Abstract
Coronavirus disease 2019 (COVID-19) seriously threatens human health and has been disseminated worldwide. Although there are several treatments for COVID-19, its control is currently suboptimal. Therefore, the development of novel strategies to treat COVID-19 is necessary. Ion channels are located on the membranes of all excitable cells and many intracellular organelles and are key components involved in various biological processes. They are a target of interest when searching for drug targets. This study aimed to reveal the relevant molecular features of ion channel genes in COVID-19 based on bioinformatic analyses. The RNA-sequencing data of patients with COVID-19 and healthy subjects (GSE152418 and GSE171110 datasets) were obtained from the Gene Expression Omnibus (GEO) database. Ion channel genes were selected from the Hugo Gene Nomenclature Committee (HGNC) database. The RStudio software was used to process the data based on the corresponding R language package to identify ion channel-associated differentially expressed genes (DEGs). Based on the DEGs, Gene Ontology (GO) functional and pathway enrichment analyses were performed using the Enrichr web tool. The STRING database was used to generate a protein–protein interaction (PPI) network, and the Cytoscape software was used to screen for hub genes in the PPI network based on the cytoHubba plug-in. Transcription factors (TF)–DEG, DEG–microRNA (miRNA) and DEG–disease association networks were constructed using the NetworkAnalyst web tool. Finally, the screened hub genes as drug targets were subjected to enrichment analysis based on the DSigDB using the Enrichr web tool to identify potential therapeutic agents for COVID-19. A total of 29 ion channel-associated DEGs were identified. GO functional analysis showed that the DEGs were integral components of the plasma membrane and were mainly involved in inorganic cation transmembrane transport and ion channel activity functions. Pathway analysis showed that the DEGs were mainly involved in nicotine addiction, calcium regulation in the cardiac cell and neuronal system pathways. The top 10 hub genes screened based on the PPI network included KCNA2, KCNJ4, CACNA1A, CACNA1E, NALCN, KCNA5, CACNA2D1, TRPC1, TRPM3 and KCNN3. The
TF–DEG and DEG–miRNA networks revealed significant TFs (FOXC1, GATA2, HINF1, USF2, JUN and NFKB1) and miRNAs (hsa-mir-146a-5p, hsa-mir-27a-3p, hsa-mir-335-5p, hsa-let-7b-5p and hsa-mir-129–2-3p). Gene-disease association network analysis revealed that the DEGs were closely associated with intellectual disability and cerebellar ataxia. Drug-target enrichment analysis showed that the relevant drugs targeting the hub genes CACNA2D1, CACNA1A, CACNA1E, KCNA2 and KCNA5 were gabapentin, gabapentin enacarbil, pregabalin, guanidine hydrochloride and 4-aminopyridine. The results of this study provide a valuable basis for exploring the mechanisms of ion channel genes in COVID-19 and clues for developing therapeutic strategies for COVID-19.

**Keywords**  Bioinformatics · Coronavirus disease 2019 (COVID-19) · Ion channels · Molecular characterisation · SARS-CoV-2

**Introduction**

The new coronavirus pneumonia disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is a severe respiratory disease, with the first case identified in December 2019. It has now spread worldwide and poses a serious threat to public health and economic conditions (Wiersinga et al. 2020; Coronaviridae Study Group of the International Committee on Taxonomy of Viruses 2020; Dhama et al. 2020; Bchetnia et al. 2020; Weston and Frieman 2020; Ahsan et al. 2021). After the COVID-19 outbreak, effective diagnostic methods and infectious disease control measures, such as new coronavirus nucleic acid detection, urban blockade and use of masks, were implemented throughout the country, which decreased the spread of the disease in some countries and regions (Lian et al. 2020). Despite the rapid and effective containment of COVID-19 outbreaks in multiple regions, the global spread of COVID-19 has not been effectively controlled in all affected countries to date (Zhang et al. 2020a). According to the data provided by the World Health Organization, as of 22 December 2020, 78,299,811 confirmed cases of COVID-19 and more than 1.7 million deaths were reported worldwide (Ahamad et al. 2020; Aktar et al. 2021; Uddin et al. 2021). In addition, by the end of May 2021, approximately, 169 million COVID-19 cases and more than 3.5 million deaths had been confirmed worldwide (Aktar et al. 2021; Auwul et al. 2021). COVID-19 has emerged as one of the most devastating and long-lasting epidemics affecting human health in the 21st century. Therefore, effectively controlling and treating COVID-19 are grave concerns worldwide. Unlike other severe infectious diseases, COVID-19 lacks a typical clinical presentation. Respiratory symptoms and others reported to be related to COVID-19 include fever, cough, headache, conjunctivitis, diarrhea and muscle or systemic pain (Rothan and Byrareddy 2020; Pascarella et al. 2020), which may be similar to the symptoms of other respiratory infections. Some patients may not have any symptoms after infection but may spread the disease. Moreover, specific drugs for treating COVID-19 have not yet been developed for clinical use, thus making the rapid diagnosis, effective control and
treatment of COVID-19 difficult. Therefore, the identification of novel biomarkers at different omic levels (genomic, transcriptional or proteomic) may facilitate large-scale screening, diagnosis and treatment of COVID-19 (Chen et al. 2021), which is crucial to reveal the underlying pathogenesis of COVID-19, develop novel therapeutic strategies, discover potential therapeutic targets and improve therapeutic efficacy.

Ion channels are specific membrane proteins present in all cell membranes and some organelle membranes (e.g., mitochondria, Golgi apparatus, endoplasmic reticulum and lysosomes) (Wu et al. 2019; Tao et al. 2016). Ion channel genes encode these specific membrane proteins (mainly pore-forming membrane proteins) expressed in each living cell, which are oligomeric protein complexes composed of multiple subunits with ion-selective and voltage-gating properties (Noskov and Roux 2007). These membrane proteins can precisely control the passive influx and efflux of signalling ions into and out of the cell, thereby regulating ion concentrations inside and outside the cell membrane, membrane potential and volume size of the cell (Kondratskyi et al. 2018). Ion channels are involved in various physiological activities (Becchetti 2011), including muscle contraction, hormone secretion, cell proliferation and immune responses (Camerino et al. 2008; Fiske et al. 2006; Roger et al. 2006), and play an important role in maintaining homeostasis of the intracellular environment. Ion channels include sodium (Na+), potassium (K+), calcium (Ca2+) and chloride (Cl-) ions and nonspecific cation channels (Lu et al. 2021a). Because ion channels play a key role in diverse biological functions, abnormal expression of ion channel genes plays a crucial role in many diseases (Sun et al. 2020). Ion channel genes are closely associated with tumour initiation and progression (e.g., breast cancer (Nelson et al. 2014), lung cancer (Ko et al. 2014), liver cancer (Lu et al. 2021b) and gastric cancer (Anderson et al. 2019)), epilepsy (Oyrer et al. 2018), kidney stones, hypertension, insulin secretion deficiency and cardiac arrhythmias (Jentsch et al. 2004). However, limited information is available regarding the molecular characteristics of ion channel genes involved in COVID-19. In addition to impairing the respiratory system, COVID-19 has been reported to present in multiple organs to produce various clinical manifestations, including cardiovascular, urological, musculoskeletal, and neurological symptoms (Chen et al. 2020), whereas ion channels are known to be highly enriched in the nervous system and cardiac organs. It has been suggested that ion channels may be involved in the inflammation, pain, fever, anosmia, ageusia, respiratory, cardiovascular, gastrointestinal and neurological complications caused by COVID-19 infection (Jaffal and Abbas 2021). Epilepsy has been reported in the literature to occur with COVID-19 infection (Nikbakht et al. 2020), and epilepsy is currently considered to be an ion channel-related disorder. Therefore, exploring the relevant features of ion channels in COVID-19 and understanding their biological mechanisms are crucial for the treatment of COVID-19.

In this study, we adopted an analytical strategy involving an integrated bioinformatic approach to explore the mechanism of ion channel-related genes in COVID-19. We used biological datasets and several online databases to identify relevant features of ion channel genes in COVID-19 and identified 29 ion channel-related differentially expressed genes (DEGs) in COVID-19. Based on this, several bioinformatic analyses were performed to understand the involvement of
these genes in the biological processes of the organism. In addition, we attempted to elucidate the pathogenic molecular mechanisms of these genes in COVID-19 and predict potential therapeutic agents. These differential genes have good application prospects for the diagnosis and treatment of COVID-19 and provide new perspectives for the discovery of potential biomarkers and drug targets of COVID-19.

Methods

Data Sources

To analyse the biological mechanisms and potential therapeutic targets of ion channel-related genes present in COVID-19, we obtained gene expression datasets (GSE152418 and GSE171110) from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/). GSE152418 is based on the Illumina NovaSeq 6000 (Homo sapiens) (GPL24676) platform for RNA-sequencing (RNA-Seq) data on COVID-19. This dataset contains information on 17 patients with COVID-19 and 17 healthy subjects, with samples collected from peripheral blood mononuclear cells (PBMCs), and was derived from the research contributions of Arunachalam et al. (2020). GSE171110 is based on the Illumina HiSeq 2500 (Homo sapiens) (GPL16791) platform for RNA-Seq data on COVID-19. This dataset contains information on 44 patients with COVID-19 and 10 healthy subjects, with samples collected from whole blood tissue, and was derived from the research contributions of Lévy et al. (2021). Table 1 shows the basic information of both datasets. Ion channel genes were downloaded from the HUGO Gene Nomenclature Committee (HGNC) database (http://www.genenames.org/), and a total of 330 ion channel genes were obtained.

Screening of Differential Genes

To identify ion channel-related DEGs, we downloaded the RStudio software (version 2022.02.0 + 443) (https://www.rstudio.com/), which is run on the R software (version 4.1.3) (https://www.r-project.org/). The RNA-Seq data of patients with COVID-19 (GSE152418 and GSE171110) were processed using RStudio based on the edgeR R package (version 3.36.0). The cut-off criteria of false discovery rate (FDR) < 0.05 and absolute value of log2-fold change (|logFC|) ≥ 1.0 were used to screen for significant DEGs in the abovementioned datasets. A Venn diagram was created using the VennDiagram R package (version 1.7.3) to show interacting genes by considering the intersection of DEGs obtained for each of the GSE152418 and GSE171110 datasets with the 330 ion channel-related genes. These interacting DEGs were used for subsequent analyses. Volcano plots were
Table 1 Two RNA-seq transcriptome datasets and differential gene number information for COVID-19

| ID       | Country | Platform | Source    | Healthy | COVID-19 | Up regulated DEGs count | Down regulated DEGs count | Total DEGs count |
|----------|---------|----------|-----------|---------|----------|-------------------------|--------------------------|------------------|
| GSE152418 | USA     | GPL24676 | PBMC      | 17      | 17       | 1905                    | 175                      | 2080             |
| GSE171110 | France  | GPL16791 | Whole Blood | 10      | 44       | 2620                    | 1366                     | 3986             |
drawn using the EnhancedVolcano R package (version 1.12.0) to show the differential genes in the GSE152418 and GSE171110 datasets.

