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Research Article

Keywords: Virus and host, protein interaction networks, cellular pathways, antiviral compounds

Posted Date: August 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-622770/v2

Version of Record: A version of this preprint was published at Pathogens on February 17th, 2022. See the published version at https://doi.org/10.3390/pathogens11020259.

Deciphering the interactions of SARS-CoV-2 proteins with human ion channels using machine learning-based method

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the worldwide COVID-19 pandemic which began in 2019. It has a high transmission rate and pathogenicity leading to health emergencies and economic crisis. Recent studies pertaining to the understanding of the molecular pathogenesis of SARS-CoV-2 infection exhibited the indispensable role of ion channels in viral infection inside the host. Moreover, machine learning (ML)-based algorithms are providing higher accuracy for host-SARS-CoV-2 protein-protein interactions (PPIs). In this study, predictions of PPIs of SARS-CoV-2 proteins with human ion channels (HICs) were performed using PPI-MetaGO algorithm. The PPIs were predicted with 82.71% accuracy, 84.09% precision, 84.09% sensitivity, 0.89 AUC-ROC, 65.17% Matthews correlation coefficient (MCC) score and 84.09% F1 score. Thereafter, PPI networks of SARS-CoV-2 proteins with HICs were generated. Furthermore, biological pathway analysis of HICs interacting with SARS-CoV-2 proteins showed the involvement of six pathways, namely inflammatory mediator regulation of transient receptor potential (TRP) channels, insulin secretion, renin secretion, gap junction, taste transduction and apelin signaling pathway. Our analysis suggests that transient receptor potential cation channel subfamily M member 4 (TRPM4), transient receptor potential cation channel subfamily A member 1 (TRPA1), gap junction protein alpha 1 (GJA1), potassium calcium-activated channel subfamily N member 4 (KCNN4), acid sensing ion channel subunit 1 (ASIC1) and inositol 1,4,5-trisphosphate receptor type 1 (ITPR1) could serve as an initial set to the experimentalists for further validation. Additionally, various US food and drug administration (FDA) approved drugs interacting with the potential HICs were also identified. The study also reinforces the drug repurposing approach for the development of host directed antiviral drugs.

Key words: Virus and host**,** protein interaction networks, cellular pathways, antiviral compounds

1. Introduction

SARS-CoV-2 is the reason for the ongoing pandemic which started in 2019. It rapidly spread to more than 175 countries within the first three months (Huang et al. 2020). As of August 2021, more than 200 million confirmed cases have been reported with 4.26 million deaths worldwide (https://coronavirus.jhu.edu/). The dearth of approved treatments specific for SARS-CoV-2 infection impeded disease containment measures and control of the spread of infection. Viruses with small-sized genomes in particular, depend on the host genomic machinery for many of their essential functions via interacting with membrane proteins and regulating HICs (Charlton et al. 2020). HICs are transmembrane proteins which allow the passive flow of ions in and out of cells and cellular organelles owing to their electrochemical gradient. Because of the exchange of ions across the membrane that results in electrical currents, ion channels serve a diverse set of roles in generating membrane potential and cellular activities such as, signal transduction, synaptic release of neurotransmitters, hormone release, muscle activity, cell volume regulation motility, and apoptosis (Kim 2014). Dysfunction of HICs leads to a class of diseases called channelopathies (Kim 2014). Numerous viral infections are involved in neuronal pathologies, diarrhoea, cardiomyopathies, bronchitis and pain disorders exploiting a variety of HICs (Charlton et al. 2020).

Ebola and influenza viruses exploit HICs to enter the host by utilizing Ca^{2+} channels for viral entry (Fujioka et al. 2018; Simmons et al. 2015). Furthermore, activation of host potassium channels during the first six hours of viral infection by Bunyamwera virus were studied (Hover et al. 2017). Likewise, the use of L-type voltage gated Ca^{2+} channel inhibitor verapamil in the treatment of infection by filoviruses implicated the importance of HICs in viral survival (Hover et al. 2017). Deregulation of potassium channels may result in congenital hyperinsulinism and some rare forms of diabetes (Ashcroft 2005). Most likely, in order to survive and replicate inside a host, viruses must exploit the cellular environment which is highly dependent on the flow of ions into and out of the cell. HICs play a crucial role in viral infection by providing an entry point, supporting viral life cycle and disease progression (Gordon et al. 2020). Moreover, SARS-CoV-2 enters the host by the process of endocytosis and exploits HICs by elevating cytosolic calcium concentration which further aids in viral replication by inhibiting host protein trafficking and maturation of viral proteins (Glebov 2020; Jayaseelan and Paramasivam 2020; Wang et al. 2008).

In view of the host-viral interactions for viral replication there are many host factors that could be potential antiviral targets. Thus, HICs interacting with viral proteins are likely to be more effective antiviral targets. Moreover, the development of HIC-viral interactions provided an

insight that channelopathies may explain some commonly observed virus induced pathologies (Charlton et al. 2020). Systematic mapping of PPIs of SARS-CoV-2 and human proteins was studied by Gordon *et al.* for exploring host dependencies of the SARS-CoV-2 virus (Gordon et al. 2020). Furthermore, ML-based algorithms provided the confidence in predicted interactions to improve efficacy of wet lab experiments for drug designing (Sarkar and Saha 2019). PPIs between SARS-CoV-2 proteins and human proteins implementing ML approaches were also reported (Dey et al. 2020; Mei and Zhang 2019; Nourani et al. 2015).

This study focuses on the understanding of the interactome of SARS-CoV-2 proteins with HICs using ML-based algorithms. Protein-protein interaction networks (PPINs) of SARS-CoV-2 proteins with HICs were generated. Moreover, biological pathways analysis of HICs interacting with SARS-CoV-2 proteins was performed. Furthermore, FDA approved drugs interacting with potential HICs were identified. This study could provide an insight towards the better understanding of interaction of SARS-CoV-2 proteins with HICs and also underlines the potential significance of repurposing of drugs.

