

Protein Domain Annotations of the SARS-CoV-2 Proteomics as a Blue-Print for Mapping the Features for Drug and Vaccine Designs

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ABSTRACT

SARS-CoV-2 virus, as the causal agent for the COVID-19 pandemic, remains an enigma in the bioinformatics sense. Current efforts in drug and vaccine design in primarily targeting general devised protein domain while overlooking the specific features in the proteomics repertoire. However, the NCBI Conserved Domain Database (CDD) could annotate the specific features that are indispensable for a more advanced drug and vaccine design. In this regard, the annotation efforts were initiated with CDD database, and visualized with the 3D Protein Visualizer of Cn3D. The existence of the ATP and ADP binding protein with respected domains were found to be a very potential target for drug design. It is recommended that nucleoside inhibitor that could mimick the ATP molecule could serve as a potential drug lead against SARS-CoV-2.

Keyword: Protein Domain, CDD, ATP, ADP, and Features

1. INTRODUCTION

As per now, the COVID-19 pandemics that was caused by the SARS-CoV-2 virus has reached unprecedented infection and mortality rate that is much worse than Hongkong Flu, SARS, MERS, Avian Influenza, and Ebola pandemics in the past [1–6]. However, bioinformaticians have already secured reference sequence from Wuhan, and it opens possibility for the development of the diagnostics, drug, and vaccines for SARS-CoV-2[7]. In this regard, it is important to devise precise annotation strategy towards the coding sequences to provide a molecular blue-print for the biomedical research.

Then, focusing in the proteomics pipelines still considered as primary references for bioinformatics research in COVID-19. In this end, investigating protein repertoire of the virus will shed light the evolutionary history of virus, in particular the protein structures and functions themselves [8–10]. Herewith, protein domain is the simplest evolutionary unit in every organism that consisted of a fine-grained three dimensional (3D) structure and clustered into different types of folding architecture [11–13]. Protein domains play important role in the gene and metabolic regulations in any organism, and also provides immunologic regulations as well [14–16].

However, relying solely on the laboratory protocols to annotate protein domain is considered insufficient. The automatics and engineered means to provide protein domain information is necessary[17]. In this regards, the development of the machine learning-based pipeline has provided significant insight on the bacterial, archeal, and eukarya proteomics repertoire, but much still need to be done on the viral annotations [18]. Thus, as conserved biological repertoire, features information is important because it provides crucial information on the conservation of the domain family in regard to the biochemical activity of the catalytic residues and binding sites within the protein domain[19–21]. The features information is necessary to be followed up with computational based pipeline for drug and vaccine design

in order to find the feasible targets. Although Computer Aided Drug Design (CADD) protocols rely heavily on proteomics-based pipelines, protein domain annotation is often overlooked due to relevancy consideration with the hunt of the drug target[22]. In this regard, utilizing protein domain annotation pipeline that scans to the specific features in the viral proteomes is indispensable. The objective of this research is to examine the important features in the SARS-CoV-2 proteomics that could be overlooked with standard run of the protein domain annotation pipeline.

2. MATERIAL AND METHODS

The first step is to go to NCBI's SARS-CoV-2 biological sequences repository as mentioned in the references (<https://www.ncbi.nlm.nih.gov/genbank/sars-cov-2-seqs/#nucleotide-sequences>) [23–25]. Then, navigate to the reference genomics sequence of the SARS-CoV-2 to obtain the annotations on the protein of the gene coding sequences, and retrieved the translated protein (https://www.ncbi.nlm.nih.gov/nucore/NC_045512). Note that the reference sequence was retrieved from an isolate of Wuhan origin. The protein data was saved in FASTA format. Moreover, employing batch CDD online program to annotate the protein domain, and download the report accordingly [26–29]. The parameters were adjusted in accordance to the references, with E-value threshold of 10^{-3} , applying low-complexity filter, limiting maximum number of hits to 100 [30,31]. Then leave the rest to the default value.

The domain hits from the PFAM/SUPERFAMILY database were analyzed with mapping to the InterPro database accordingly for the specific enzymatic and/or protein activities that could be leveraged by the drug and vaccine design. In this end, analyze the 'features' report for the specific information on the Batch CDD annotations, and click the CDD ID for accessing the 3D structures of the featured protein domains. The structural files could be

opened with the Cn3D version 4.3.1 (<https://www.ncbi.nlm.nih.gov/Structure/CN3D/cn3d.shtml>) [32–34].

3. RESULT

The inputted and generated data from this research was deposited here [35]. The Batch CDD program was employed because the protein sequences were comprised of 12 headers of annotations that represent 12 different protein-coding genes. Statistics wise, the Table 1 shows the Batch CDD program performance accordingly.

Table 1: Batch CDD Program Statistics for the SARS-CoV-2 CDS sequences

No.	Indicators	Result
1.	Runtime	46 seconds
2.	Queries with no domain hits	3
3.	Total domain found	43
4.	Total features found	2

As seen in the Table 1, the runtime of the program to compute the whole proteins is pretty fast. It is not surprising provided that the viral proteomes are considered smaller than bacteria and especially other single-cell eukaryotes. Moreover, although it was found significant hit of 43 domains overall, 3 sequences query has nothing. Possibly, it is due the unavailability of the domain annotation in the CDD database.

The, in regard of the recapitulation of the Batch CDD-run result, the table 2 shows that there are protein domain annotation hits for the SARS-CoV-2 protein sequences after the E-value was filtered to 0. It means that the hits will show the highest homology possible.

