An Exploration of CFTR Missense Swap G500D compared to Phe508del

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Abstract

This work is an undergraduate research project from University of North Alabama. The project is meant to analyze specific VUS mutations of CFTR. CFTR is associated with Cystic Fibrosis which is associated with abnormal body liquid composition. The mutation pursued in this project is a missense mutation at position 500 swapping glycine with aspartic acid (G500D). This is classified as a non-conservative mutation since the amino acids do not share similar biochemical properties, i.e., one had a negative charge while the other is nonpolar. Since the discovery of Phe508del was determined to be the main cause of cystic fibrosis, genetic researchers have made great strides to determine other mutation causes of cystic fibrosis. Unfortunately, there are still many VUS associated with CFTR that could prove to be factors of cystic fibrosis.

Introduction

Cystic fibrosis is characterized by the loss-of-function of the CFTR gene. Cystic Fibrosis symptoms include coughing, congestion, lung infections, and can cause death. CF is a dangerous disease that has no known cure at this time, but through further analysis of G500D, we can determine if we have another cause of CF. Comparing G500D to Phe508del will give good insight to G500D's significance.

Methods

The first step was to select a genetic disease and a VUS associted with the gene. We constructed and analyzed slow and fast homology modeling. We viewed the databases of our disease to construct various charts on different factors of our variants. We viewed multiple journal articles and gathered information on how to properly construct and read CFTR graphs. From this information, It could be deduced what each VUS selected could be identified as.

Results

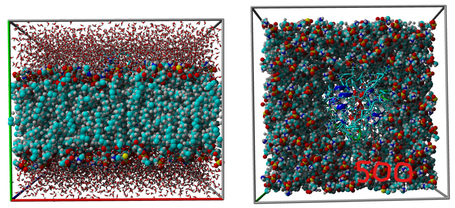

Figure 1:Protein model for CFTR G500D generated and embedded into a lipid membrane. Top view of the lipid membrane showing the exact position of G500. Side view is showing the lipid membrane in water.

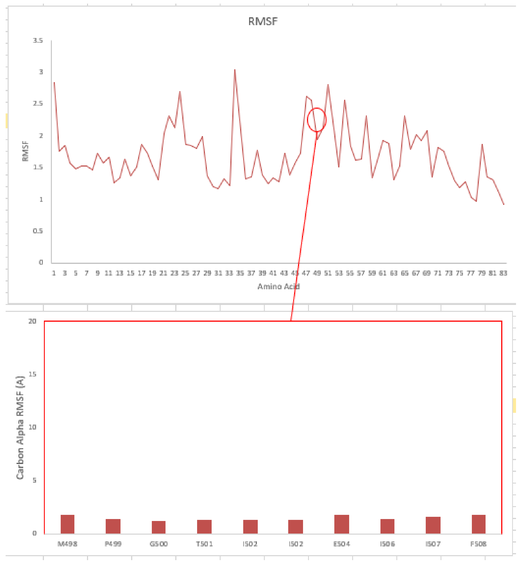

Figure 3:G500 is well packed within the structure. G500 has an above average RMSF and a similar RMSF to F508.

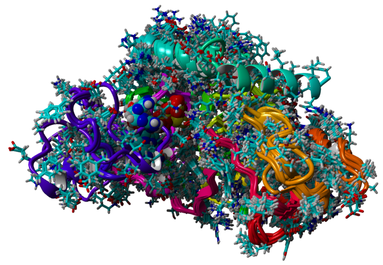

Figure 2:CFTR homology model. G500 is found at the base of an alpha helix located closely to other pathogenic variants along with F508.

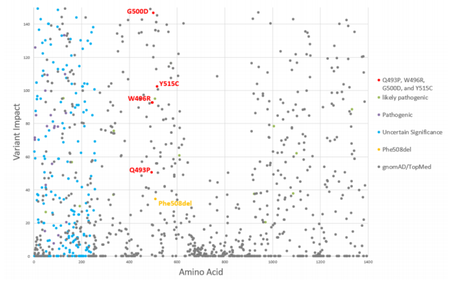

Figure 4:Variant impact for all gnomAD/TopMed, ClinVar, and patient variants reveals the G500D to fall near several other ClinVar variants with high variant impact scores

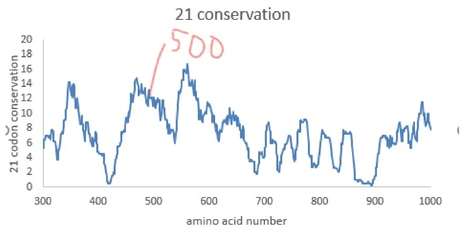

Figure 5:Conservation scores shown around position 500 are relatively high. Position 508 also has a similar score to position 500.

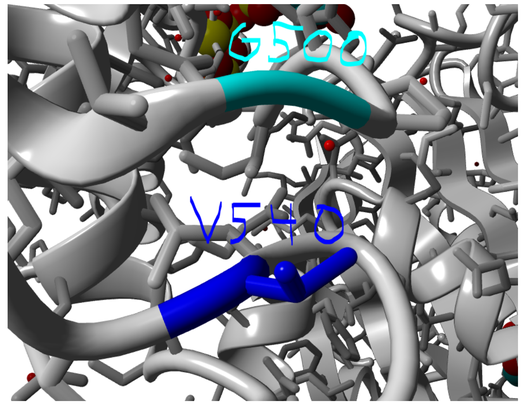

Figure 6:Falls three dimensionally near V540. V540 has a different structure than G500 and is only pathogenic when a deletion mutation occurs.

References

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Acknowledgements

Dr. Cynthia Stenger, Dr. Jeremy Prokop, and Dr. Jared Painter

University of NORTH ALABAMA MATHEMATICS

HudsonAlpha Institute for Biotechnology CODE Characterizing Our DNA Exceptions