**Functional and Pathway Enrichment Analyses**

A comprehensive gene set enrichment web tool, Enrichr (https://maayanlab.cloud/Enrichr/), was used for functional annotation and pathway enrichment analysis of DEGs (Chen et al. 2013; Kuleshov et al. 2016; Xie et al. 2021). Gene set enrichment analysis (GSEA) is an important effort that enables the classification and summarisation of common biological insights to help understand the underlying biological mechanisms of target gene sets (Subramanian et al. 2005). We used Gene Ontology (GO) terms for functional enrichment analysis, which included the three aspects of biological process (BP), cellular composition (CC) and molecular function (MF). The Kyoto Encyclopedia of Genes and Genomes (KEGG), WikiPathways and Reactome databases were used as data sources for pathway enrichment analysis. An adjusted \( p \) value of <0.05 was considered statistically significant GO terms and pathways.

**Protein–Protein Interaction Networks and Screening of Hub Genes**

In cell biology and systems biology, the evaluation and analysis of protein–protein interaction (PPI) networks and their functions are fundamental and key to the interpretation and understanding of cellular activities (Szklarczyk et al. 2019; Ewing et al. 2007; Ben-Hur and Noble 2005). We input the 29 identified DEGs into the STRING database (https://string-db.org/) to generate PPI networks (Szklarczyk et al. 2017). Furthermore, we downloaded the Cytoscape software (version 3.9.1) (https://cytoscape.org/) and imported the constructed PPI networks into this software for further processing and analysis (Shannon et al. 2003; Smoot et al. 2011). The Cytoscape software is an open platform that includes a number of plug-ins with scalable visualisation options and network analysis (Shannon et al. 2003). We used the cytoHubba plug-in in the Cytoscape software (http://apps.cytoscape.org/apps/cytohubba) to screen for hub genes. CytoHubba is a plug-in for ranking and extracting central, potential or targeted elements of a biological network based on various network features and contains 11 methods to score networks based on different perspectives, with the best one being Maximal Clique Centrality (MCC) at present (Chin et al. 2014). We used the MCC method to identify the top 10 hub genes in the PPI network.

**Transcriptional and Post-transcriptional Regulatory Networks Analyses**

Transcription factors (TFs) are proteins that attach to specific genes and control the rate of transcription of genetic information (Caramori et al. 2013). MicroRNAs (miRNAs) are a class of short, endogenously initiated and non-coding RNAs that repress or degrade messenger RNAs (mRNAs) through translation, thereby controlling gene expression at the post-transcriptional level (Cai et al. 2009). TFs and
miRNAs are essential for molecular biology research. We used the online web tool NetworkAnalyst (Zhou et al. 2019; Xia et al. 2015) (https://www.networkanalyst.ca/) to construct TF–DEG and DEG–miRNA regulatory networks to analyse relevant TFs and miRNAs. The TF–DEG network was established using the JASPAR database. JASPAR is a publicly available repository that provides maps of TFs for multiple species in six major taxa (Khan et al. 2018). The DEG–miRNA network was established using the TarBase database. TarBase is the main experimental validity database for miRNAs interacting with target genes (Sethupathy et al. 2006).

**Gene–Disease Association Analysis**

We analysed DEGs using the DisGeNET database through the online web tool NetworkAnalyst to examine the association of these DEGs with diseases. DisGeNET is a comprehensive database exploring the association of genes and diseases based on various biomedical aspects of diseases, which synchronises relationships from multiple sources (Pinero et al. 2017). It provides and highlights new insights into the study of human genetic diseases (Pinero et al. 2020).

**Protein–Drug Interaction Analysis**

It is important to predict protein–drug interaction (PDI) based on target genes or identify potential drug molecules. We used the gene set enrichment network tool Enrichr based on the Drug Signature Database (DSigDB) to identify potential drugs that significantly interact with genes through PPI network pairs of the screened 10 hub genes (Yoo et al. 2015). DSigDB is a free web-based resource repository containing relevant information on drugs and their target genes for GSEA (Yoo et al. 2015). DSigDB currently contains a total of 22,527 gene sets, including 17,389 drugs and 19,531 genes (Auwul et al. 2021; Mahmud et al. 2021). An adjusted $p$ value of $<0.05$ was set as the statistical criteria for identifying drugs significantly associated with target genes.

**Results**

**Identification of Differentially Expressed Genes**

The COVID-19 datasets GSE152418 and GSE171110 from the GEO database were used for analysis. We used the RStudio software to process the data using the edgeR R package. The criteria for screening DEGs were as follows: FDR $<0.05$ and $|\text{logFC}| \geq 1.0$. In the GSE152418 dataset, a total of 2080 genes were screened; of which, 1905 were upregulated and 175 were downregulated. In the GSE171110 dataset, a total of 3986 genes were screened; of which, 2620 were upregulated and 1366 were downregulated. Table 1 shows information regarding the number of DEGs in the two datasets. The VennDiagram R package was used for Venn analysis. The 330 ion channel-related genes obtained from the HGNC database were
intersected with the DEGs of the GSE152418 and GSE171110 datasets, and 29 ion channel-related DEGs were eventually identified. Table 2 shows the expression information of 29 DEGs in the GSE152418 and GSE171110 datasets. The Venn diagram is shown in Fig. 1A. The visualization of differential genes in the GSE152418 and GSE171110 datasets is shown in Fig. 1B and C.

### GO and Pathway Enrichment Analyses

GO and pathway enrichment analyses were performed to identify the biological significance and enriched pathways of the 29 DEGs of interest using the online

Table 2  Expression information of 29 DEGs in the GSE152418 and GSE171110 datasets

| Gene   | GSE152418 |  | GSE171110 |  |
|--------|-----------|---|-----------|---|
|        | Log2FC    | FDR | Type | Log2FC | FDR | Type |
| KCNN3  | 3.875565247 | 5.06E−22 | Up | 3.71805478 | 7.96E−14 | Up |
| CACNA2D3 | −1.934427624 | 7.81E−11 | Down | −3.224177117 | 7.06E−17 | Down |
| SCN1B  | 1.694963987 | 1.59E−10 | Up | 1.925623978 | 4.24E−09 | Up |
| KCNA2  | 1.88179351 | 4.16E−06 | Up | 1.043307154 | 0.003261774 | Up |
| AQP10  | 1.853616625 | 6.08E−06 | Up | 1.891566838 | 0.001042295 | Up |
| ANO2   | 2.739331713 | 1.02E−05 | Up | 2.601512862 | 3.36E−06 | Up |
| CACNA1E | 1.951378596 | 5.47E−05 | Up | 1.782979464 | 4.19E−05 | Up |
| GJA4   | 2.811774491 | 9.77E−05 | Up | 2.209293255 | 0.00160142 | Up |
| CACNA1A| 1.03471284 | 0.000146293 | Up | 1.332922487 | 2.75E−05 | Up |
| CATSPERD | 2.776130738 | 0.000226835 | Up | 1.504241193 | 0.026799943 | Up |
| TRPC1  | −1.033107512 | 0.00024422 | Down | −1.457710412 | 1.73E−06 | Down |
| KCNT2  | 2.646145885 | 0.000286884 | Up | 3.745253923 | 0.000357053 | Up |
| TRPM1  | 2.259304259 | 0.000323608 | Up | 1.657205891 | 0.001286955 | Up |
| ASIC4  | 2.064311007 | 0.000479613 | Up | 1.69682146 | 0.00085695 | Up |
| NALCN  | 2.206464254 | 0.000638513 | Up | 1.675033515 | 0.000173107 | Up |
| KCNG2  | 1.50487903 | 0.001142459 | Up | 3.019338629 | 1.24E−05 | Up |
| TRPM3  | 2.010824749 | 0.001300631 | Up | 1.281553025 | 0.00692089 | Up |
| AQP9   | 1.060161386 | 0.001965165 | Up | 1.185764556 | 0.000137696 | Up |
| GRIK5  | 1.698068032 | 0.002540449 | Up | 1.232928314 | 0.000137696 | Up |
| KCNJ4  | 2.11639305 | 0.00385028 | Up | 3.155367763 | 0.001483182 | Up |
| CHRNA2 | 1.659963162 | 0.005103148 | Up | 1.82443945 | 0.000381008 | Up |
| KCNA5  | −1.170337718 | 0.005329720 | Down | −1.790680806 | 0.004616677 | Down |
| GABRD  | 1.656924477 | 0.00725023 | Up | 1.481505214 | 0.030444915 | Up |
| SCN1B  | 2.131785521 | 0.009464007 | Up | 3.803559267 | 3.58E−08 | Up |
| TRPV5  | 1.442177547 | 0.010570825 | Up | 2.045644869 | 1.65E−05 | Up |
| CHRNB2 | 1.154450485 | 0.022489232 | Up | 1.760804737 | 5.78E−05 | Up |
| CNGB1  | 1.505139155 | 0.027513742 | Up | 1.175020522 | 0.000297923 | Up |
| GJB5   | 1.361208469 | 0.034618091 | Up | 1.373879663 | 0.003175905 | Up |
| CACNA2D1 | 1.767534655 | 0.041805155 | Up | 3.068993135 | 0.003340999 | Up |
web tool Enrichr. GO analysis included the following three categories: BP, CC and MF. GO enrichment analysis revealed that DEGs in BP were significantly enriched in ‘inorganic cation transmembrane transport’, ‘calcium ion transport’ and ‘calcium ion transmembrane transport’. The bar graph is shown in Fig. 2A. DEGs in CC were significantly enriched in ‘integral component of plasma membrane’, ‘voltage-gated potassium channel complex’, ‘potassium channel complex’ and ‘voltage-gated calcium channel complex’. The bar graph is shown in Fig. 2B. DEGs in MF were significantly enriched in the categories ‘ion channel activity’, ‘ligand-gated cation channel activity’, ‘calcium channel activity’, ‘voltage-gated cation channel activity’ and ‘cation channel activity’. The bar graph is shown in Fig. 2C. Table 3 enlists the top 10 terms enriched by DEGs in BP, CC and MF.

