An Exploration of GRIN2A with Landau-Kleffner Syndrome with a Missense Swap at G97D

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Abstract

Landau-Kleffner Syndrome (LKS), is a neurological syndrome that is characterized by the sudden or gradual development of aphasia (the inability to understand or express language) and recurrent seizures.In some cases, LKS is is thought to be caused by mutations in the GRIN2A gene which provides instructions to the body to make a protein to send signals to the nerve cells in the brain. This has been classified as a variant of uncertain significance due to a silent change in the sequence meaning that it does not change the encoded amino acid sequence of the GRIN2A protein. Compiled metrics through our custom tools on sequence, structure, and protein dynamics combined with PolyPhen2, Provean, SIFT, and Align-GVGD reveal this variant to rank in the top functional outcome changes relative to gnomAD, TopMed, and ClinVar variants known to date.

Introduction

I chose GRIN2A since it is the gene thought to cause Landau-Kleffner Syndrome since my uncle suffers from this disease [3]. GRIN2A had many variants of uncertain significance [1] since it had not been studied very much but I specifically chose the mutation from glycine to aspartic acid at position 97. This missense swap is from a hydrophillic to hydrophobic nucleic acid that is non-polar with a negative charge [2]. This information tells us that my mutation would resist water and not dissolve in it. I further studied this mutation in YASARA and created models that would better visualize these mutation findings that gives the reader a view of the side chain formed with my mutation. A spreadsheet was used that had all of my known data about GRIN2A which is how I made my graphs.

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Methods

The workflow known as sequence to structure to function was used to assess GRIN2A. The program YASARA was used to create visuals of the gene and VUS. A compilation of other GRIN2A variants was provided by ClinVAr, gnomAD, TOPmed, and COSMIC. Structural and evolutionary assessments establish this variant as a loss-to-loss function to the protein. Compiled metrics through our custom tools on sequence, structure, and protein dynamics combined with PolyPhen2, Provean, SIFT, and Align-GVGD reveal this variant to rank in the top functional outcome changes relative to gnomAD, TopMed, and ClinVar variants known to date. Introduction

Results

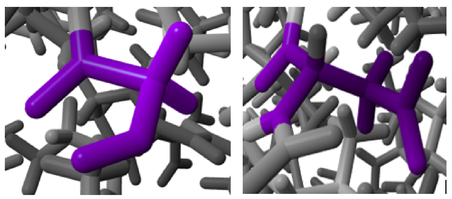

Figure 2:Pictured on the left is the wild type glycine at position 97 and pictured on the right is the mutation aspartic acid at position 97. Note that on the mutation a hydrophobic side chain is formed.

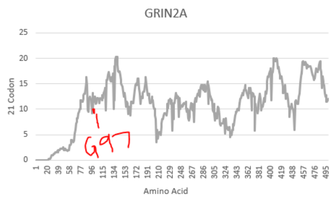

Figure 3:21 Codon Window with approximately 500 variants with variant G97D highlighted in red with a rough score of 0.95

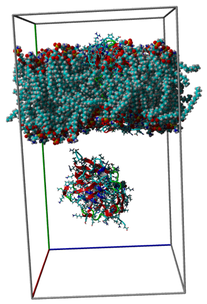

Figure 1:Side view of lipid membrane with no water added to the model. Note how my model is composed of many double helix's which suggests that my gene has many nucleic acids intertwined in it.

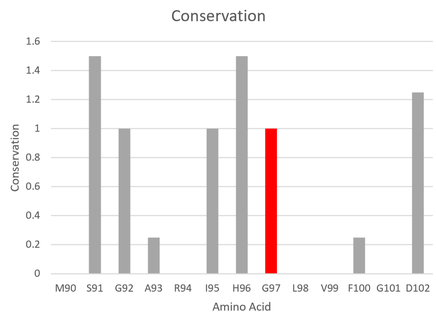

Figure 4:Conservation scores of variants M90 to D102 with position 97 highlighted in red with a score of 1. Note how other variants near mine share the same conservation score

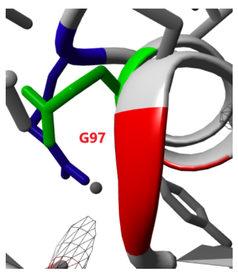

Figure 5:Zoomed in view of GRIN2A with position 97 highlighted in red

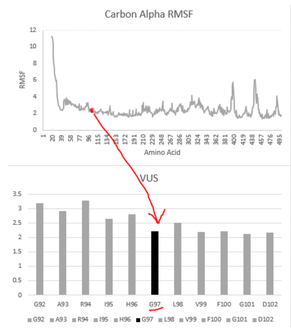

Figure 6:Root Mean Squared Fluctuation with position 97 highlighted in red in the above line graph and variant G97D represented as the black column with an approximate score of 0.945

Conclusion

There is still much to be researched with respect to Landau-Kleffner Syndrome, but specifically, the gene GRIN2A. My variant has not been classified as pathogenic, benign, or likely pathogenic at the moment, but I have hopes that this gene can be explored more and that this contribution to the research community was influential to this goal.

References

1. https://www.uniprot.org/uniprot/Q12879/protvista
2. https://proteinstructures.com/Structure/Structure/amino-acids.html
3. https://rarediseases.info.nih.gov/diseases/6855/landau-kleffner-syndrome

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