2. Prediction of interactions between SARS-CoV-2 proteins and HICs using PPI-MetaGO

To predict the PPIs between SARS-CoV-2 proteins and HICs a ML-based approach was used. An overview of the methodology followed to study the PPIs between SARS-CoV-2 and HICs is described in Figure 1.

2.1 Data collection

One of the most crucial steps while building any model based on a ML algorithm is the extraction and enhancement of a good dataset. Primarily, a list of 28 unique SARS-CoV-2 proteins were downloaded from the RefSeq database and 328 HICs were retrieved using the HGNC database (Bruford et al. 2008). Interactions between HICs and SARS-CoV-2 proteins were parsed using the BioGRID database (release 4.92.192). Dataset included 181 interactions of HICs with SARS-CoV-2 proteins (Supplementary Table 1) and 21 interactions among SARS-CoV-2 proteins (Supplementary Table 2). The positive dataset consists of 202 interactions that were used as input for PPI-MetaGO. PPIs of SARS-CoV-2 proteins with HICs are depicted as a network (Supplementary Figure 1). There are no ‘gold standard’ negative datasets available. Therefore, for PPIs prediction, protein pairs were chosen randomly from the set of protein pairs that are not known to interact, and treat them as a negative dataset (Ben-Hur and Noble 2006). For the negative set, first the complement graph of the positive interactions was made and random interactions were taken to generate the negative set. Furthermore, the

protein sequences were parsed using RefSeq database and gene ontology terms for SARS-CoV-2 proteins were downloaded from Gene Ontology knowledgebase (Ashburner et al. 2000; Seth Carbon 2021).

2.2 Feature extraction and stacked generalisation method for prediction

PPI-MetaGO algorithm (Chen et al. 2019a) was applied for the extraction of features of the protein pairs. It is an ensemble supervised meta learner algorithm for PPI prediction. The feature vectors consisting of physicochemical properties of proteins were extracted using protein sequences. Furthermore, semantic similarities were extracted using the provided GO terms (Chen et al. 2019a).

Dataset was split into a training and testing set of 80:20 ratios. Thereafter, protein sequences and the GO terms were provided as input to the PPI-MetaGO program for the calculation of features and prediction model building. Customized Python scripts were used for the generation of input for PPI-MetaGO. PPI-MetaGO uses a stacked generalisation method that allows combining multiple ML algorithms to maximise accuracy. Usage of a single ML-based method may lead to overfitting or underfitting of data even when the parameters are optimised maximally. Bagging and boosting which allow multiple ML-based algorithms only permit combining algorithms of the same type and focus on reducing the variance from multiple classifiers (Chen et al. 2019a). Stacked generalisation uses a meta-ML model which allows combination of different algorithms and aims to reduce the bias of the base generalisers (Ma et al. 2018). ML-based methods utilized by PPI-MetaGO include random forest, artificial neural network, Naïve Bayes, K-nearest neighbors and support vector machine.

2.3 Evaluation

The PPIs were evaluated using the following performance measures:

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN}$$

$$\text{Precision} = \frac{TP}{TP+FP}$$

$$\text{F-score} = \frac{2\ X\ TPR\ X\ Precision}{TPR+Precision}$$

$$\text{MCC} = \frac{TP\ X\ TN-FP\ X\ FN}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}}$$

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

$$\text{False Positive Rate} = \frac{FP}{FP+TN}$$

where TPR, TP, TN, FP, and FN represent true positive rate, true positive, true negative, false positive, and false negative, respectively. In addition, PPI-MetaGO also calculates area under the curve (AUC). AUC is the probability that a random positive sample will have a higher score than a random negative sample. Accuracy of 84.09% and AUC of 0.89 was obtained for SARS-CoV-2 and HIC interactions (Table 1). Confusion matrix obtained for the dataset represents 37 true positives, 7 false positives, 7 false negatives, and 30 true negatives (Table 2).

3. Protein-protein interactions of SARS-CoV-2 proteins with HICs

Of the 328 HICs, 40 were found to interact with SARS-CoV-2 proteins. Functions of HICs interacting with SARS-CoV-2 proteins are provided in Supplementary Table 3. ITPR1, inositol 1,4,5-trisphosphate receptor type 2 (ITPR2) and inositol 1,4,5-trisphosphate receptor type 3 (ITPR3) receptors were found to be involved in the release of calcium from the endoplasmic reticulum (ER) (Atakpa et al. 2018; Kuchay et al. 2018; Vervloessem et al. 2015; Wiel et al. 2014). ANO5, ANO6, ANO8, ANO10 belongs to anoctamin family that are calcium dependent channel proteins and may be accountable for the entry of viral proteins into the cells. (Bushell et al. 2019; Ishihara et al. 2016; Jha et al. 2019a; Lin et al. 2019; Lin et al. 2018; Oh and Jung 2016; Veit et al. 2018). Out of 40 HICs, a group of leucine rich volume regulated anion channels were identified. These proteins were involved in various functions such as, B cell development, maintenance of constant cell volume, efflux of amino acids and import of antibiotic blasticidin-S into the cells (Chen et al. 2019b; Lee et al. 2014; Lu et al. 2019; Lutter et al. 2017; Schober et al. 2017; Voss et al. 2014). The potassium voltage gated channels are known to act as modulators of potassium flow into the cell and also have a role in reactivation of naïve T-cells (Babenko et al. 1998; Cooper et al. 2017; Delaney et al. 2012; Du et al. 2013; Fu et al. 2017; Maekawa et al. 2014; Mederos et al. 2009; Srivastava et al. 2006; Srivastava et al. 2008; Tammaro and Ashcroft 2007; Yan et al. 2004; Zhang et al. 2016). Proteins belonging to the transient receptor potential cation channel family are known to have a role in signal transduction (Jha et al. 2019b; Xian et al. 2020; Zhao et al. 2020). The TRPM7 is both an ion channel as well as serine/threonine protein kinase (Lee et al. 2020). The proteins belonging to voltage dependent anion channels play a role involving Ca^{2+} ions during viral entry (Fujioka et al. 2018; Jitobaom et al. 2016; Luzio et al. 2007). Another important voltage gated channel showing interaction with the viral proteins were the chloride voltage gated channels which help in maintaining homeostasis and also contributes to acidification thus maintaining lysosomal pH (Bourdin et al. 2015; Hansen et al. 2020; Leisle et al. 2011; Muller et al. 2019; Yang et al. 2011).