Pathway analysis is a technique to deduce the interaction between various diseases by modelling a molecular or biological process underlying the organism (Wittig and De Beuckelaer 2001), which can reveal the organism’s response to its intrinsic modifications. Three global databases, KEGG, WikiPathways and Reactome, were used as data sources for pathway enrichment analysis. The analysis showed that DEGs in the KEGG database were significantly enriched in ‘nicotine
Fig. 2 GO enrichment analysis bar plot of DEGs obtained by Enrichr web tool. A Biological processes; B Cellular composition; C Molecular function
| Category                          | ID          | Term                                      | Adjusted p-value | Number | Genes                                                                 |
|----------------------------------|-------------|-------------------------------------------|------------------|--------|------------------------------------------------------------------------|
| **Biological Process**           | GO:0098662  | Inorganic cation transmembrane transport  | 7.47E-17         | 14     | KCNJ4; KCNG2; TRPC1; KCNA2; CACNA1A; KCNA5; NALCN; TRPV5; KCNN3; SCN1B; TRPM3 |
|                                 | GO:0006816  | Calcium ion transport                     | 4.47E-12         | 9      | TRPM1; CHRN8B2; TRPC1; CACNA2D1; TRPV5; CACNA1A; CACNA1E; NALCN; TRPM3 |
|                                 | GO:0070588  | Calcium ion transmembrane transport      | 2.18E-09         | 7      | TRPM1; TRPC1; CACNA2D1; TRPV5; CACNA1A; NALCN; TRPM3                   |
|                                 | GO:0006812  | Cation transport                          | 5.05E-09         | 8      | TRPM1; KCNJ4; KCNG2; SCN1B; KCNA2; KCNA5; TRPM3; SCN1B                 |
|                                 | GO:0071805  | Potassium ion transmembrane transport    | 3.64E-08         | 7      | KCNJ4; KCNG2; KCNT2; KCNA2; KCNA5; KCNN3; NALCN                       |
|                                 | GO:0030001  | Metal ion transport                       | 8.77E-08         | 6      | CHRN8B2; TRPC1; CACNA2D1; TRPV5; CACNA1A; CACNA1E                    |
|                                 | GO:0006813  | Potassium ion transport                   | 5.42E-07         | 6      | KCNJ4; KCNG2; KCNA2; KCNA5; KCNN3; NALCN                            |
|                                 | GO:0051899  | Membrane depolarization                   | 3.07E-06         | 4      | CHRN8B2; CACNA1A; CACNA1E; SCN1B                                     |
|                                 | GO:0006811  | Ion transport                             | 1.40E-05         | 5      | CHRN8B2; CHRNA2; KCNN3; TRPM3; SCN1B                                 |
|                                 | GO:0090276  | Regulation of peptide hormone secretion  | 7.08E-05         | 4      | KCNG2; CACNA1A; KCNA5; CACNA1E                                      |
| **Cellular Component**           | GO:0005887  | Integral component of plasma membrane    | 2.99E-11         | 17     | KCNJ4; CHRN8B2; KCNG2; CHRNA2; AQP10; TRPC1; KCNA2; AQP9; KCNA5; TRPM3 |
|                                 | GO:0008076  | Voltage-gated potassium channel complex   | 5.75E-05         | 4      | KCNJ4; KCNG2; KCNA2; KCNA5                                          |
|                                 | GO:0034705  | Potassium channel complex                 | 5.75E-05         | 4      | KCNJ4; KCNG2; KCNA2; KCNA5                                          |
|                                 | GO:0005891  | Voltage-gated calcium channel complex     | 9.89E-05         | 3      | CATSPERD; CACNA2D1; CACNA2D3                                        |
|                                 | GO:0034702  | Ion channel complex                       | 0.0001114755     | 3      | CHRN8B2; CHRNA2; TRPC1                                              |
|                                 | GO:0034703  | Cation channel complex                    | 0.000861526      | 3      | TRPC1; SCN1B; KCNA5                                                  |
| Category ID | Term                                | Adjusted p-value | Number | Genes                        |
|-------------|-------------------------------------|------------------|--------|------------------------------|
| GO:0005892  | Acetylcholine-gated channel complex | 0.000861526      | 2      | CHRNB2;CHRNA2                |
| GO:0005922  | Connexin complex                    | 0.001728713      | 2      | GJA4;GJB5                    |
| GO:0005921  | Gap junction                        | 0.001968584      | 2      | GJA4;GJB5                    |
| GO:0034706  | Sodium channel complex              | 0.001968584      | 2      | SCNN1B;SCN1B                 |
| Molecular Function | GO:0005216 | Ion channel activity | 1.86E−13 | 9 | TRPM1;CHRNB2;ASIC4;GRIK5;TRPC1;TRPV5;NALCN;TRPM3;CNGB1 |
| GO:0099094  | Ligand-gated cation channel activity| 6.55E−10         | 7      | KCNJ4;CHRNB2;ASIC4;CHRNA2;GRIK5;SCNN1B;KCNN3 |
| GO:0005262  | Calcium channel activity            | 6.55E−10         | 7      | TRPM1;TRPC1;CACNA2D1;TRPV5;CACNA2D3;CACNA1A;CACNA1E |
| GO:0022843  | Voltage-gated cation channel activity| 1.18E−09        | 7      | KCNG2;CACNA2D1;KCNA2;CACNA2D3;CACNA1A;KCNA5;CACNA1E |
| GO:0005261  | Cation channel activity             | 1.18E−09         | 7      | TRPM1;TRPC1;KCNA2;TRPV5;CACNA1E;NALCN;TRPM3 |
| GO:0005249  | Voltage-gated potassium channel activity| 2.20E−08      | 6      | KCNJ4;KCNG2;KCNT2;KCNA2;KCNA5;KCNN3 |
| GO:0005267  | Potassium channel activity          | 2.06E−06         | 5      | KCNG2;KCNT2;GRIK5;KCNA2;KCNA5 |
| GO:0005245  | Voltage-gated calcium channel activity| 2.15E−06       | 4      | CACNA2D1;CACNA2D3;CACNA1A;CACNA1E |
| GO:0005272  | Sodium channel activity             | 2.15E−06         | 4      | ASIC4;GRIK5;SCNN1B;SCN1B     |
| GO:0015267  | Channel activity                    | 4.24E−06         | 4      | ASIC4;AQP10;AQP9;TRPV5       |
Fig. 3 Pathway enrichment analysis bar plot of DEGs obtained by Enrichr web tool. A KEGG; B WikiP-pathways; C Reactome
addiction’, ‘cholinergic synapse’, ‘glutamatergic synapse’, ‘MAPK signaling pathway’, ‘adrenergic signaling in cardiomyocytes’, ‘neuroactive ligand-receptor interaction’ and ‘oxytocin signaling pathway’. The bar graph is shown in Fig. 3A. DEGs in the WikiPathways database were significantly enriched in ‘calcium regulation in the cardiac cell’, ‘MAPK signaling pathway’ and ‘arrhythmogenic right ventricular cardiomyopathy’. The bar graph is shown in Fig. 3B. DEGs in the Reactome database were significantly enriched in ‘neuronal system’, ‘stimuli-sensing channels’ and ‘ion channel transport’. The bar graph is shown in Fig. 3C. Table 4 provides information regarding the top 10 pathways enriched by DEGs in the three databases, namely, KEGG, WikiPathways and Reactome.

PPI Networks and Hub Genes

PPI analysis was performed using the STRING database to identify key molecules. We input the 29 DEGs into the STRING database to generate a PPI network, setting the minimum required interaction score (MIS) to 0.150 and hiding disconnected nodes in the network. The analysis revealed that this PPI network contained 29 nodes and 161 edges (Fig. 4A). In the PPI network, the most interconnected nodes were considered hub genes. We imported the PPI network results into the Cytoscape software for network visualisation, and hub genes were screened using the MCC method in the cytoHubba plug-in. The top 10 hub genes screened were KCNA2, KCNJ4, CACNA1A, CACNA1E, NALCN, KCNA5, CACNA2D1, TRPC1, TRPM3 and KCNN3. The hub gene network is presented in Fig. 4B, and relevant information regarding these 10 hub genes is provided in Table 5. These hub genes may be potential biomarkers for COVID-19.

Correlation Analysis of DEGs with TFs and miRNAs

To understand the transcriptional and post-transcriptional regulatory characteristics of DEGs, TF–DEG and DEG–miRNA interaction networks were constructed using the network database. The TF–DEG network contained 86 nodes and 193 edges, and TFs closely associated with DEGs were FOXC1, GATA2, HINFP, USF2, JUN and NFKB1. The TF–DEG network is presented in Fig. 5. The miRNA–DEG network contained 161 nodes and 246 edges, and miRNAs closely associated with DEGs were hsa-mir-146a-5p, hsa-mir-27a-3p, hsa-mir-335-5p, hsa-let-7b-5p and hsa-mir-129–2-3p. The DEG–miRNA network is shown in Fig. 6. These TFs and miRNAs may play an important regulatory role on DEGs.

Analysis of the Association between DEGs and Diseases

Different diseases may have one or more genes in common, making it possible for diseases to be interrelated (Al-Mustanjid et al. 2020). Discovering associations between genes and diseases can help in the development and design of disease treatment strategies (Moni and Lio 2014). The online web tool
| Category          | Term                                      | Adjusted \( p \)-value | Number | Genes                                                                 |
|------------------|-------------------------------------------|-------------------------|--------|-----------------------------------------------------------------------|
| KEGG 2021 Human  | Nicotine addiction                       | 0.000966407             | 3      | CHRNB2;CACNA1A;GABRD                                                 |
|                  | Cholinergic synapse                       | 0.007295400             | 3      | KCNJ4;CHRNB2;CACNA1A                                                 |
|                  | Glutamatergic synapse                     | 0.007295400             | 3      | GRIK5;TRPC1;CACNA1A                                                 |
|                  | MAPK signalling pathway                   | 0.007465173             | 4      | CACNA2D1;CACNA2D3;CACNA1A;CACNA1E                                    |
|                  | Adrenergic signalling in cardiomyocytes   | 0.007465173             | 3      | CACNA2D1;CACNA2D3;SCN1B                                              |
|                  | Neuroactive ligand-receptor interaction   | 0.007465173             | 4      | CHRNB2;CHRNA2;GRIK5;GABRD                                           |
|                  | Oxytocin signalling pathway               | 0.007465173             | 3      | KCNJ4;CACNA2D1;CACNA2D3                                             |
|                  | Type II diabetes mellitus                 | 0.009340756             | 2      | CACNA1A;CACNA1E                                                     |
| WikiPathway 2021 | Calcium Regulation in the Cardiac Cell WP536 | 0.001559627             | 4      | GJA4;GJB5;CACNA1A;CACNA1E                                           |
| Human            | MAPK Signalling Pathway WP382             | 0.005206294             | 4      | CACNA2D1;CACNA2D3;CACNA1A;CACNA1E                                    |
|                  | Arrhythmogenic Right Ventricular Cardiomyopathy WP2118 | 0.042832475            | 2      | CACNA2D1;CACNA2D3                                                   |
|                  | Cell-type Dependent Selectivity of CCK2R Signalling WP3679 | 0.087319584            | 1      | TRPC1                                                                |
|                  | Osteoclast Signalling WP12                | 0.087319584             | 1      | TRPV5                                                                |
|                  | 15q13.3 copy number variation syndrome WP4942 | 0.087319584           | 1      | TRPM1                                                                |
|                  | Nicotine Activity on Dopaminergic Neurons WP1602 | 0.087319584           | 1      | CHRNB2                                                               |
|                  | PKC-gamma calcium signalling pathway in ataxia WP4760 | 0.087319584            | 1      | CACNA1A                                                              |
|                  | Type II diabetes mellitus WP1584          | 0.087319584             | 1      | CACNA1A                                                              |
|                  | GABA receptor Signalling WP4159           | 0.095884738             | 1      | GABRD                                                                |
| Category | Term | Adjusted $p$-value | Number | Genes |
|----------|------|-------------------|--------|-------|
| Reactome 2016 | Neuronal System Homo sapiens R-HSA-112316 | 3.05E − 13 | 12 | KCNJ4;CHRNB2;KCNG2;CHRNA2;GRIK5;CACNA2D1;KCNA2;CACNA2D3;CACNA1A;KCNA5;KCNN3;CACNA1E |
| | Stimuli-sensing channels Homo sapiens R-HSA-2672351 | 3.93E − 11 | 8 | TRPM1;ASIC4;TRPC1;SCNN1B;TRPV5;NALCN;TRPM3;ANO2 |
| | Ion channel transport Homo sapiens R-HSA-983712 | 7.95E − 09 | 8 | TRPM1;ASIC4;TRPC1;SCNN1B;TRPV5;NALCN;TRPM3;ANO2 |
| | Transmission across Chemical Synapses Homo sapiens R-HSA-112315 | 8.10E − 09 | 8 | KCNJ4;CHRNB2;CHRNA2;GRIK5;CACNA2D1;CACNA2D3;CACNA1A;CACNA1E |
| | Depolarization of the Presynaptic Terminal Triggers the Opening of Calcium Channels Homo sapiens R-HSA-112308 | 3.43E − 08 | 4 | CACNA2D1;CACNA2D3;CACNA1A;CACNA1E |
| | Transmembrane transport of small molecules Homo sapiens R-HSA-382551 | 6.76E − 08 | 10 | TRPM1;ASIC4;AQP10;TRPC1;SCNN1B;AQP9;TRPV5;NALCN;TRPM3;ANO2 |
| | TRP channels Homo sapiens R-HSA-3295583 | 4.29E − 07 | 4 | TRPM1;TRPC1;TRPV5;TRPM3 |
| | Potassium Channels Homo sapiens R-HSA-1296071 | 2.47E − 06 | 5 | KCNJ4;KCNG2;KCNA2;KCNA5;KCNN3 |
| | Cardiac conduction Homo sapiens R-HSA-5576891 | 1.02E − 05 | 5 | KCNJ4;TRPC1;CACNA2D1;CACNA2D3;SCN1B |
| | Muscle contraction Homo sapiens R-HSA-397014 | 5.73E − 05 | 5 | KCNJ4;TRPC1;CACNA2D1;CACNA2D3;SCN1B |
Fig. 4  PPI network analysis of DEGs. A PPI network obtained from STRING database. B 10 hub genes screened by cytoscape software.
Table 5  Information of the 10 hub genes screened by PPI network analysis