Table 2: Batch CDD Protein Domain Annotation Hits for the SARS-CoV-2 CDS sequences with E-value equal to 0

No.	Query Genbank ID	PSSM-ID	From	To	Accession	Short name
1.	YP_009724389.1	284002	5928	6520	pfam06471	NSP11
2.		284009	4406	4758	pfam06478	Coro-na_R Pol_N
3.		368920	6800	7095	pfam06460	NSP13
4.	YP_009724390.1	279881	662	1232	cl20218	Coro-na_S2 superfamily

In the Table 1, based on PFAM to InterPro mapping information, NSP11 protein domain is known for having exonuclease, methyltransferase, endopeptidase, and supporting RNA polymerase activities. Then, based on the same mapping information, the coronavirus Rpol N-terminus domain also provides RNA binding, ATP Binding, supporting RNA polymerase, and transcription, DNA-templated activities. Thus, the NSP13 protein domain name was known to change into NSP16, and has a function as mRNA cap-1 methyltransferase activity. Lastly, the mapping information for Corona_S2 superfamily is a spike protein that is more fit as vaccine target. Beside Corona_S2 superfamily, the others could serve as targets for drug design by designing proper inhibitors that block the enzymatic and/or protein activities [36,37].

Table 3. Annotated Domain Features

No.	Query Genbank ID	Title	Source Domain ID
1.	YP_009724389.1	ADP-ribose binding site	239235
2.	YP_009724389.1	ATP binding site	350692
3.	YP_009724389.1	ATP binding site	350195
4.	YP_009725295.1	ADP-ribose binding site	239235

However, as seen in the references, the drug and vaccine targets that annotated in the Table 1 are considered common spots for that regards. A more specific and featured targets are needed, and it is shown in the Table 3. They are the ATP and ADP-ribose binding sites. Moreover, figure 1 shows the depiction of the ATP binding site protein that comprises of three different domains. Based on the annotations in the CDD database, this family of proteins involved in ATP-dependent RNA or DNA unwinding.

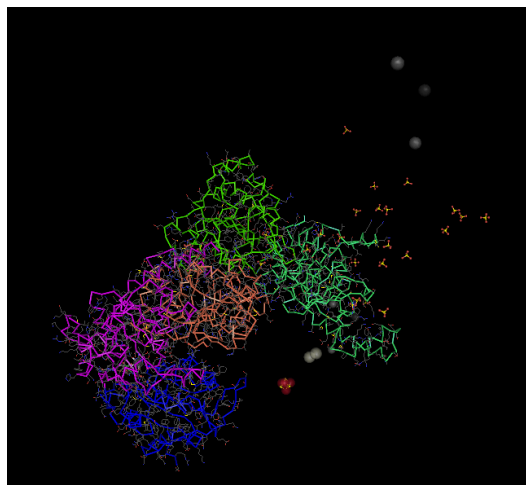


Figure 1: ATP Binding site with the proteins domains colored accordingly. Visualized with Cn3D version 4.3.1

Then, the figure 2 depicts the ADP-ribose binding site protein that comprises with three different domains. Based

on CDD annotations data, the protein domains may play roles in distinct ADP-ribose pathways, such as the ADP-ribosylation of proteins, an important post-translational modification that occurs in DNA repair, transcription, chromatin biology, and long-term memory formation, among other processes.

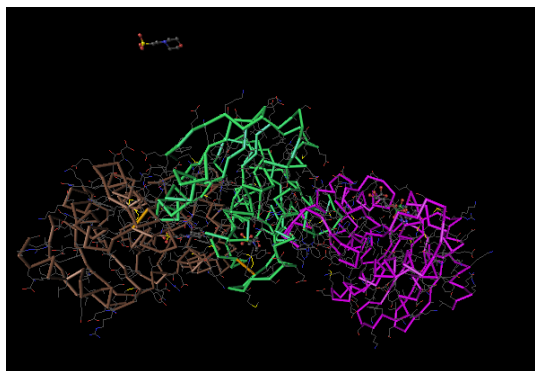


Figure 2: ADP-ribose Binding site with the proteins domains colored accordingly. Visualized with Cn3D version 4.3.1

4. DISCUSSION

Based upon the findings of the CDD annotations data, there are basically two types of domain hits. The first one is the general hits. It comprises with the common protein targets of the SARS-CoV-2 virus. The second one is the featured domain that comprises with very specific target protein for the respective virus. The earlier hits type already became extensive targets for SARS-CoV-2 drug development initiatives world-wide, and references already provided to the scientific community accordingly[38–43]. However, the featured part that annotated ATP and ADP dependent proteins should be carefully examined as drug target because they confer a very specific metabolic pathway in the host cell of the virus, namely the bioenergetics pathways themselves. Disrupting the bioenergetics pathways with depleting ATP supplies to the host cells will eventually extinguish virus' effort to replicate [44]. Designing an inhibitor that mimics the structure of both ATP and ADP is crucial to inhibit the replication of the coronavirus in general, and it was done by targeting the non-structural proteins that responsible in the viral replication[45–47]. One of the such drug candidates examples are the nucleoside inhibitors that hampers the viral replication because their structures mimicked the ATP[48,49]. In this regards, it is recommended to focus on the annotated domain features that most of the times did not fit into the mainstream strategy of drug and vaccine development. However, the strategy to comprehend the pharmacological and toxicological properties should be devised accordingly[50].

5. CONCLUSION

It is concluded that the Batch CDD Hits of SARS-CoV-2 Proteomes could provide fine-grained annotation result on both the general and featured domain information. In this regard, the general hits already becoming target of exten-

sive drug development, while the featured ATP and ADP binding sites are still largely overlooked. One of the strategies to incorporate the featured annotation is the development of the nucleoside inhibitors for SARS-CoV-2.

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