Gap junction proteins may be involved in the cell to cell spread of the virus. GJA1 is a component of gap junctions which enables communication between adjacent cells. It was found to interact with M, nsp4, nsp6, ORF7a, ORF7b viral proteins. Viruses destroy cell junctions to invade the host (Dong et al. 2020). Also, another role of gap junctions reported in viral infection, was the amplification of antiviral signaling in neighbouring cells. It was studied that STING dependent recognition was essential for limiting virus replication in influenza virus (Platt et al. 2017). Thus, it could be inferred that gap junctions can act as a port of entry for the virus and may limit the immune reaction against SARS-CoV-2 infection (Ahn and Barber 2019). Also, gap junction proteins play a major role in contraction of the heart (Brink et al. 2020; Martins-Marques et al. 2020; Ye et al. 2017). One of the important HICs found to be interacting was the ASIC1 which is usually involved in learning, pain, sensation, memory and fear (Waldmann et al. 1997). PKD2, TPCN1, HCN2, SCN9A, GRID1, CHRNA5 and MCOLN3 were also identified. These proteins function as calcium permeable cation channel, voltage-gated calcium channels across lysosomal membranes, native pacemaker currents in heart, sodium selective channels allowing Na+ to pass according to electrochemical gradient, channels at synapses and cation channels for inwardly rectifying activity respectively (Ahuja et al. 2015; Brailoiu et al. 2009; Coverstone et al. 2018; Huttlin et al. 2017; Ludwig et al. 1999; Martina et al. 2009; Pena-Oyarzun et al. 2020). The glycine receptor beta protein is a part of ligand gated chloride channels (Handford et al. 1996). The GABRA5 is a component for heteropentameric receptor for gamma-aminobutyric acid (GABA) and may be involved in GABA-A receptor assembly (Butler et al. 2018).

3.1 PPIs maps of HICs-SARS-CoV-2 proteins

Predicted PPIs maps of HICs-SARS-CoV-2 proteins (Figure 2) were visualized using Cytoscape-3.8 (Shannon et al. 2003). E, M, ORF7b, ORF7a and nsp4 (Figure 2 - i, iii, iv, vii and ix) were found to be interacting with ITPR1, ITPR2 and ITPR3. Nsp6 and ORF8 (Figure 2 - viii and x) were identified to be interacting with ITPR2 and ITPR3. Also, S and ORF6 (Figure 2 - ii and vi) interacted with ITPR3. Viruses exploiting ITPRs were reported to affect the host by increasing metabolic stress and enterotoxicity (Clark and Eisenstein 2013). Moreover, it was reported that viral infections promote depletion of ER Ca^{2+} storage using ITPRs that in turn promote viral replication (Clark and Eisenstein 2013). Interaction of SARS-CoV-2 proteins with ITPRs may promote viral replication inside the host cells.

E, M, ORF7b, ORF3a, ORF7a, nsp6, nsp4 and ORF8 proteins (Figure 2 - i, iii, iv, v, vii, viii, ix and x) were found to be interacting with leucine rich repeat containing 8 VRAC subunit A

(LRRC8A). LRRC8A plays an important role in T-cell/ B-cell development. It also plays a role in development and function of lymphocytes (Platt et al. 2017). Thus, it could be that interaction between LRRC8A and SARS-CoV-2 proteins may play a role in impairment of T-cell development during the course of a disease.

M, ORF3a, nsp6 and nsp4 (Figure 2 - iii, v, viii and ix) were found to be interacting with voltage dependent anion channels VDAC2 and VDAC3 and E, ORF7b, ORF6, ORF7a, nsp14, nsp5 and nsp13 (Figure 2 - i, iv, vi, vii, xii, xiii, xiv) were found to be interacting with VDAC3. Voltage dependent anion channels (VDACs) were found to be involved in transportation of metabolites from mitochondria to ER during viral replication and interacting with structural and non-structural proteins (nsps) of dengue virus (Jitobaom et al. 2016).

It was known that the coronavirus family uses E protein to induce intracellular membrane remodelling generating new membrane vesicles which serve as a viral replication site. They were responsible for depolarisation of membranes (Arya et al. 2020). Furthermore, E protein helped in budding and release of virus particles (Arya et al. 2020). Likewise, the M protein along with E protein was responsible for the determination of virion assembly (Arya et al. 2020). The nsp3, nsp4 and nsp6 interacting with the HICs were also found to contain a transmembrane domain. These nsps were involved in host membrane remodelling and known to act as membrane anchors for replication and transcription complexes (Angelini et al. 2013; Snijder et al. 2016). This could shed light on the fact that these viral proteins have similar properties and may be involved in host invasion by mimicking the ion channels present in the host. This could as well be attributed to the presence of a signature sequence in the chlorella virus (PBCV-1) Kcv protein that showed architectural similarity with eukaryotic Kir channels (Wang et al. 2010). Hence it is important to understand the function of viroporins in the manipulation of host-specific processes. However, targeting them can be a challenge due to resistance polymorphism exhibited by viruses.