| Rank | Gene symbol | Gene name                                | Chromosome | Group name                                           | Score  |
|------|-------------|------------------------------------------|------------|------------------------------------------------------|--------|
| 1    | KCNA2       | Potassium voltage-gated channel subfamily A member 2 | 1p13.3     | Potassium voltage-gated channels                     | 180,284|
| 2    | KCNJ4       | Potassium inwardly rectifying channel subfamily J member 4 | 22q13.1     | Potassium inwardly rectifying channel subfamily J    | 177,840|
| 3    | CACNA1A     | Calcium voltage-gated channel subunit alpha1 A | 19p13.13    | Calcium voltage-gated channel alpha1 subunits        | 173,700|
| 4    | CACNA1E     | Calcium voltage-gated channel subunit alpha1 E | 1q25.3      | Calcium voltage-gated channel alpha1 subunits        | 173,592|
| 5    | NALCN       | Sodium leak channel, non-selective        | 13q32.3-q33.1 | Sodium leak channels, non-selective                   | 138,376|
| 6    | KCNA5       | Potassium voltage-gated channel subfamily A member 5 | 12p13.32    | Potassium voltage-gated channels                     | 124,560|
| 7    | CACNA2D1    | Calcium voltage-gated channel auxiliary subunit alpha2-delta 1 | 7q21.11     | Calcium voltage-gated channel auxiliary alpha2-delta subunits | 105,192|
| 8    | TRPC1       | Transient receptor potential cation channel subfamily C member 1 | 3q23       | Transient receptor potential cation channels         | 82,254 |
| 9    | TRPM3       | Transient receptor potential cation channel subfamily M member 3 | 9q21.12-q21.13 | Transient receptor potential cation channels        | 81,414 |
| 10   | KCNN3       | Potassium calcium-activated channel subfamily N member 3 | 1q21.3     | Potassium calcium-activated channels                 | 63,386 |
NetworkAnalyst was used to obtain a DEG–disease association network, which contained 248 nodes and 280 edges. We found that intellectual disability and cerebellar ataxia were more closely associated with the DEGs. This finding suggests that COVID-19 may be associated with intellectual disability and cerebellar ataxia. The DEG–disease association network is presented in Fig. 7.

**Drug Prediction Analysis**

Assessment and analysis of protein–drug interactions are essential to understand the structural features required for receptor sensitivity (Mahmud et al. 2020; Mosharaf et al. 2020). In addition to investigating protein–drug interactions, we screened for candidates that could affect COVID-19. We considered the screened 10 hub genes as drug targets and performed drug-target enrichment analysis using the online web tool Enrichr based on DSigDB. The results showed that the drugs gabapentin, gabapentin enacarbil, pregabalin, guanidine hydrochloride and 4-aminopyridine, which act on five pivotal genes, namely, CACNA2D1,
CACNA1A, CACNA1E, KCNA2 and KCNA5, respectively, may be potential drugs for the treatment of patients with COVID-19. Table 6 provides relevant information regarding these drugs.

**Discussion**

COVID-19 is an emerging and rapidly growing pandemic with increasing infection and mortality rates worldwide (Team CC-R, 2020). COVID-19 has spread worldwide and poses a significant threat to humans. The current situation has prompted researchers to discover effective treatments against COVID-19 (Kumar et al. 2021). The causative agent of COVID-19, SARS-CoV-2, is highly pathogenic to humans. However, it is currently poorly understood, and specific treatments for COVID-19 remain unexplored. Hence, it is difficult to overcome this life-threatening prevalent disease (Li et al. 2021). Therefore, it is important to use bioinformatic methods to analyse the characteristics and pathogenesis of COVID-19 and discover novel
therapeutic targets for the development of effective drugs and vaccines, thus providing a basis for public health decision-making (Ma et al. 2021). Ion channels are pore-forming membrane proteins that allow the passage of ions through the channel pore. Their functions include establishing the resting membrane potential (Abdul Kadir et al. 2018), shaping action potentials and other electrical signals by controlling ion flow across cell membranes, controlling ion flow in secretory and epithelial cells and regulating cell volume. Ion channels play an important role in various biological functions (Sun et al. 2020). However, the role of ion channel genes in COVID-19 remains unclear.

