. The network was visualized by Cytoscape (Shannon et al., 2003).

Functional enrichment analysis of antiviral and proviral genes

To investigate the biological functions of antiviral and proviral genes, respectively, we performed a pathway-based analysis based on KEGG annotations by R package clusterProfiler (Wu et al., 2021).

Gene sets in KEGG pathways with 2–500 genes were included. Genes in the network were analyzed, and significantly enriched pathways were identified with FDR < 0.05.

Directional human interactome

We constructed a directional human interactome by integrating three resources, including human PPIs from STRING, and human signaling pathways from KEGG and Reactome (Jassal et al., 2020; Kanehisa et al., 2019; Szklarczyk et al., 2019). Specifically, for PPIs in STRING, only interactions with clear directions and scores of more than 700 were included. Interactions with explicit actions, either activation or inhibition, were selected when both source and target were protein-coding genes.

Drugs and drug targets

Drug-target information, including ancillary data such as interacting scores, and MoAs, was retrieved from DGIdb (Cotto et al., 2018). The direction of the drug to the target is determined by MoAs. If the MoA is inhibitory, the direction of the drug is negative and vice versa. Drug-target interactions with unclear directions are removed. Clinical stage information for the drug was obtained from ChEMBL (Gaulton et al., 2017).

Drugs repositioning for CoVs

By integrating the directional networks described above, we can identify the potential repositioning of known drugs on CoVs. We searched the appropriate drug-gene(s)-CoVs paths for each compound. Since drugs can directly or indirectly affect viral infections, we searched for repurposed drug candidates by directed mapping and network mapping as described in our previous paper (Cui et al., 2020). Briefly, in directed mapping, we search for the drugs that target the host genes. For network mapping, we applied the random walk with restart algorithm to seek the shortest paths from the drug target to host genes and removed the unlikely paths by measuring the relatedness scores between the start node and end nodes using Python package networkx (https://github.com/networkx/networkx). Then, we inspected the accessibility of each drug to host genes and assembled directional drug-gene(s)-CoVs paths. Since all the interactions in networks were labeled with directions encoded as 1 and -1 (for positive effect and negative effect, respectively), we multiply the directions to infer the drug's effect on CoVs. Drugs that have a negative impact on the CoV are considered a potential repositioning, and the proviral drugs were removed.

Unwanted side effects and underlying additional treatment

To predict the impact of repurposed drugs on comorbidities, we first selected the largest GWAS for 17 complex diseases (including diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic liver disease, chronic kidney injury, autoimmune disease, and many cancers) from CAUSALdb (Table S8) (Wang et al., 2020). We retrieved the 95% credible sets of fine-mapping results of each GWAS from CAUSALdb. Results of FINEMAP were used (Benner et al., 2016). We further selected variants in credible sets with GWAS p-value < 1E-8 as credible risk variants (CRVs). Then we predicted disease-associated genes and their directions of effect on diseases by the same approach linking COVID-19 risk SNPs to genes. After identifying the associated genes and their directions of effect on comorbidities, we checked the effects of repositioned drugs on these diseases using the directed mapping strategy described above. We termed negative effects as additional treatment and positive effects as unwanted side effects. Drugs with unwanted side effects were removed.

Prioritization of repositioning candidate

We designed a plain scoring system to prioritize repositioning candidates. A drug may have multiple drug-gene(s)-CoV paths. For each Drug-Gene(s)-CoV path, we assigned a DGV score, which equals the accumulation of drug target score, mapping score, and host gene score. For drug target scores, we retrieved drug-target interaction scores of each drug from DGIdb. One point was given to the drug when the score was higher than the median of all interacting scores of the drug; otherwise, half a point. For the mapping score, the score is set as the inverse of the number of genes. For the host gene score, it got 1 point if the direction of the interaction was identified by eQTLs and CRISPR screen or half a point if the direction was identified by gene expression profile. The score for each drug is equal to the sum of all its DGV scores. Drugs with higher scores were regarded as having higher antiviral potential.

Assess the performance of drug repurposing

To compare our method with other methods, we used a commonly-used transcriptome analysis approach, connectivity map (CMAP) (Subramanian et al., 2017). We used gene expression profiles of SARS-CoV-2 infected samples and a control group from alveolar type II cells and African green monkey kidney cells (Katsura et al., 2020; Wei et al., 2021). We input the top-50 up- and downregulated genes into the web tool (https://clue.io/query) and got the drug candidates ranked by connectivity map scores. We take as ground truth all drugs currently in clinical trials for COVID-19. Then we computed the receiver operating characteristic (ROC) curve and estimated the area under the curve (AUC).

QUANTIFICATION AND STATISTICAL ANALYSIS

Functional enrichment analysis was conducted using clusterProfiler with significance threshold set at FDR<0.05.