3.2 The protein-protein interaction networks (PPINs) of HICs-SARS-CoV-2 proteins

PPINs of HICs interacting with SARS-CoV-2 proteins were generated using STRING database (v11) (Szklarczyk et al. 2019). Furthermore, visualization of PPINs of HICs-SARS-CoV-2 proteins were performed using Cytoscape-3.8 (Shannon et al. 2003). PPINs for the SARS-CoV-2 proteins and HICs served in the identification of major HICs that were common interactors of SARS-CoV-2 proteins S, M, E, ORF3a, ORF6, ORF7a, ORF7b, ORF8, nsp4, nsp6 (Figure 3).

4. Biological interpretation of HICs-SARS-CoV-2 PPINs

The KEGG PATHWAY analysis of HIC dataset interacting with SARS-CoV-2 proteins was performed using STRING database (v11) and a total forty-one biological pathways were identified. Statistical measures including strength and false discovery rate (FDR) score provided by p-values were considered. And six pathways were further selected for the biological interpretation of PPINs (Table 3).

4.1 KEGG PATHWAY analysis of HICs interacting with SARS-CoV-2 proteins

Inflammatory mediator regulations of TRP channels pathway include TRP channels (ITPR1, ITPR2 and ITPR3). TRP channels that respond to temperature are known as thermo-TRPs. Among them TRPA1, TRPM8, TRPV1-4 were found in the nerve endings and play a major role in pain perception. These proteins could be modulated indirectly by inflammatory mediators such as proinflammatory cytokines (Parenti et al. 2016). Activation of TRPV1 increased the release of several pro-inflammatory molecules, including substance P (sP) and cytokines such as, interleukin-6. Respiratory pathophysiology in SARS-CoV-2 infection may show mechanisms related to TRPV1 receptor sensitization that could result in hyper inflammation of the lungs and associated complication (Groneberg et al. 2004). TRP channels also have role in the transmission of sensory stimuli of taste (Talavera 2015). Furthermore, TRPA1 may increase the sensitivity to evoke pain and several other symptoms associated with SARS-CoV-2 infection (Silvagno et al. 2020). *ACE2* and *TMPRSS2* expression has been reported in salivary gland cells of the tongue and tonsils. It might allow virus to fuse its membrane with the host cells as compared to other oral tissues (Huang et al. 2021). SARS-CoV-2 may cause changes in the production or quality of saliva, contributing to the symptoms of loss of taste in the oral cavity of patients infected with SARS-CoV-2.

Glucose-induced insulin secretion is the main principle of insulin release (Komatsu et al. 2013). Deterioration in glycemic levels including both insulin resistance and impaired insulin secretion were recently reported upon SARS-CoV-2 infection (Gianchandani et al. 2020; Wu et al. 2020). Also, a recent study showed that *ACE2* expression increased considerably in human pancreatic beta cells in response to inflammatory cytokines thus rendering the beta cells more susceptible to SARS-CoV-2 infections (Muller et al. 2021). However, roles of HICs including TRPM4, KCNN4, KVNJ11 and ITPR3 need to be explored further.

Gap junctions contain the intercellular channels that allowed a direct communication between the cellular compartments. These channels permitted the direct transfer of ions, amino acids, second messengers and other metabolites between adjacent cells. Change in the intracellular

Ca^{2+} levels acted as stimuli to the gap junctions. ITPRs (ITPR1, ITPR2, ITPR3) play a crucial role in maintaining the intracellular Ca^{2+} as they acted on the ER for the regulation of cytoplasmic calcium concentration (Ivanova et al. 2014).

The renin-angiotensin-aldosterone system (RAAS) is an essential system for electrolyte homeostasis and blood pressure management through the ACE2 axis. Deregulation of RAAS homeostasis resulted in development of distress in lungs, induced apoptosis, vasoconstriction, increased oxidative stress and edema (Gao et al. 2020). ACE2 acted as a port of entry for SARS-CoV-2 (D'Ardes et al. 2020) and its expression decreased as infection progressed. Moreover, reduction in expression level of ACE2 could be correlated to the increase in Ca^{2+} concentration dependent metalloproteinase domain-containing protein (ADAM10). Furthermore, increase in the Ca^{2+} concentration could further be attributed to viral proteins interacting with ITPR3 (Scialo et al. 2020). Additionally, decrease in ACE2 level led to accumulation of angiotensin II which further activated angiotensin II type 1 receptor (AT1R) axis thus, worsening the disease outcome. Also, apelin signaling could also be suggested to be involved in disease progression. Apelin peptides are endogenous ligands of G protein coupled receptors APJ. Apelin played a number of roles in the mammalian system by protecting cardiac health and calcium modulation (Wang et al. 2013). Experimental studies exhibited that apelin administration had anti-inflammatory effects (Saeedi Saravi and Beer 2020).

4.2 Drugs interacting with potential HICs

HICs interacting with viral proteins could be potential drug targets for drug repurposing. Also, the traditional drug development method is considerably expensive and time consuming. Drug repurposing is an efficacious process by which effective drugs can be identified. The FDA approved drugs interacting with HICs were identified using DGIdb (Freshour et al. 2021; Griffith et al. 2013). Table 4 contains the list of HICs including TRPM4, TRPA1 and ITPR1 interacting with FDA approved drugs. Drugs interacting with HICs were overlaid on HICs-SARS-CoV-2 PPINs highlighting potential drug targets (Figure 4). List of drugs interacting with HICs and SARS-CoV-2 protein is listed in Supplementary Table 4. Drugs targeted against HICs can be toxic in some cases (Feng et al. 2004). Furthermore, these drugs can be tested for antiviral activity.