In this study, we used an integrated bioinformatic approach to gain insights into the associated features of ion channel-related genes in COVID-19. A total of 29 ion channel-related DEGs were identified in two RNA-Seq datasets (GSE152418 and GSE171110) containing data derived from the blood tissues of 61 patients with COVID-19 and 27 healthy subjects and including 330 ion channel gene sets. To
| Drug Name               | Adjusted $p$-value | Chemical formula | Structure | Genes                        |
|------------------------|--------------------|------------------|-----------|------------------------------|
| Gabapentin             | 5.13E − 06         | C$_9$H$_{17}$NO$_2$ | ![Gabapentin Structure] | CACNA2D1; CACNA1A; CACNA1E |
| Gabapentin enacarbil   | 5.13E − 06         | C$_{16}$H$_{27}$NO$_6$ | ![Gabapentin Enacarbil Structure] | CACNA2D1; CACNA1A; CACNA1E |
| Pregabalin             | 5.13E − 06         | C$_8$H$_{17}$NO$_2$ | ![Pregabalin Structure] | CACNA2D1; CACNA1A; CACNA1E |
| Guanidine hydrochloride| 0.001705731        | CH$_6$ClN$_3$     | ![Guanidine Hydrochloride Structure] | KCNA2; KCNA5 |
| 4-aminopyridine        | 0.001705731        | C$_2$H$_6$N$_2$   | ![4-Aminopyridine Structure] | KCNA2; KCNA5 |
examine the biological significance of these DEGs in the pathogenesis of COVID-19, we performed GO and pathway analyses on the DEGs. GO is a general theoretical model in gene regulation that outlines the functions of genes and their interrelationships (Al-Mustanjid et al. 2020). It develops progressively through the acquisition of biological knowledge regarding gene function and its regulation based on linguistic relationships among various ontological categories (Rana et al. 2019). The GO database was used as an annotation source for ontology to analyse the three categories, namely, BP, CC and MF, of the target genes. According to GO term interpretation, BP is the molecular activity, CC is the cellular structure in which genes regulate their function and MF is a description of activity at the molecular level (Moni and Lio 2015). Pathway analysis is a modern scientific strategy that helps to understand and reveal how biologically or molecularly complex diseases are connected and is the best way to obtain an organism’s response triggered by internal changes (Rana et al. 2020). In this study, GO enrichment analysis revealed that the DEGs were integral components of the plasma membrane (CC) and were significantly enriched in relevant functions such as inorganic cation transmembrane transport (BP) and ion channel activity (MF), and these processes mainly involved calcium and potassium channels. Furthermore, pathway enrichment analysis revealed that the DEGs were significantly enriched in pathways related to nicotine addiction (KEGG), calcium regulation in the cardiac cell (WikiPathways) and the neuronal system (Reactome). Calcium channels are activated upon membrane depolarisation to conduct calcium ions into the cell and organelles while initiating many physiological responses, including secretion, contraction and gene transcription (Zamponi et al. 2015). Calcium channel mutations and their dysfunctions have been associated with several diseases, such as disorders of the cardiovascular system (e.g., hypertension, arrhythmias and heart failure (Liao and Soong 2010; Venetucci et al. 2012)), periodic skeletal muscle paralysis (Jurkat-Rott and Lehmann-Horn 2006), impaired insulin release and islets β-cell apoptosis in patients with diabetes (Yang et al. 2014), chronic pain and migraine (Bourinet et al. 2014; Kowalska et al. 2021) and numerous brain disorders (Heyes et al. 2015; Ortner and Striessnig 2016). However, the mechanism of action of calcium channels in COVID-19 remains unclear. Several studies (Neuraz et al. 2020; Peng et al. 2021; Kow et al. 2022) have suggested that the use of calcium channel blockers (CCBs), which reduce mortality in patients with COVID-19, has a therapeutic effect on COVID-19. However, other studies have reported (Mancia et al. 2020) that CCBs have no significant therapeutic effect on COVID-19 but increase the risk of tracheal intubation and death in patients with COVID-19 (Mendez et al. 2021). Potassium channels are located on the cell membrane and control the efflux and influx of potassium ions out of and into the cell (Kuang et al. 2015). They play a crucial role in both excitable and non-excitable cells. They are found in almost all species except some parasites (Kuo et al. 2005). The role of potassium channels in COVID-19 remains unknown; however, several studies have highlighted that multiple anti-COVID-19 drugs and inflammatory cytokines can interfere with cardiac potassium channels, such as the use of antibiotics (azithromycin and fluoroquinolones), antimalarials (hydroxychloroquine and chloroquine) and antivirals (lopinavir/ritonavir and atazanavir). In addition, some tyrosine kinase inhibitors (vandetanib) can inhibit hERG potassium channels and/
or impair channel transport, thereby causing prolongation of the QT interval and increasing the risk of ventricular arrhythmias (Carpenter et al. 2020; Cubeddu et al. 2022). The smoke of inhaled cigarettes contains nicotine. Smoke particles carry nicotine to the pulmonary organs and are rapidly absorbed into the pulmonary venous circulation and subsequently into the arterial circulation, from where they move rapidly to the brain and bind to nicotinic cholinergic receptors (ligand-gated ion channels that normally bind to acetylcholine), producing and maintaining tobacco addiction (nicotine addiction) by acting on nicotinic cholinergic receptors in the brain and triggering the release of dopamine and other neurotransmitters, which is a major cause of disability and premature death in patients (Benowitz 2010). Although the association of smoking with the morbidity and mortality of a wide range of respiratory infections is well recognised, it remains unclear in COVID-19. Studies have suggested that active smokers do not have a high prevalence of COVID-19, which may be related to the ability of smoking to modulate angiotensin-converting enzyme-2 (ACE2) expression; however, the exact effects remain unclear (Usman et al. 2021). A recent study reported that smoking and nicotine may upregulate ACE2 (Brake et al. 2020). If smoking can upregulate ACE2, it may be a protective factor for COVID-19 (Verdecchia et al. 2020). However, studies published before the COVID-19 pandemic have reported that smoking and nicotine contribute to the downregulation of ACE2 (Oakes et al. 2018), which may promote increased expression of ACE2 receptors and viral receptors in smokers, thus increasing the opportunity for SARS-CoV-2 to invade the body (Berlin et al. 2020). However, the role of nicotine in COVID-19 requires further investigation. The regulatory role of calcium ions as intracellular second messengers (Bers 2008) in the heart is self-evident. It is well known that myocardial contraction is controlled by intracellular calcium ion concentration changes. The concentration of calcium ions in cardiomyocytes should be high enough to activate contractile proteins to pump blood out of the heart. During diastole, the concentration of calcium ions in cardiomyocytes should decrease to a sufficiently low level, which in turn relaxes the heart muscles so that the heart chamber becomes congested (Eisner 2018). This process relies on the regulation of calcium ion concentration, in which calcium channels play an important role. Studies have suggested a potential susceptibility of cardiomyocytes to COVID-19 (Yang et al. 2021). Cardiomyocytes contain abundant calcium ion channels; therefore, calcium regulation in cardiomyocytes may be one of the mechanisms of myocardial injury in patients with COVID-19. Ion channel-related genes, initially considered to be associated with inherited excitability disorders in the muscle and heart, play an important role in the molecular diagnosis of central nervous system diseases (Noebels 2017). Ion channels underlie the genesis of nerve impulses and are therefore an important component of the nervous system. Related studies have reported that SARS-CoV-2 can invade the nervous system (Liu et al. 2021; Mukerji and Solomon 2021) and heart (Van Cleemput et al. 2021) in humans. In this study, enrichment analysis suggested that ion channel-related genes play an important role. Overall, the results of GO and pathway analyses in this study partly explained the molecular basis and mechanism of action of the identified DEGs in the pathogenesis of COVID-19.
PPI networks are used to decode the key signalling molecules in molecular networks (Rahman et al. 2019). In this study, PPI network analysis revealed the most important hub proteins. We built a PPI network based on the 29 DEGs and screened 10 hub genes from them, which may be key drug targets or biomarkers for COVID-19. The KCNA2 gene encodes potassium voltage-gated channel subfamily A member 2, which is a member of the oscillator-like delayed rectifier potassium channel family (Corbett et al. 2016). It is mainly expressed in axons and presynaptic terminals in the central nervous system (Gu et al. 2003; Lorincz and Nusser 2008). It is now known that KCNA2 mutations can cause various neurological disorders, such as epileptic encephalopathy, mental retardation and motor disorders caused by cerebellar dysfunction (Doring et al. 2021). The KCNJ4 gene encodes potassium voltage-gated channel subfamily J member 4, which is an inward rectifier potassium channel family member. Studies have shown that KCNJ4 is associated with the progression and poor prognosis of lung adenocarcinoma (Wu and Yu 2019), dilated cardiomyopathy (Szuts et al. 2013) and prostate cancer (Kim et al. 2016). The CACNA1A gene encodes a subunit of the voltage-dependent P/Q-type calcium channel α-1A (Zhang et al. 2020b), and the CACNA1E gene encodes a subunit of the voltage-dependent R-type calcium channel α-1E (Helbig et al. 2018). These genes are widely expressed throughout the central nervous system and are strongly associated with epilepsy and intellectual developmental disorders (Hommersom et al. 2021; Royer-Bertrand et al. 2021). In addition, CACNA1E is of potential therapeutic value in non-small cell lung cancer (Gao et al. 2022). The NALCN gene encodes a non-selective cation channel that conducts a permanent sodium leak current and regulates the resting membrane potential and neuronal excitability associated with respiration, locomotion and circadian rhythms (Bramswig et al. 2018; Lutas et al. 2016; Shi et al. 2016). NALCN is essential for mammalian survival; however, the gating, ion selectivity and pharmacological properties of NALCN remain unclear (Chua et al. 2020; Kschonsak et al. 2020). The KCNA5 gene encodes potassium voltage-gated channel subfamily A member 5, which is involved in the regulation of several functions including cardiac action potential, vascular smooth muscle cell activity, insulin release and tumour cell proliferation (Bossini-Castillo et al. 2012; Ahmed et al. 2016). The CACNA2D1 gene encodes a calcium voltage-gated channel α2δ-1 subunit, which enhances channel transport, increases the expression of functional calcium channels at the plasma membrane and affects the biophysical properties of the channel (Dolphin 2012). It has been widely implicated in the regulation of neuronal excitability, action potential firing patterns and neurotransmission in nociceptive pathways (Gribkoff 2006). The TRPC1 gene encodes the transient C-potential subfamily channel 1 (Zeng et al. 2021), which is involved in the regulation of intracellular calcium ion concentration and plays an important role in cell proliferation, differentiation, apoptosis and migration and is expressed in almost all normal tissues and many tumours (Berridge et al. 2000; Zeng et al. 2016). Studies have shown that TRPC1 is a therapeutic target against herpes simplex virus type 1 (He et al. 2020). The TRPM3 gene encodes the transient receptor potential channel melastatin subfamily member 3, which is a non-selective calcium ion-permeable cation channel that can be activated by diverse stimuli including heat, osmotic pressure and chemically related activators (Held and Toth 2021). It activates/modulates
calcium channels or transporters by guiding calcium ions through their pores or regulating membrane potential, which in turn increases the levels of intracellular calcium (Wu et al. 2010). TRPM3 is a recognised temperature receptor in the peripheral sensory neurons of the dorsal root ganglion, and mutations in TRPM3 in humans have recently been reported to be associated with epilepsy and intellectual disability (Zhao et al. 2020). KCNN3 encodes a neuronal small-conductance calcium-activated potassium channel containing two polyglutamine chains, which plays a key role in determining neuronal firing patterns and regulating intracellular calcium channels (Curtain et al. 2005). In this study, we screened 10 hub genes via the PPI network using COVID-19 datasets; however, the associated features are not reported. These genes may be potential therapeutic targets for COVID-19.

Because gene expression regulation is controlled by TFs and miRNAs at the transcriptional and post-transcriptional levels, changes in these molecules may provide critical information regarding the dysregulated expression of the 29 DEGs. Among the identified TFs, FOXC1, GATA2 and NFKB1 have been identified as important regulators of COVID-19 (Islam et al. 2020). HINFP, a histone cell cycle regulator, is a unique zinc-finger TF (Medina et al. 2008). Upstream stimulatory factor 2 (USF2), a TF involved in various cellular processes that is essential for maintaining reactive oxygen radical levels and mitochondrial morphology and function, is particularly prominent in tumour development (Chi et al. 2020). JUN is a subunit of activator protein 1 (an inducible transcription factor composed of multiple protein complexes), which plays a role in many types of cellular differentiation and inflammatory processes (Chang et al. 2013) and plays a specific role in the regulation of angiogenesis and endothelial cell proliferation (Yoshitomi et al. 2021). miRNAs are emerging as attractive biomarkers in numerous diseases. Among the identified miRNAs, hsa-mir-146a-5p is thought to regulate natural killer cells (innate lymphocytes with cytotoxic properties), thereby allowing the host to play an important role in early defence against infectious pathogens and surveillance against tumours (Pesce et al. 2018). The gene encoding hsa-mir-27a-3p is located on human chromosome 19, and its downregulation promotes tumour cell proliferation and the development of neurological diseases and is an important suppressor in diseases (Wu et al. 2015; Sala Frigerio et al. 2013). hsa-mir-335-5p plays an important role in regulating cardiac differentiation (Kay et al. 2019). hsa-let-7b-5p is a potential therapeutic target for tuberculosis (Tripathi et al. 2018). However, these miRNAs have not been reported to be associated with COVID-19 thus far. In conclusion, the TFs and miRNAs identified based on bioinformatic analyses in this study may serve as important regulators in the pathogenesis of COVID-19. In addition, we analysed the gene–disease relationship to predict the association of DEGs with diseases and found that intellectual disability and cerebellar ataxia were strongly associated with DEGs and may share common pathogenic features with COVID-19. It has been reported that the intellectually challenged population is at a greater risk of developing COVID-19 (Turk et al. 2020). Neurological symptoms have been suggested as potential complications of COVID-19, and cerebellar ataxia is a rare post-infectious or post-parainfection immune-mediated phenomenon associated with COVID-19 (Chan et al. 2021). The DEGs identified in this study may act as a “bridge” in these diseases. Finally, we used DSigDB to identify drugs that may target the five screened pivotal
genes, namely, CACNA2D1, CACNA1A, CACNA1E, KCNA2 and KCNA5. These drugs included gabapentin, gabapentin enacarbil, pregabalin, guanidine hydrochloride and 4-aminopyridine. Among these drugs, gabapentin can treat cough induced by acute and chronic COVID-19 infection, thereby reducing clinical symptoms (Song et al. 2021). Pregabalin may play a role in reducing the mortality of COVID-19 (Oddy et al. 2021). Guanidine alkaloids may have strong antiviral activity, thus providing a basis for the study of anti-COVID-19 (El-Demerdash et al. 2021). Further biological and clinical studies of these candidates are recommended to evaluate their potential therapeutic significance in patients with COVID-19.

In this study, we used bioinformatic analyses to investigate the features of ion channel-related genes associated with COVID-19 to identify key candidate genes and their regulatory molecules, examine the gene–disease association and discover potential therapeutic agents. To improve the reliability of the results, we used two datasets with data derived from blood tissues for analysis to avoid the influence of sample size and different tissue samples on the results. However, this study has some limitations owing to the lack of clinical validation of the identified molecules. Therefore, further validation is required to interpret the results.

