Adriana Mercedes

Dr. Christina Steel

BIOL293

6-2-2022

Scientific literacy background essay part 1&2

In this essay we will be reviewing the changes to 5 mutations in the spike protein that have been used to determine the strains of SARS-Cov-2. The five mutations we will be going over are L452R, E484K, E484Q, N501Y, and P681H.

The RNA genomes of SARS. COV is made up of six to ten open reading forms (ORFs) which are responsible for encoding the replicase and structural proteins for the virus. (Cuffari,2021) Sars Cov viral envelope is normally made up of three proteins-membrane protein M; envelope protein E: and the spike protein, S.

The spike protein is the presence of spiked prongs that cover the surface of the virus. These prongs allow this virus to penetrate the host cells leading to infection by changing and folding on itself allowing the virus to fuse its membrane into the membrane of our cells. (Cuffari,2021) The S protein allows Sars-Cov to penetrate other cells because the S1 subunit binds to the hosts cells receptors, and the S2 subunits become helical, causing the fusion peptide to anchor itself to the membrane of the host cell. (Cuffari,2021) If there were a spike protein change this would mean that there is a mutation, spike protein changes can slow down the virus, and any change in shape makes it more difficult for our immune system to contain it. (Fliesler,2021)

The first mutation we will look over is the dominant mutation L452R which was first found and designated by B.1.427 and B.1.429*(Gray,2021)*. This mutation takes non-charged leucine (L) and replaces it with highly charged arginine (R) at position 452 (*Wiki, 2022).* Leucine-452 is the spike protein that is located near the aera that meets the ACE2 (angiotensin converting enzyme 2) cell receptor of Covid. It increases viral infectivity and host immune evasion potency by binding to the host cell and creating a pathway to insert its genetic makeup *(Gray,2021);* causing this mutation to be at fault for multiple outbreaks *(Gray,2021).*

Mutation E484K deals with the exchanging of glutamic acid (E) and lysine (K) at position 484. This mutation decreases binding affinity between RBD (receptor binding domain) and the hACE2 (receptor human angiotensin converting enzyme) *(Wang et al, 2021);* and is a defining factor of variants B.1.1.351 and P.1. This mutation favors electrostatic interactions that ruin the burial of the charged polar groups during the binding of RBD and hACE2, it also rearranges the loop region that holds the mutant leftovers which then leads to tighter binding and some new formations of hydrogen bonds *(Wang et al, 2021).* The tight binding affinity may be responsible for the increase in transmissibility since mutation E484K reduces the binding affinities between RBD and antibodies/nanobodies that can potentially evade a response from the immune system *(Wang et al, 2021).*

Mutation E484Q is the exchange of glutamic acid (E) and glutamine (Q) at position 484 which occurs in the spike protein *(Cherian et al,2021)* and is specific to variants B.1.617.1 and B.1.617.3. This spike mutation is in the critical RBD site that binds ACE2 and is also a target for neutralizing antibodies. This mutation showed decreased binding to select monoclonal antibodies that affects neutralization *(Cherian et al,2021).*

Variants B.1.1.7, B.1.351 and P1 share mutation N501Y which causes a change from asparagine (N) to tyrosine (Y) at position 501 of the virus genome because of how close it is to the RBD inside the spike glycoprotein. *(Fang et, al 2021).* RBDs that also have this mutation were more likely to interact with a faster association rate and a slower dissociation rate. Since it slows down the dissociation of the RBD from the ACE2 receptor it results in a weaker affinity to cell-surface ACE2 also showing that N501Y is the main factor to increased binding affinity *(Fang et, al 2021).*

Variant B.1.1.7 has mutation P681H that causes proline (P) to histidine (H) at position 681. This mutation is within the spike S1/S2 cleavage site which does take part in the proteolytic cleavage site *(Lubinski et,al 2021).* This mutation is also found in variants B.1.243, B.1.222 and is in lineage with B.1 *(Lubinski et,al 2021).*

A structural biology study lead by Bing, Chen, PhD, - found a mutation: D614G that alters the genetic code and they found that it made the spikes more stable than on the original virus. This spike protein change made them more function and made binding to the angiotensin converting enzyme 2 easier. Chen and Colleagues also stated that in the original virus the spike proteins would prematurely fall off, slowing down the virus; but the change in shape still made It difficult for our immune systems to handle it.