5. Conclusions

Several computational approaches including ML-based algorithms were applied to study the interactome of SARS-CoV-2 proteins with HICs. Biological insights of HICs interacting with

SARS-CoV-2 proteins were gained using pathway analysis. TRPM4 and KCNN4 were found to a play role in insulin secretion. TRPA1 was found as an important molecule in heat, pain, and taste sensitivity inside the host. GJA1 has a crucial role in pathways involving gap junctions and ASIC1 was found to be a part of inflammatory mediator regulation of TRP channels. ITPR1 was found to be involved in four predicted pathways including inflammatory mediator regulation of TRP channels, gap junction, renin secretion and apelin signaling pathways. Moreover, FDA approved drugs interacting with potential HICs were identified. Most likely, our predictions showed promising results that further require experimental validation. HICs could be further explored as a potential class of targets for the better management of infection caused by SARS-CoV-2.

6. Declarations

Funding Information: This work was funded by the intramural funds of Institute of Bioinformatics, India and Bio-CARe by Department of Biotechnology (DBT), Government of India, grant number BT/PR19924/BIC/101/568/2016.

Conflict of interest: The authors declare that no competing financial interests exist.

Availability of data and material: Publicly available datasets were analyzed in this study. The data can be accessible using following resources: RefSeq database (https://www.ncbi.nlm.nih.gov/refseq/), BioGRID database (https://thebiogrid.org/) and Gene Ontology knowledgebase (http://geneontology.org/).

Authors' contribution: JS conceptualized and designed the study. NSM, DS, AG, AP, MB and JS analyzed and interpreted the data. NSM, AG, KTSP, AP, MB and JS contributed to the writing of the manuscript and the figures were prepared by KTSP.

Acknowledgements*:* The authors thank the Department of Biotechnology (DBT), Government of India for research support to the Institute of Bioinformatics (IOB), Bangalore. JS is a recipient of Bio-CARe Women Scientists award by Department of Biotechnology (DBT), Government of India (Grant number-BT/PR19924/BIC/101/568/2016).

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Tables

Table 1: Overall Performance of PPI-MetaGO

Accuracy	Precision	F1 Score	AUC-ROC	MCC	Sensitivity	False Positive Rate
82.71	84.09	84.09	0.89	65.17	84.09	18.91

Table 2: Confusion matrix obtained from PPI-MetaGO

	True Positive	True Negative
Predicted Positive	37	7
Predicted Negative	7	30

Table 3: List of KEGG pathways and potential target proteins

KEGG Pathway	Potential Target Proteins	Strength	False Discovery Rate
Inflammatory mediator regulation of TRP channels	ASIC1,TRPA1,ITPR1,ITPR2, ITPR3	1.46	0.0000328
Taste transduction	GABRA5,ITPR3,SCN9A	1.29	0.0017
Insulin secretion	TRPM4,KCNN4,KCNJ11, ITPR3	1.4	0.00022
Gap junction	GJA1,ITPR1,ITPR3,ITPR2	1.39	0.00022
Renin secretion	ITPR1,ITPR3,ITPR2	1.4	0.0012
Apelin signaling pathway	ITPR1,ITPR3,ITPR2	1.08	0.004

Table 4: List of drugs associated with potential target proteins and processes involved

	Drug Name	Target Protein	Biological Processes
1	Adenosine Diphosphate, Clotrimazole, Adenosine, Spermine, Adenosine Triphosphate, Glyburide	TRPM4	Insulin secretion
2	Thymol, Benzoquinone, Chloropicrin, Allicin, Morphanthridine, Polygodial, Methylglyoxal, Isovelleral, Acrolein, Nicotine, Menthol, Acetaldehyde, Salirasib, Auranofin, Apomorphine, Cannabidivarin, Tetrahydrocannabivarin, Levomenthol, Butamben, Camphor, Cannabidiol, Nabiximols, Phenethylisothiocyanate, Benzyl isothiocyanate, Isopropyl isothiocyanate, Voacangine, Erucin, Allyl isothiocyanate, 4-Hydroxynon-2-enal	TRPA1	Inflammatory mediator regulation of TRP channels
3	Carbenoxolone, Octanol, Carvedilol, Epigalocatechin Gallate, Bleomycin, Propylthiouracil, Labetalol, Atenolol	GJA1	Gap junction
4	Chlorzoxazone, Senicapoc, Clotrimazole, Nitredipine, Riluzole, Quinine, Halothane	KCNN4	Insulin secretion
5	Diminazene, Amiloride, Ibuprofen, Nafamostat, Benzamil	ASIC1	Inflammatory mediator regulation of TRP channels
6	Caffeine, Adenosine Triphosphate, Nitroprusside, Glycerin,	ITPR1	Renin secretion, Apelin signaling pathway

Figure Legends

Fig. 1 A schematic overview of several analyses carried out to study the interactome of SARS-CoV-2 proteins with human ion channels

Fig. 2 A depiction of protein-protein interactions of SARS-CoV-2 proteins (i) E (ii) S (iii) M (iv) ORF7b (v) ORF3a (vi) ORF6 (vii) ORF7a (viii) nsp6 (ix) nsp4 (x) ORF8 (xi) nsp3 (xii) nsp14 (xiii) nsp5 (xiv) nsp13 and (xv) nsp16 with human ion channels (HICs). Yellow colour diamond shaped node represents SARS-CoV-2 proteins and HICs are represented as blue colour diamond

Fig. 3 A schematic representation of protein-protein interaction networks of human-SARS-CoV-2 proteins: proteins-proteins interactions of human ion channels (HICs) were generated using STRING database (purple colour nodes). Furthermore, HICs interaction networks were overlaid with SARS-CoV-2 proteins (i) M, (ii) E, (iii) ORF7a (iv) S, (v) ORF6, (vi) ORF3a, (vii) ORF8, (viii) ORF7b, (ix) nsp6 and (x) nsp4. Yellow colour node represents SARS-CoV-2 proteins and human ion channels are represented in purple colour node