Conclusions

In this study, we examined the molecular features of ion channel genes associated with COVID-19. On analysing the RNA-Seq transcriptome datasets (GSE152418 and GSE171110) and 330 ion channel-related genes downloaded from the HGNC database, we identified 29 DEGs. GO analysis revealed that these DEGs were integral components of the plasma membrane (CC) and were enriched in inorganic cation transmembrane transport (BP) and ion channel activity (MF). Pathway analysis revealed that the DEGs were enriched in pathways related to nicotine addiction (KEGG), calcium regulation in the cardiac cell (WikiPathways) and the neuronal system (Reactome). PPI networks were constructed using 29 DEGs, and 10 important hub genes (KCNA2, KCNJ4, CACNA1A, CACNA1E, NALCN, KCNA5, CACNA2D1, TRPC1, TRPM3 and KCNN3) were identified. Significant TFs (FOXC1, GATA2, HINFP, USF2, JUN and NFkB1) and miRNAs (hsa-mir-146a-5p, hsa-mir-27a-3p, hsa-mir-335-5p, hsa-let-7b-5p and hsa-mir-129–2-3p) were identified through the TF–DEG and DEG–miRNA networks. The DEG–disease association network revealed that intellectual disability and cerebellar ataxia were highly associated with these DEGs. Drug–target enrichment analysis based on DSigDB identified relevant drugs (gabapentin, gabapentin enacarbil, pregabalin, guanidine hydrochloride and 4-aminopyridine) targeting five hub genes (CACNA2D1, CACNA1A, CACNA1E, KCNA2 and KCNA5, respectively), which may have potential value for the treatment of COVID-19. Because the present study was based on bioinformatic analyses, further clinical studies should be performed to validate the identified molecular features. We hope that the results of this study will be helpful for the rapid control of COVID-19.
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Author contributions
Conception and design: HZ; Administrative support: HZ; Provision of study materials or patients: HZ, TF; Collection and assembly of data: HZ, TF; Data analysis and interpretation: HZ, TF; Manuscript writing: All authors; Final approval of manuscript: All authors.

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Data Availability
The datasets analysed in the study are available at the public database NCBI GEO (https://www.ncbi.nlm.nih.gov/geo/). All data generated or analysed during this study are included in this published article.

Declarations

Conflict of Interest
The authors declare that they have no conflict of interest.

References

Abdul Kadir L, Stacey M, Barrett-Jolley R (2018) Emerging roles of the membrane potential: action beyond the action potential. Front Physiol 9:1661. https://doi.org/10.3389/fphys.2018.01661
Ahamad MM, Akhtar S, Rashid Al-Mahfuz M, Uddin S, Lio P, Xu H et al (2020) A machine learning model to identify early stage symptoms of SARS-CoV-2 infected patients. Expert Syst Appl 160:113661. https://doi.org/10.1016/j.eswa.2020.113661
Ahamd M, Fezai M, Uzcategui NL, Hosseinzadeh Z, Lang F (2016) SGK3 sensitivity of voltage gated K+ channel Kv1.5 (KCNA5). Cell Physiol Biochem 38(1):359–367. https://doi.org/10.1159/000438636
Ahsan MA, Liu Y, Feng C, Zhou Y, Ma G, Bai Y et al (2021) Bioinformatics resources facilitate understanding and harnessing clinical research of SARS-CoV-2. Brief Bioinform 22(2):714–725. https://doi.org/10.1093/bib/bbaa416
Aktor S, Talukder A, Ahamad MM, Kamal AHM, Khan JR, Protikuzzaman M et al (2021) Machine learning approaches to identify patient comorbidities and symptoms that increased risk of mortality in COVID-19. Diagnostics (Basel) 11(8):1383. https://doi.org/10.3390/diagnostics11081383
Al-Mustanjid M, Mahmud SMH, Royel MRI, Rahman MH, Islam T, Rahman MR et al (2020) Detection of molecular signatures and pathways shared in inflammatory bowel disease and colorectal cancer: a bioinformatics and systems biology approach. Genomics 112(5):3416–3426. https://doi.org/10.1016/j.ygeno.2020.06.001
Anderson KJ, Cormier RT, Scott PM (2019) Role of ion channels in gastrointestinal cancer. World J Gastroenterol 25(38):5732–5772. https://doi.org/10.3748/wjg.v25.i38.5732
Arunachalam PS, Wimmers F, Mok CKP, Perera R, Scott M, Hagan T et al (2020) Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. Science 369(6508):1210–1220. https://doi.org/10.1126/science.abc6261
Auwul MR, Zhang C, Rahman MR, Shahjaman M, Alyami SA, Moni MA (2021) Network-based transcriptomic analysis identifies the genetic effect of COVID-19 to chronic kidney disease patients: a bioinformatics approach. Saudi J Biol Sci 28(10):5647–5656. https://doi.org/10.1016/j.sjbs.2021.06.015
Bchetnia M, Girard C, Duchaine C, Laprise C (2020) The outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): a review of the current global status. J Infect Public Health 13(11):1601–1610. https://doi.org/10.1016/j.jiph.2020.07.011
Becchetti A (2011) Ion channels and transporters in cancer: 1. Ion channels and cell proliferation in cancer. Am J Physiol Cell Physiol 301(2):C255–C265. https://doi.org/10.1152/ajpcell.0047.2011
Ben-Hur A, Noble WS (2005) Kernel methods for predicting protein-protein interactions. Bioinformatics 21(Suppl 1):i38–i46. https://doi.org/10.1093/bioinformatics/bti1016
Benowitz NL (2010) Nicotine addiction. N Engl J Med 362(24):2295–2303. https://doi.org/10.1056/NEJMra0809890
Cubbedu LX, de la Rosa D, Ameruso M (2022) Antiviral and anti-inflammatory drugs to combat COVID-19: Effects on cardiac ion channels and risk of ventricular arrhythmias. Bioimpacts 12(1):9–20

Curtain R, Sundholm J, Lea R, Ovcaric M, MacMillan J, Griffiths L (2005) Association analysis of a highly polymorphic CAG Repeat in the human potassium channel gene KCNN3 and migraine susceptibility. BMC Med Genet 6:32. https://doi.org/10.1186/1471-2350-6-32

Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS et al (2020) Coronavirus disease 2019-COVID-19. Clin Microbiol Rev 33(4):e00028-e120. https://doi.org/10.1128/CMR.00028-20

Dolphin AC (2012) Calcium channel auxiliary alpha2delta and beta subunits: trafficking and one step beyond. Nat Rev Neurosci 13(8):542–555. https://doi.org/10.1038/nrn3311

Doring JH, Schotro J, Jungling J, Biskup S, Klotz KA, Bast T et al (2021) Refining genotypes and phenotypes in KCNA2-related neurological disorders. Int J Mol Sci 22(6):2824. https://doi.org/10.3390/ijms22062824

Eisner DA (2018) Ups and downs of calcium in the heart. J Physiol 596(1):19–30. https://doi.org/10.1113/JP275130

El-Demerdash A, Metwaly AM, Hassan A, Abd El-Aziz TM, Elkaeed EB, Essa IH et al (2021) Comprehensive virtual screening of the antiviral potentialities of marine polycyclic guanidine alkaloids against SARS-CoV-2 (COVID-19). Biomolecules 11(3):460. https://doi.org/10.3390/biom11030460

Ewing RM, Chu P, Elisma F, Li H, Taylor P, Climie S et al (2007) Large-scale mapping of human protein-protein interactions by mass spectrometry. Mol Syst Biol 3:89. https://doi.org/10.1038/msb4100134

Fiske JL, Fomin VP, Brown ML, Duncan RL, Sikes RA (2006) Voltage-sensitive ion channels and cancer. Cancer Metastasis Rev 25(3):493–500. https://doi.org/10.1007/s10555-006-9017-z

Gao SH, Wang GZ, Wang LP, Feng L, Zhou YC, Yu XJ et al (2022) Mutations and clinical significance of calcium voltage-gated channel subunit alpha 1E (CACNA1E) in non-small cell lung cancer. Cell Calcium 102:102527. https://doi.org/10.1016/j.ceca.2022.102527

Gribkoff VK (2006) The role of voltage-gated calcium channels in pain and nociception. Semin Cell Dev Biol 17(5):555–564. https://doi.org/10.1016/j.semcdb.2006.09.002

Gu C, Jan YN, Jan LY (2003) A conserved domain in axonal targeting of Kv1 (Shaker) voltage-gated potassium channels. Science 301(5633):646–649. https://doi.org/10.1126/science.1086998

He D, Mao A, Li Y, Tam S, Zheng Y, Yao X et al (2020) TRPC1 participates in the HSV-1 infection process by facilitating viral entry. Sci Adv 6(12):eaaz3367. https://doi.org/10.1126/sciadv.aaz3367

Helbig KL, Lauerer RJ, Bahr JC, Souza IA, Myers CT, Uysal B et al (2018) De novo pathogenic variants in CACNA1E cause developmental and epileptic encephalopathy with contractures, macrocephaly, and dyskinesias. Am J Hum Genet 103(5):666–678. https://doi.org/10.1016/j.ajhg.2018.09.006

Held K, Toth BI (2021) TRPM3 in brain (Patho)physiology. Front Cell Dev Biol 9:635659. https://doi.org/10.3389/fcell.2021.635659

Heyes S, Pratt WS, Rees E, Dahimene S, Ferron L, Owen MJ et al (2015) Genetic disruption of voltage-gated calcium channels in psychiatric and neurological disorders. Prog Neurobiol 134:36–54. https://doi.org/10.1016/j.pneurobio.2015.09.002

Hommersom MP, van Prooije TH, Pennings M, Schouten MI, van Bokhoven H, Kamsteeg EJ et al (2021) The complexities of CACNA1A in clinical neurogenetics. J Neurol. https://doi.org/10.1007/s00415-021-10897-9

Islam T, Rahman MR, Aydin B, Beklen H, Arga KY, Shahjaman M (2020) Integrative transcriptomics of lung epithelial cells and identification of repurposable drug candidates for COVID-19. Eur J Pharmacol 887:173594. https://doi.org/10.1016/j.ejphar.2020.173594

Jaffal SM, Abbas MA (2021) TRP channels in COVID-19 disease: potential targets for prevention and treatment. Chem Biol Interact 345:109567. https://doi.org/10.1016/j.chembi.2021.109567

Jentsch TJ, Hubner CA, Fuhrmann JC (2004) Ion channels: function unravelled by dysfunction. Nat Cell Biol 6(11):1039–1047. https://doi.org/10.1038/nclb1104-1039

Jurkat-Rott K, Lehmann-Horn F (2006) Paroxysmal muscle weakness: the familial periodic paralyses. J Neurol 253(11):1391–1398. https://doi.org/10.1007/s00415-006-0339-0