Sars Cov normally binds to the ACE2 (Angiotensin converting enzyme 2) granting it access to our cells. There are two forms of angiotensin converting enzyme: the full-length; mACE2 which is located on cell membranes and has a transmembrane anchor and an extracellular domain. The second form of ACE2; can be dissolved into a liquid which is shed into the circulation- this form lacks a membrane anchor and circulates in low concentrations. (Lung,2020)

We all have different amounts of ACE2 present in our different cell types and tissues. (Sriram, Insel and Loomba, 2020) It Is an extremely vital element that is needed to regulate normal processes like blood pressure, wound healing and to help with inflammation. ACE2 also helps regulate a protein called Angiotensin II (ANG II) and the functions it carries out. ACE2 converts ANG II to other molecules that counteract its effects. (Srirm,Insel and Loomba.)

A recent analysis showed that there were 46 nucleotide subunits and 37 deletions that occurs. This resulted in 30 amino acid substitutions and 12 deletions. 14 of the substitutions including N501Y and E484K as well as 9 other deletions were all located int eh spike protein. These changes in pattern are what lead us to the new pangolin lineage-B.1.640.2. (Philippe *et al*., 2020) Due to this variant being recently detected we are still unsure and cannot determine the virological, epidemiological and any clinical factors of this variant. Overall, these observations prove that Sars Cov mutations are unpredictable and can happen quickly.

Anon, 2022. Variants of SARS-COV-2. *Wikipedia*. Available at: https://en.wikipedia.org/wiki/Variants\_of\_SARS-CoV-2#L452R [Accessed February 14, 2022].

Dutta, D.S.S., 2021. L452R mutation potentially favors adaptive evolution of SARS-COV-2. *News*. Available at: https://www.news-medical.net/news/20210223/L452R-mutation-potentially-favors-adaptive-evolution-of-SARS-CoV-2.aspx [Accessed February 14, 2022].

Dutta, D.S.S., 2021. L452R mutation potentially favors adaptive evolution of SARS-COV-2. *News*. Available at: https://www.news-medical.net/news/20210223/L452R-mutation-potentially-favors-adaptive-evolution-of-SARS-CoV-2.aspx [Accessed February 14, 2022].

Ferreira, I.A.T.M. et al., 2021. SARS-COV-2 B.1.617 mutations L452R and E484Q are not synergistic for antibody evasion. *The Journal of infectious diseases*. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8420622/ [Accessed February 14, 2022].

Gray, L., 2021. UPDATE: L452 mutations set off several COVID-19 variants. *Newsroom*. Available at: https://newsroom.uw.edu/news/update-l452-mutations-set-several-covid-19-variants [Accessed February 6, 2022].

Team, N.I.C., 2021. SARS-COV-2 spike mutations, L452R, T478K, E484Q and P681R, in the second wave of covid-19 in Maharashtra, India. *MDPI*. Available at: https://www.mdpi.com/2076-2607/9/7/1542/htm [Accessed February 14, 2022].

Wang, W.B. et al., 2021. E484K mutation in SARS-COV-2 RBD enhances binding affinity with hACE2 but reduces interactions with neutralizing antibodies and nanobodies: Binding free energy calculation studies. *Journal of molecular graphics & modelling*. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8447841/ [Accessed February 14, 2022].

Colson, Philippe, et al. “Emergence in Southern France of a New SARS-COV-2 Variant Harbouring Both n501y and E484K Substitutions in the Spike Protein - Archives of Virology.” *SpringerLink*, Springer Vienna, 18 Feb. 2022, https://link.springer.com/article/10.1007/s00705-022-05385-y.

Cuffari, Benedette. “What Are Spike Proteins?” *News*, News Medical Life Sciences, 24 Feb. 2021, https://www.news-medical.net/health/What-are-Spike-Proteins.aspx.

Fliesler, Nancy. “Altered Spike Protein Makes SARS-COV-2 Variants More Infectious.” *Boston Children's Answers*, 23 Mar. 2021, https://answers.childrenshospital.org/sars-cov-2-variants-spike/.

Krishna Sriram, Paul Insel. “What Is the ACE2 Receptor?” *American Society for Biochemistry and Molecular Biology*, AsbmbToday, 16 May 2020, https://www.asbmb.org/asbmb-today/science/051620/what-is-the-ace2-receptor.

Scialo, Filippo, et al. “ACE2: The Major Cell Entry Receptor for SARS-COV-2.” *Lung*, Springer US, 10 Dec. 2020, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7653219/.

Turner, Anthony J. “Ace2 Cell Biology, Regulation, and Physiological Functions.” *The Protective Arm of the Renin Angiotensin System (RAS)*, U.S. National Library of Medicine, 24 Apr. 2015, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7149539/.