Fig. 4 Representation of human ion channels-drug target network: Significant interactions between SARS-CoV-2 proteins (i) M, (ii) E, (iii) ORF7a, (iv) nsp6, (v) S, (vi) ORF8, (vii) ORF7b and (viii) nsp4 (yellow colour nodes), potential human ion channels (HICs) (blue colour nodes), and FDA approved drugs (black) as identified by DGIdb. HICs-drug interactions were overlaid on protein-protein interaction networks and potential drug-target interactions are presented in the network

Figures

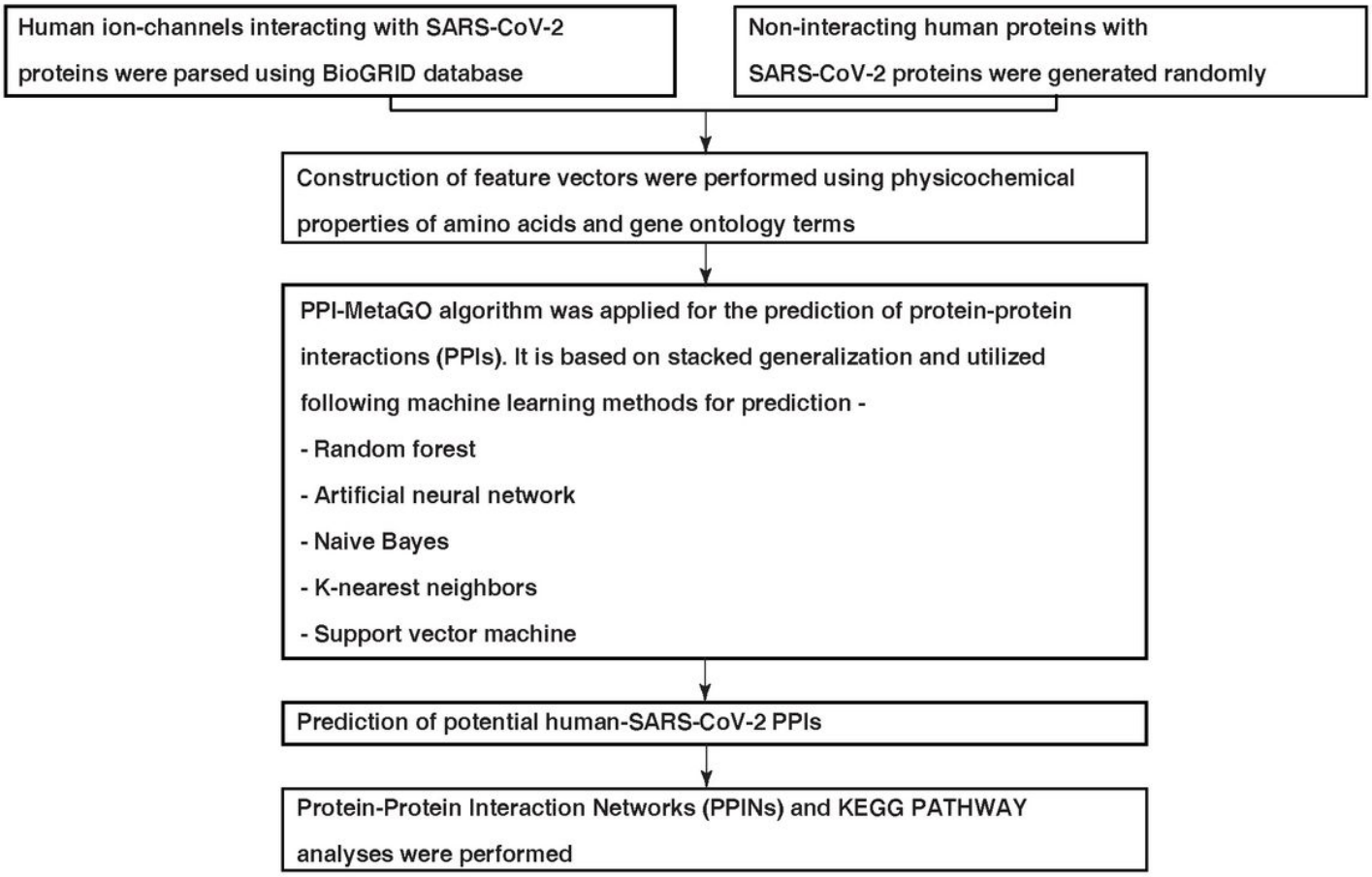

Figure 1

A schematic overview of several analyses carried out to study the interactome of SARSCoV-2 proteins with human ion channels