Kay M, Soltani BM, Aghdehaf FAH, Ansari H, Baharvand H (2019) Hsa-miR-335 regulates cardiac mesoderm and progenitor cell differentiation. Stem Cell Res Ther 10(1):191. https://doi.org/10.1186/s13287-019-1249-2
Khan A, Fornes O, Stigliani A, Gheorghe M, Castro-Mondragon JA, van der Lee R et al (2018) JASPAR 2018: update of the open-access database of transcription factor binding profiles and its web framework. Nucleic Acids Res 46(D1):D260–D266. https://doi.org/10.1093/nar/gkx1126
Kim YS, Kim Y, Choi JW, Oh HE, Lee JH (2016) Genetic variants and risk of prostate cancer using pathway analysis of a genome-wide association study. Neoplasma 63(4):629–634. https://doi.org/10.4149/neo_2016_418
Ko JH, Gu W, Lim I, Bang H, Ko EA, Zhou T (2014) Ion channel gene expression in lung adenocarcinoma: potential role in prognosis and diagnosis. PLoS ONE 9(1):e86569. https://doi.org/10.1371/journal.pone.0086569
Kondratskyi A, Kondratska K, Skryma R, Klionsky DJ, Prevarskaya N (2018) Ion channels in the regulation of autophagy. Autophagy 14(1):3–21. https://doi.org/10.1002/aut.22871
Kow CS, Ramachandram DS, Hasan SS (2022) Clinical outcomes of hypertensive patients with COVID-19 receiving calcium channel blockers: a systematic review and meta-analysis. Hypertens Res 45(2):360–363. https://doi.org/10.1080/01445983.2021.1834266
Kowalska M, Prendeeck M, Piektut K, Kozubska W, Dorszewska J (2021) Migraine: calcium channels and glia. Int J Mol Sci 22(5):2688. https://doi.org/10.3390/ijms22052688
Kschonsak M, Chua HC, Noland CL, Weidling C, Clairfeuille T, Bahlke OO et al (2020) Structure of the human sodium leak channel NALCN. Nature 587(7833):313–318. https://doi.org/10.1038/s41586-020-2570-8
Kuang Q, Purhonon P, Hebert H (2015) Structure of potassium channels. Cell Mol Life Sci 72(19):3677–3693. https://doi.org/10.1007/s00018-015-1948-5
Kuleshov MV, Jones MR, Rouillard AD, Fernandez NF, Duan Q, Wang Z et al (2016) Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. Nucleic Acids Res 44(W1):W90–W97. https://doi.org/10.1093/nar/gkw377
Kumar R, Kumar V, Lee KW (2021) A computational drug repurposing approach in identifying the cephalosporin antibiotic and anti-hepatitis C drug derivatives for COVID-19 treatment. Comput Biol Med 130:104186. https://doi.org/10.1016/j.compbiomed.2020.104186
Kuo MM, Haynes WJ, Loukin SH, Kung C, Saimi Y (2005) Prokaryotic K(+) channels: from crystal structures to diversity. FEMS Microbiol Rev 29(5):961–985. https://doi.org/10.1016/j.femsre.2005.03.003
Levy Y, Wiedemann A, Hejblum BP, Durand M, Lefebvre C, Surenaud M et al (2021) CD177, a specific marker of neutrophil activation, is associated with coronavirus disease 2019 severity and death. iScience 24(7):102711. https://doi.org/10.1016/j.isci.2021.102711
Li R, Li Y, Liang X, Yang L, Su M, Lai KP (2021) Network pharmacology and bioinformatics analyses identify intersection genes of niacin and COVID-19 as potential therapeutic targets. Brief Bioinform 22(6):1279–1290. https://doi.org/10.1093/bib/bbaa300
Lian X, Huang J, Huang R, Liu C, Wang L, Zhang T (2020) Impact of city lockdown on the air quality of COVID-19-hit of Wuhan city. Sci Total Environ 742:140556. https://doi.org/10.1016/j.scitotenv.2020.140556
Liao P, Soong TW (2010) CaV1.2 channelopathies: from arrhythmias to autism, bipolar disorder, and immunodeficiency. Pflugers Arch 460(2):353–359. https://doi.org/10.1007/s00424-009-0753-0
Liu JM, Tan BH, Wu S, Gui Y, Suo JL, Li YC (2021) Evidence of central nervous system infection and neuroinvasive routes, as well as neurological involvement, in the lethality of SARS-CoV-2 infection. J Med Virol 93(3):1304–1313. https://doi.org/10.1002/jmv.26570
Lorincz A, Nusser Z (2008) Cell-type-dependent molecular composition of the axon initial segment. J Neurosci 28(53):14329–14340. https://doi.org/10.1523/JNEUROSCI.1383-08.2008
Lu A, Shi Y, Liu Y, Lin J, Zhang H, Guo Y et al (2021a) Integrative analyses identified ion channel genes GJB2 and SCN1B as prognostic biomarkers and therapeutic targets for lung adenocarcinoma. Lung Cancer 158:29–39. https://doi.org/10.1016/j.lungcan.2021.06.001
Lu S, Dai M, Hu X, Yi H, Zhang Y (2021b) A new survival model based on ion channel genes for prognostic prediction in hepatocellular carcinoma. Genomics 113(1 Pt 1):171–182. https://doi.org/10.1016/j.ygeno.2020.12.028
Lutas A, Lahmann C, Soumillon M, Yellen G (2016) The leak channel NALCN controls tonic firing and glycolytic sensitivity of substantia nigra pars reticulata neurons. Elife 5:e15271. https://doi.org/10.7554/eLife.15271
Ma L, Li H, Lan J, Hao X, Liu H, Wang X et al (2021) Comprehensive analyses of bioinformatics applications in the fight against COVID-19 pandemic. Comput Biol Chem 95:107599. https://doi.org/10.1016/j.compbiolchem.2021.107599
Mahmud SMH, Chen W, Meng H, Jahan H, Liu Y, Hasan SMM (2020) Prediction of drug-target interaction based on protein features using undersampling and feature selection techniques with boosting. Anal Biochem 589:113507. https://doi.org/10.1016/j.ab.2019.113507

Mahmud SMH, Al-Mustanjid M, Akter F, Rahman MS, Ahmed K, Rahman MH et al (2021) Bioinformatics and system biology approach to identify the influences of SARS-CoV-2 infections to idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease patients. Brief Bioinform 22(5):bbab115. https://doi.org/10.1093/bib/bbab115

Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G (2020) Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med 382(25):2431–2440. https://doi.org/10.1056/NEJMoa2006923

Medina R, Buck T, Zaidi SK, Miele-Chamberland A, Lian JB, Stein JL et al (2008) The histone gene cell cycle regulator HnIF-P is a unique zinc finger transcription factor with a novel conserved auxiliary DNA-binding motif. Biochemistry 47(44):11415–11423. https://doi.org/10.1021/bi800961d

Mendez SR, Frank RC, Stevenson EK, Chung M, Silverman MG (2021) Dihydropyridine Calcium Channel Blockers and the Risk of Severe COVID-19. Chest 160(1):89–93. https://doi.org/10.1016/j.chest.2021.01.073

Moni MA, Lio P (2014) comoR: a software for disease comorbidity risk assessment. J Clin Bioinforma 4:8. https://doi.org/10.1186/2043-9113-4-8

Moni MA, Lio P (2015) How to build personalized multi-omics comorbidity profiles. Front Cell Dev Biol 3:28. https://doi.org/10.3389/fcell.2015.00028

Mosharaf MP, Hassan MM, Ahmed FF, Khatun MS, Moni MA, Mollah MNH (2020) Computational prediction of protein ubiquitination sites mapping on Arabidopsis thaliana. Comput Biol Chem 85:107238. https://doi.org/10.1016/j.compbiolchem.2020.107238

Munker SS, Solomon IH (2021) What can we learn from brain autopsies in COVID-19? Neurosci Lett 742:135528. https://doi.org/10.1016/j.neulet.2020.135528

Nelson M, Millican-Slater R, Forrest LC, Brackenbury WJ (2014) The sodium channel beta1 subunit mediates outgrowth of neurite-like processes on breast cancer cells and promotes tumour growth and metastasis. Int J Cancer 135(10):2338–2351. https://doi.org/10.1002/ijc.28890

Neuraz A, Lerner I, Digan P, Paris N, Tsopra R, Rogier A et al (2020) Natural Language Processing for Rapid Response to Emergent Diseases: Case Study of Calcium Channel Blockers and Hypertension in the COVID-19 Pandemic. J Med Internet Res 22(8):e20773. https://doi.org/10.2196/20773

Nikkakh F, Mohammadkhizadeh A, Mohammadi E (2020) How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. Mult Scler Relat Disord 46:102535. https://doi.org/10.1016/j.msard.2020.102535

Noebels J (2017) Precision physiology and rescue of brain ion channel disorders. J Gen Physiol 149(5):533–546. https://doi.org/10.1085/jgp.201711759

Noskov SY, Roux B (2007) Importance of hydration and dynamics on the selectivity of the KcsA and NaK channels. J Gen Physiol 129(5):135–143. https://doi.org/10.1085/jgp.200609633

Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X (2018) Nicotine and the renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol 315(5):R895–R906. https://doi.org/10.1152/ajpregu.00099.2018

Oddy C, McCaul J, Keeling P, Allington J, Senn D, Soni N et al (2021) Pharmacological Predictors of Morbidity and Mortality in COVID-19. J Clin Pharmacol 61(10):1286–1300. https://doi.org/10.1002/jcph.1878

Oertner NJ, Striessnig J (2016) L-type calcium channels as drug targets in CNS disorders. Channels (Austin) 10(1):7–13. https://doi.org/10.1080/19336950.2015.1048936

Oyrier J, Maljevic S, Scheffer IE, Berkovic SF, Petrou S, Reid CA (2018) Ion Channels in Genetic Epilepsy: From Genes and Mechanisms to Disease-Targeted Therapies. Pharmacol Rev 70(1):142–173. https://doi.org/10.1124/pr.117.014456

Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F et al (2020) COVID-19 diagnosis and management: a comprehensive review. J Intern Med 288(2):192–206. https://doi.org/10.1111/joim.13091

Peng C, Wang H, Guo YF, Qi GY, Zhang CX, Chen T et al (2021) Calcium channel blockers improve prognosis of patients with coronavirus disease 2019 and hypertension. Chin Med J (Engl) 134(13):1602–1609. https://doi.org/10.1097/CMA.0000000000001479

Pesce S, Squillario M, Greppi M, Loiacono F, Moretta L, Moretta A et al (2018) New miRNA Signature Heralds Human NK Cell Subsets at Different Maturation Steps: Involvement of miR-146a-5p in the Regulation of KIR Expression. Front Immunol 9:2360. https://doi.org/10.3389/fimmu.2018.02360
Pinero J, Bravo A, Queralt-Rosinach N, Gutierrez-Sacristan A, Deu-Pons J, Centeno E et al (2017) DisGeNET: a comprehensive platform integrating information on human disease-associated genes and variants. Nucleic Acids Res 45(D1):D833–D839. https://doi.org/10.1093/nar/gkw943

Pinero J, Ramirez-Anguita JM, Sauch-Pitarach J, Ronzano F, Centeno E, Sanz F et al (2020) The DisGeNET knowledge platform for disease genomics: 2019 update. Nucleic Acids Res 48(D1):D845–D855. https://doi.org/10.1093/nar/gkz1021

