Understanding the evolution of SARS-CoV-2 Nsp15 in three dimensions

Sophia Staggers[1,3]. Erika McCarthy[1,4]. Lindsey Whitmore[1,5]. Elliot Dolan[2]. Changpeng Lu[2]. Vidur Sarma[2]. Zhuofan Shen[2]. Maria Szegedy[2]. Lingjun Xie[2]. Christine Zardecki[1,2]. Sagar Khare[2]. Stephen K. Burley[1,2].

[1]RCSB Protein Data Bank, Rutgers University, Piscataway, NJ 08854. [2]Institute for Quantitative Biomedicine, Rutgers University, Piscataway, NJ 08854.
[3]Department of Chemistry, Frostburg State University, Frostburg, MD 21532. [4] Department of Chemistry and Chemical Biology, Stevens Institute of Technology, Hoboken, NJ 07030.
[5]Department of Chemistry, Howard University, Washington, D.C. 20059.

OVERVIEW

SARS-CoV-2 is the coronavirus responsible for the global COVID-19 pandemic. There is currently little information on SARS-CoV-2 and the proteins encoded by its positive-strand RNA genome. Our research utilizes computational structural biology tools to explore the evolution of SARS-CoV-2 proteins in 3D since the virus left the People's Republic of China in late 2019.

METHODOLOGY

As part of an online summer research experience with the RCSB Protein Data Bank, we studied how SARS-CoV-2 proteins evolved during the first six months of the COVID-19 pandemic by exploring amino acid sequence and 3D atomic-level structure using various structural bioinformatics tools, including Clustal Omega (www.ebi.ac.uk/Tools/msa/clustalo/) for sequence alignments and phylogenetic trees; Mol* (molstar.org) for 3D molecular visualization; and Foldit (fold.it) for structural/energetic effects of sequence mutations.

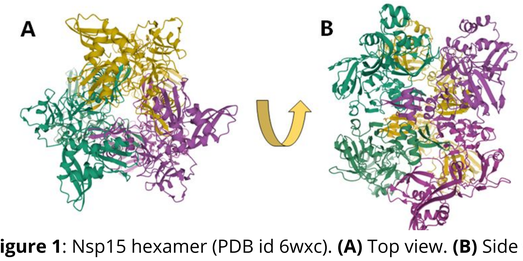

Figure 1: Nsp15 hexamer (PDB id 6wxc). **(A)** Top view. **(B)** Side view.

FOCUS: Non-structural protein 15 (Nsp15)

Nsp15 (PDB id 6wxc) assembles into a symmetric hexamer that functions as a uridylate-specific endoribonuclease.

SIGNIFICANT MUTANT VARIANTS OF Nsp15

*Calculation of energy change accounts for the difference steric interactions of the mutant variant compared to the wild-type protein.
**Conservative mutations occur within the same class of amino acids.

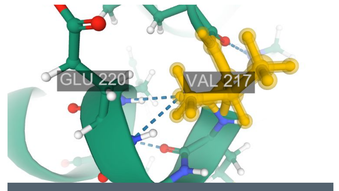

Figure 2: A217V

- 189 recorded instances
- First observed England
- -8.49 J/mol energy change*
- surface
- conservative**

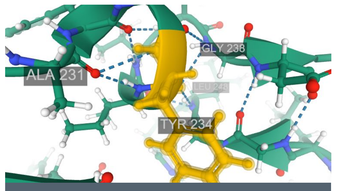

Figure 3: H234Y

- 8 recorded instances
- First observed Australia
- -30.3 J/mol energy change
- boundary
- nonconservative

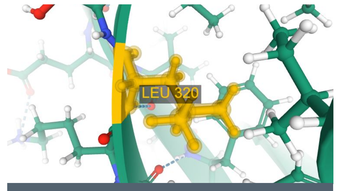

Figure 4: V320L

- 216 recorded instances
- First observed England
- 47.9 J/mol energy change
- boundary
- conservative

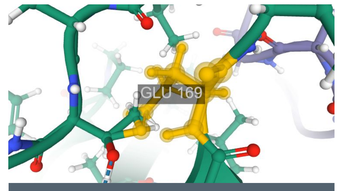

Figure 5: G169E

- 1 recorded instance
- First observed England
- 8760 J/mol energy change
- boundary
- nonconservative

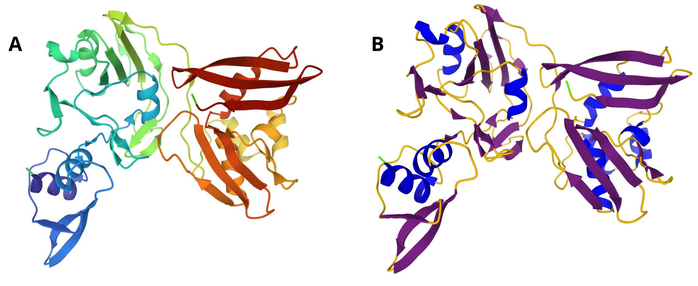

Figure 6: Nsp15 monomer. **(A)** Rainbow view. **(B)** Secondary structure (α-helices in blue, β strands in purple, random coil in gold).

CONCLUSION

Over 300 mutant variants of Nsp15 were analyzed. A217V and V320L appeared in multiple variants. H234Y stabilized the catalytic site indicated by its favorable energy change. G169E was the most unfavorable energy change and is most likely unviable. The data will provide significant information regarding the role of Nsp15 in SARS-CoV-2.

RCSB PDB is funded by the National Science Foundation (DBI-1832184), the US Department of Energy (DE-SC0019749), and the National Cancer Institute, National Institute of Allergy and Infectious Diseases, and National Institute of General Medical Sciences of the National Institutes of Health under grant R01GM133198. S.S. was supported by an NSF REU and worked under the RISE program at Rutgers University.