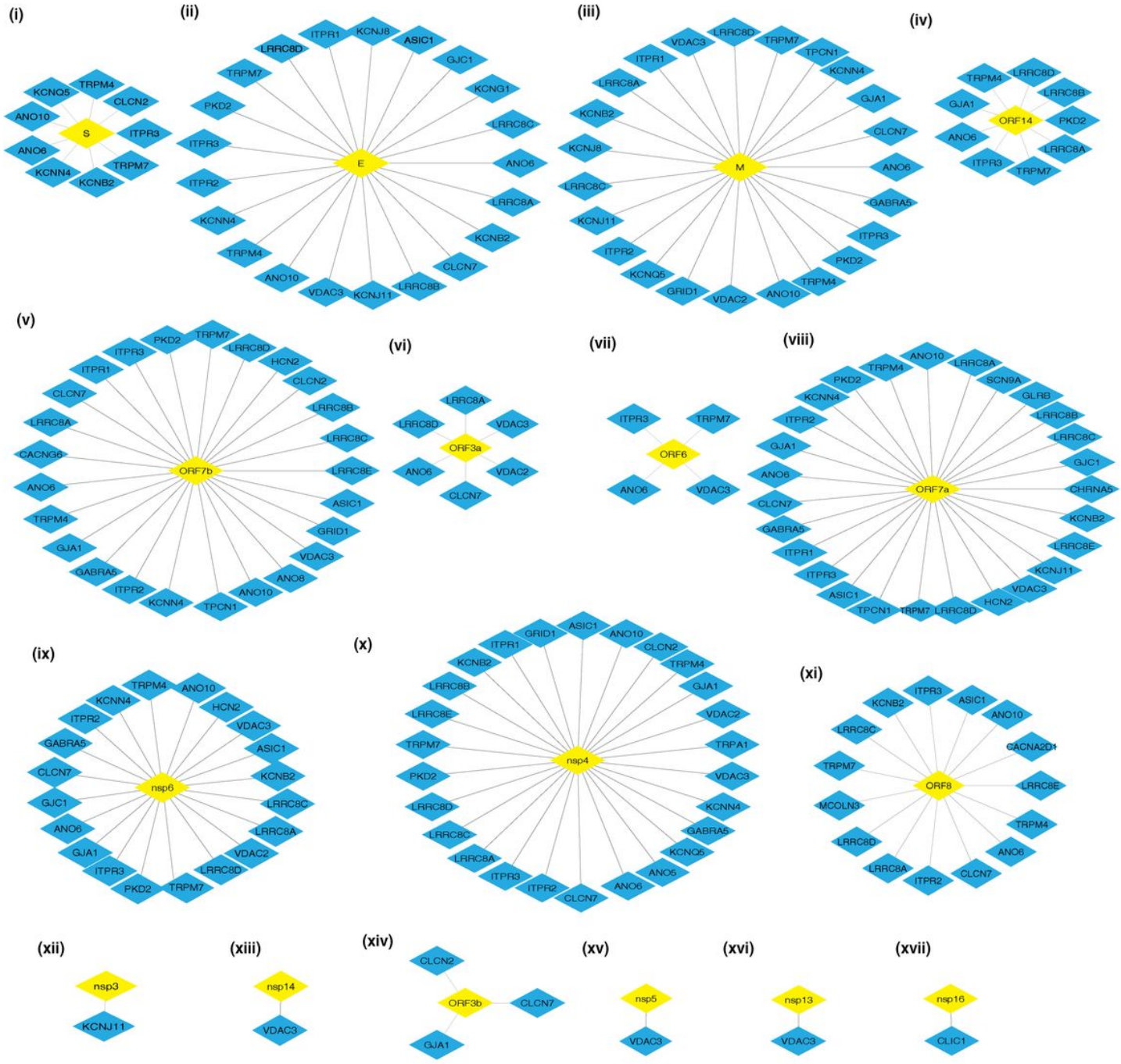

Figure 2

A depiction of protein-protein interactions of SARS-CoV-2 proteins (i) E (ii) S (iii) M (iv) ORF7b (v) ORF3a (vi) ORF6 (vii) ORF7a (viii) nsp6 (ix) nsp4 (x) ORF8 (xi) nsp3 (xii) nsp14 (xiii) nsp5 (xiv) nsp13 and (xv) nsp16 with human ion channels (HICs). Yellow colour diamond shaped node represents SARS-CoV-2 proteins and HICs are represented as blue colour diamond

