An Exploration of FGFR3 Missense Swap R669G

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Abstract

There are four principal Fibroblast Growth Factor Receptors (FGFRs) in the human body, each playing a critical role in adult and developmental cells. This work focuses on FGFR3 which is responsible for bone development. The project used various resources to generate information and visuals. Molecular dynamics simulations yielded RMSD and RMSF data on FGFR3. Most mutations in the FGFR3 gene are dominant activating mutations that cause a variety of bone dysplasias such as syndromic craniosynostosis [1]. The mutation pursued in this project is a missense mutation at position 669 swapping arginine with glycine (R669G). The results of this work show the known data on R669G. At the start of this project, R669G was considered a variant of uncertain significance (VUS). However, the UniProt database classified this mutation as having "Moderate" impact. Additionally, PolyPhen suggests R669G is "possibly damaging" which is consistent with the results of this study.

Introduction

FGFR3 is known as Fibroblast Growth Factor Receptor 3. FGFR3 is responsible for healing wounds, embryo development and regulating cell proliferation. Mutations in FGFR3 result in skeletal dysplasias of variable severity [2]. The mutation R669G is linked to craniosynostosis, a birth defect that causes a patient's head to be misshapen due to the skull fusing together too early in the developmental process [2]. Many FGFR3 mutations originate from an unaffected father and are associated with increased paternal age at the time of conception. This finding has led to efforts to identify these specific mutations in sperm, which have been successful [4]. The variant takes basic, positively charged arginine and replaces it with neutral glycine. Position 669 is located at the end of an alpha helix and chemical shift perturbations or CSPs reveal there is a molecular brake due to this specific mutation [4].

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Methods

The workflow known as "sequence to structure to function" was used to assess R669G [3]. The program YASARA was used to create visuals of the gene and VUS. A protein model for FGFR3 was generated using I-TASSER. A compilation of other FGFR3 variants was provided by ClinVAr, gnomAD, TOPmed, and COSMIC. R669G was compared to other variants of the gene using software such as Provean and SIFT. The protein was embedded in a lipid membrane and molecular dynamics similations (mds) were performed for 20 nanoseconds.

Results

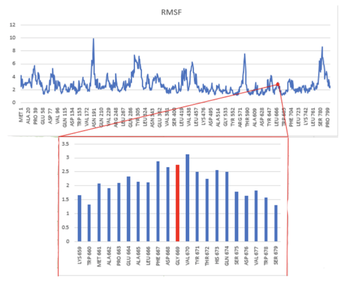

Figure 2:Molecular dynamic simulation of the FGFR3 protein model shown for the carbon alpha root mean squared fluctuation - The red box is a zoom in view of amino acids close to the variant with R669G highlighted in red

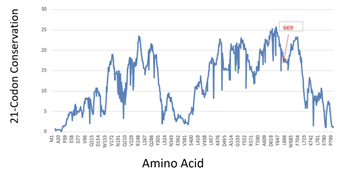

Figure 3:Based on a deep evolutionary analysis of 225 species open reading frames (ORFs) for FGFR3, reveal F669G to fall in a notably conserved region. The plot shows a sliding window calculation for each site (plus ten up and downstream), identifying the most selected and conserved linear motifs within FGFR3.

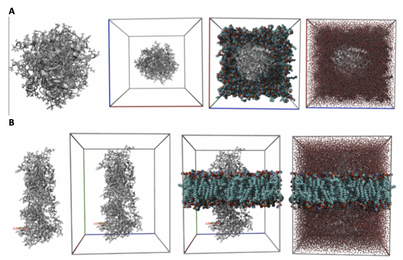

Figure 1:(A) - Top view of FGFR3 embedded in lipid membrane with water (B) - Side view of FGFR3 embedded in lipid membrane with water added

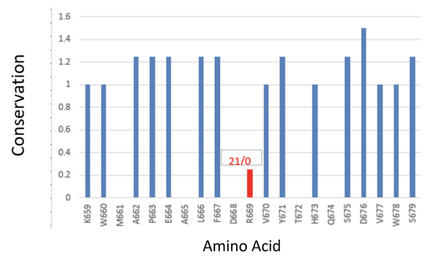

Figure 4:Zoomed in view of conservation score for amino acid 669's linear motif in red. The 21/0 represents the synonymous/nonsynonmyous variants throught evolution.

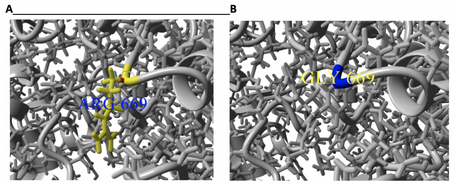

Figure 5:(A) - Wild type arginine at position 669 (B) - amino acid glycine which corresponds to the mutation in this study Notice the difference in the side chain of arginine and glycine and the impact the mutation has on the position 669's structure. The differences seen between the wild type and mutation are a result of the charge of arginine which is postive switching to neutral glycine

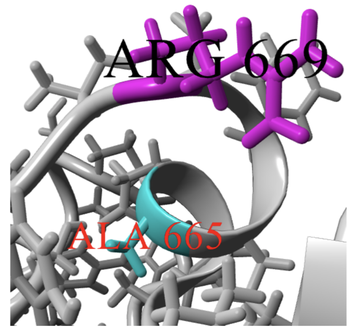

Figure 6:ALA 665 (cyan) is classified as "Likely Disease," 669 (magenta) is located close in proximity to ALA 665

Conclusion

As position 669 is in a notably high conservation region, it is likely to induce function changes when mutations occur. On October 12, 2020, R669G became classified by UniProt. Since FGFR3 is expressed in the brain, it is congruent that R669G is associated with Craniosynostosis. When arginine is swapped for glycine, a loss-of-function occurs. Regardless of this particular variant becoming classified by UniProt, more research needs to be done on FGFR3 in order to make advances and further study other FGFR3 mutations.

References

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University of North Alabama MATHEMATICS

HudsonAlpha CODE Characterizing Our DNA Exceptions