Rahman MR, Islam T, Gov E, Turanli B, Gullidan G, Shahjaman M et al (2019) Identification of Prognostic Biomarker Signatures and Candidate Drugs in Colorectal Cancer: Insights from Systems Biology Analysis. Medicina (kaunas) 55(1):20. https://doi.org/10.3390/medicina5501002

Rana HK, Akhtar MR, Islam MB, Ahmed MB, Lio P, Quinn JMW et al (2019) Genetic effects of welding fumes on the development of respiratory system diseases. Comput Biol Med 108:142–149. https://doi.org/10.1016/j.compbiomed.2019.04.004

Rana HK, Akhtar MR, Islam MB, Ahmed MB, Lio P, Huq F et al (2020) Machine Learning and Bioinformatics Models to Identify Pathways that Mediate Influences of Welding Fumes on Cancer Progression. Sci Rep 10(1):2795. https://doi.org/10.1038/s41598-020-57916-9

Roger S, Potier M, Vandier C, Besson P, Le Guennec JY (2006) Voltage-gated sodium channels: new targets in cancer therapy? Curr Pharm Des 12(28):3681–3695. https://doi.org/10.2174/13816120678522047

Rothan HA, Byrareddy SN (2020) The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 109:102433. https://doi.org/10.1016/j.jaut.2020.102433

Royer-Bertrand B, Jequier Gygas M, Cisarova K, Rosenfeld JA, Bassetti JA, Moldovan O et al (2021) De novo variants in CACNA1E found in patients with intellectual disability, developmental regression and social cognition deficit but no seizures. Mol Autism 12(1):69. https://doi.org/10.1186/s13229-021-00473-3

Rushworthy P, Corda B, Hatzigeorgiou AG (2006) TarBase: A comprehensive database of experimentally supported animal microRNA targets. RNA 12(24):2103–2106. https://doi.org/10.1221/01.wnl.0000437306.37850.22

Sala Frigerio C, Lau P, Salta E, Tournoy J, Bossers K, Vandenberghe R et al (2013) Reduced expression of hsa-miR-27a-3p in CSF of patients with Alzheimer disease. Neurology 81(24):2103–2106. https://doi.org/10.1212/01.wnl.0000437306.37850.22

Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D et al (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 13(11):2498–2504. https://doi.org/10.1101/gr.1239303

Shi Y, Abe C, Holloway BB, Shu S, Kumar NN, Weaver JL et al (2016) Nalcn Is a “Leak” Sodium Channel That Natl Acad Sci U S A 102(43):15545–15550. https://doi.org/10.1073/pnas.0506580102

Song WJ, Hui CKM, Hull JH, Birring SS, McGarvey L, Mazzone SB et al (2021) Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. Lancet Respir Med 9(5):533–544. https://doi.org/10.1016/S2213-2600(21)00125-9

Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA et al (2005) Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proc Natl Acad Sci U S A 102(43):15545–15550. https://doi.org/10.1073/pnas.0506580102

Sun J, Yu X, Xue L, Li S, Li J, Tong D et al (2020) TP53-Associated Ion Channel Genes Serve as Prognostic Predictor and Therapeutic Targets in Head and Neck Squamous Cell Carcinoma. Technol Cancer Res Treat 19:1533033820972344. https://doi.org/10.1177/1533033820972344

Szklarczyk D, Morris JH, Cook H, Kuhn M, Wyder S, Simonovic M et al (2017) The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible. Nucleic Acids Res 45(D1):D362–D368. https://doi.org/10.1093/nar/gkw937

Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J et al (2019) STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genomewide experimental datasets. Nucleic Acids Res 47(D1):D607–D613. https://doi.org/10.1093/nar/gky1131

Szuts V, Menesi D, Varga-Orvos Z, Zvara A, Houshmand N, Bitay M et al (2013) Altered expression of genes for Kir ion channels in dilated cardiomyopathy. Can J Physiol Pharmacol 91(8):648–656. https://doi.org/10.1139/cjpp-2012-0413
Tao H, Chen X, Lu M, Wu Y, Deng M, Zeng X et al (2016) Molecular determinant for the tarantula toxin Jingzhaoxin-I slowing the fast inactivation of voltage-gated sodium channels. Toxicon 111:13–21. https://doi.org/10.1016/j.toxicon.2015.12.009

Team CC-R (2020) Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep 69(12):343–346. https://doi.org/10.15585/mmwr.mm6912e2

Tripathi A, Srivastava V, Singh BN (2018) hsa-let-7b-5p facilitates Mycobacterium tuberculosis survival in THP-1 human macrophages by Fas downregulation. FEMS Microbiol Lett 365(7).

Turk MA, Landes SD, Formica MK, Goss KD (2020) Intellectual and developmental disability and COVID-19 case-fatality trends: TriNetX analysis. Disabil Health J 13(3):100942. https://doi.org/10.1016/j.dhjo.2020.100942

Uddin S, Imam T, Moni MA, Thow AM (2021) Onslaught of COVID-19: How Did Governments React and at What Point of the Crisis? Popul Health Manag 24(1):13–19. https://doi.org/10.1089/pop.2020.0138

Usman MS, Siddiqui TJ, Khan MS, Patel UK, Shahid I, Ahmed J et al (2021) Is there a smoker’s paradox in COVID-19? BMJ Evid Based Med 26(6):279–284. https://doi.org/10.1136/bmjebm-2020-111492

Van Cleemput J, van Snippenberg W, Lambrechts L, Dendooven A, D’Onofrio V, Couck L et al (2021) Organ-specific genome diversity of replication-competent SARS-CoV-2. Nat Commun 12(1):6612. https://doi.org/10.1038/s41467-021-26884-7

Venetucci L, Denegri M, Napolitano C, Priori SG (2012) Inherited calcium channelopathies in the pathophysiology of arrhythmias. Nat Rev Cardiol 9(10):561–575. https://doi.org/10.1038/nrccardio.2012.93

Verdecchia P, Cavallini C, Spanevello A, Angeli F (2020) The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med 76:14–20. https://doi.org/10.1016/j.ejim.2020.04.037

Weston S, Frieman MB (2020) COVID-19: Knowns, Unknowns, and Questions. mSphere 5(2):e00203–20. https://doi.org/10.1128/mSphere.00203-20

Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC (2020) Pathophysiology, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA 324(8):782–793. https://doi.org/10.1001/jama.2020.12839

Wittig U, De Beuckelaer A (2001) Analysis and comparison of metabolic pathway databases. Brief Bioinform 2(2):126–142. https://doi.org/10.1093/bib/2.2.126

Wu XY, Yu XY (2019) Overexpression of KCNJ4 correlates with cancer progression and unfavorable prognosis in lung adenocarcinoma. J Biochem Mol Toxicol 33(4):e22270. https://doi.org/10.1002/jbt.22270

Wu T, Wang M, Wu W, Luo Q, Jiang L, Tao H et al (2019) Spider venom peptides as potential drug candidates due to their anticancer and antinociceptive activities. J Venom Anim Toxins Incl Trop Dis 25:e146318. https://doi.org/10.1590/1678-9199-JVATITD-14-63-18

Wu LJ, Sweet TB, Clapham DE (2010) International Union of Basic and Clinical Pharmacology. LXXVI. Current progress in the mammalian TRP ion channel family. Pharmacol Rev 62(3):381–404. https://doi.org/10.1124/pr.110.002725

Wu XZ, Wang KP, Song HJ, Xia JH, Jiang Y, Wang YL (2015) MiR-27a-3p promotes esophageal cancer cell proliferation via F-box and WD repeat domain-containing 7 (FBXW7) suppression. Int J Clin Exp Med 8(9):15556–15562. https://www.ncbi.nlm.nih.gov/pubmed/26629048.

Xia J, Gill EE, Hancock RE (2015) NetworkAnalyst for statistical, visual and network-based meta-analysis of gene expression data. Nat Methods 12(10):835–840. https://doi.org/10.1038/nmeth.3359

Xie Z, Bailey A, Kuleshov MV, Clarke DJB, Evangelista JE, Jenkins SL et al (2021) Gene Set Knowledge Discovery with Enrichr. Curr Protoc 13(3):e90. https://doi.org/10.1002/cpr.110.002725

Yang SN, Shi Y, Yang G, Li Y, Yu J, Berggren PO (2014) Ionic mechanisms in pancreatic beta cell signaling. Cell Mol Life Sci 71(21):4149–4177. https://doi.org/10.1007/s00018-014-1680-6

Yang J, Chen T, Zhou Y (2021) Mediators of SARS-CoV-2 entry are preferentially enriched in cardiomyocytes. Hereditas 158(1):4. https://doi.org/10.1186/s41065-020-00168-4

Yang J, Shin J, Kim J, Ryall KA, Lee K, Lee S et al (2015) DSIGDB: drug signatures database for gene set analysis. Bioinformatics 31(18):3069–3071. https://doi.org/10.1093/bioinformatics/btv313

Yoshitomi Y, Ikeda T, Saito-Takatsuji H, Yonekura H (2021) Emerging Role of AP-1 Transcription Factor JunB in Angiogenesis and Vascular Development. Int J Mol Sci 22(6):2804. https://doi.org/10.3390/ijms22062804

Springer
Zamponi GW, Striessnig J, Koschak A, Dolphin AC (2015) The Physiology, Pathology, and Pharmacology of Voltage-Gated Calcium Channels and Their Future Therapeutic Potential. Pharmacol Rev 67(4):821–870. https://doi.org/10.1124/pr.114.009654

Zeng C, Tian F, Xiao B (2016) TRPC Channels: Prominent Candidates of Underlying Mechanism in Neuropsychiatric Diseases. Mol Neurobiol 53(1):631–647. https://doi.org/10.1007/s12035-014-9004-2

Zeng YZ, Zhang YQ, Chen JY, Zhang LY, Gao WL, Lin XQ et al (2021) TRPC1 Inhibits Cell Proliferation/Invasion and Is Predictive of a Better Prognosis of Esophageal Squamous Cell Carcinoma. Front Oncol 11:627713. https://doi.org/10.3389/fonc.2021.627713

Zhang YH, Li H, Zeng T, Chen L, Li Z, Huang T et al (2020a) Identifying Transcriptomic Signatures and Rules for SARS-CoV-2 Infection. Front Cell Dev Biol 8:627302. https://doi.org/10.3389/fcell.2020.627302

Zhang L, Wen Y, Zhang Q, Chen Y, Wang J, Shi K et al (2020b) CACNA1A Gene Variants in Eight Chinese Patients With a Wide Range of Phenotypes. Front Pediatr 8:577544. https://doi.org/10.3389/fped.2020.577544

Zhao S, Yudin Y, Rohacs T (2020) Disease-associated mutations in the human TRPM3 render the channel overactive via two distinct mechanisms. Elife 9:e55634. https://doi.org/10.7554/eLife.55634

Zhou G, Soufan O, Ewald J, Hancock REW, Basu N, Xia J (2019) NetworkAnalyst 3.0: a visual analytics platform for comprehensive gene expression profiling and meta-analysis. Nucleic Acids Res 47(W1):W234-W241. https://doi.org/10.1093/nar/gkz240

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