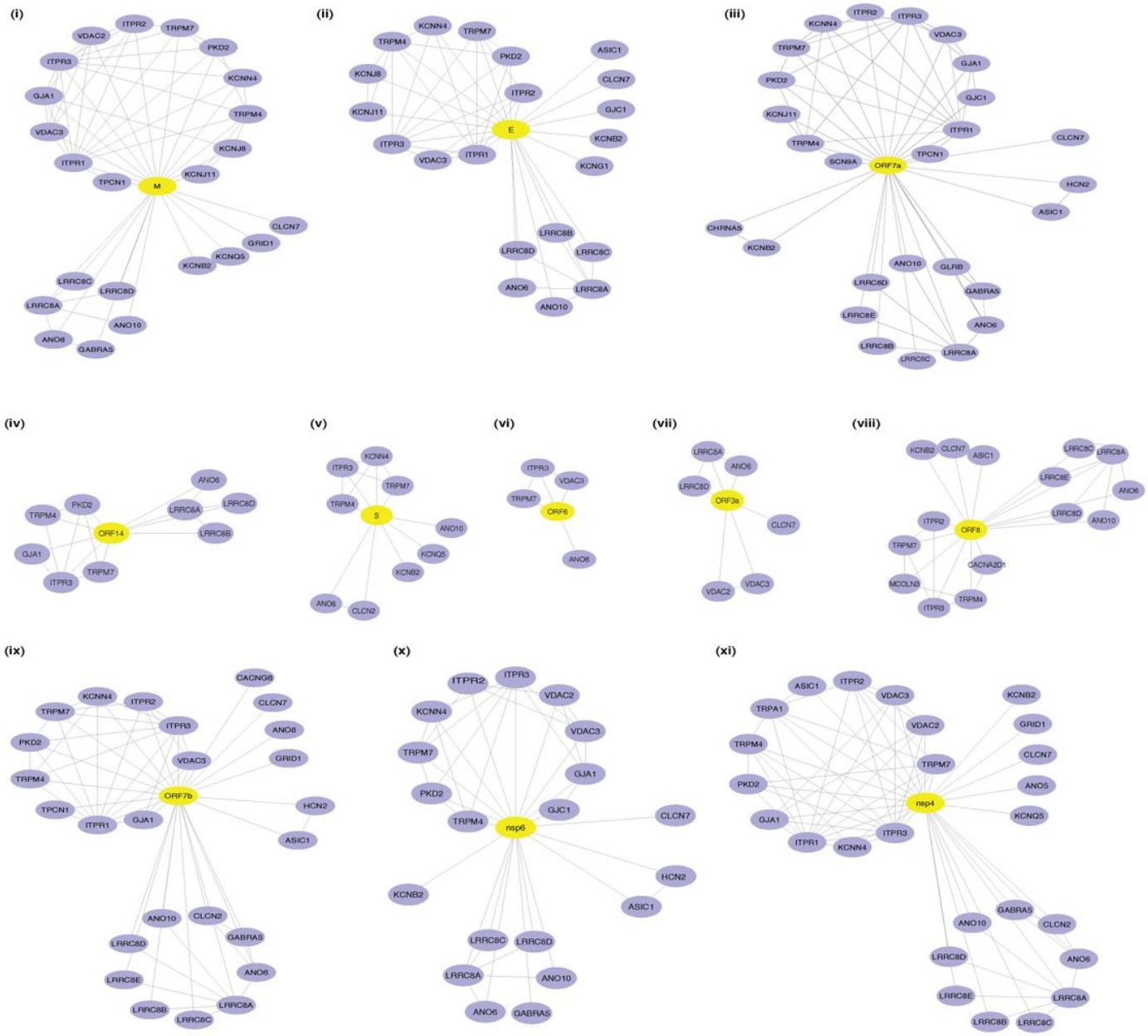

Figure 3

A schematic representation of protein-protein interaction networks of human-SARSCoV-2 proteins: proteins-proteins interactions of human ion channels (HICs) were generated using STRING database (purple colour nodes). Furthermore, HICs interaction networks were overlaid with SARS-CoV-2 proteins (i) M, (ii) E, (iii) ORF7a (iv) S, (v) ORF6, (vi) ORF3a, (vii) ORF8, (viii) ORF7b, (ix) nsp6 and (x) nsp4. Yellow colour node represents SARS-CoV2 proteins and human ion channels are represented in purple colour node

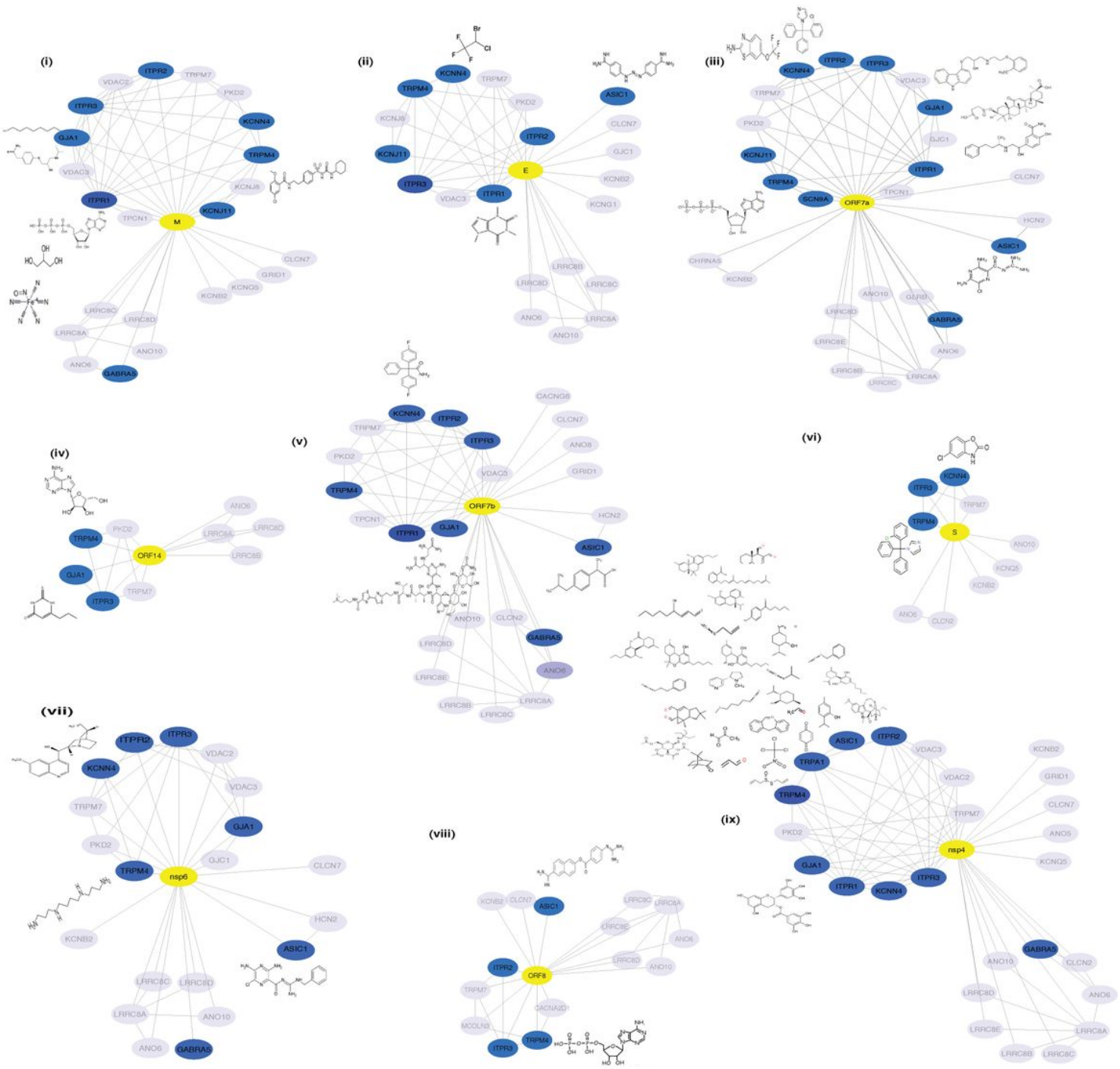

Figure 4

Representation of human ion channels-drug target network: Significant interactions between SARS-CoV-2 proteins (i) M, (ii) E, (iii) ORF7a, (iv) nsp6, (v) S, (vi) ORF8, (vii) ORF7b and (viii) nsp4 (yellow colour nodes), potential human ion channels (HICs) (blue colour nodes), and FDA approved drugs (black) as identified by DGIdb. HICs-drug interactions were overlaid on protein-protein interaction networks and potential drug-target interactions are presented in the network

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