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Analysis RABL3 Variants and its Link to Pancreatic Cancer

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ABSTRACT

•Pancreatic cancer is difficult to treat as it is normally diagnosed when it is at an advanced stage. Certain environmental factors include smoking and obesity. In the United States pancreatic cancer has a survival rate of 12.5%. It is hard to detect early on because symptoms do not appear until the cancer is in a dangerous state. This is an important disease to study because of its high lethality rate. Around 52,000 people die a year due to pancreatic cancer. In the United States pancreatic cancer is responsible for 3% of all cancer deaths.

•ClinVar was used to do research on pancreatic cancer and what genes effect it. Including gene mapping, analysis of phenotypes, and mutations. ClinVar was also used to obtain the FASTA files which is used as a title or tag for researching the gene. PolyPhen2 was used to predict the functional effects the mutation would have on humans. SIFT was used to predict the effects that the mutation would have on protein function. Swiss and NCBI were used to study a 3D model of the gene. RABL3 is a member of the Ras family which are GTPases, they are used to regulate cellular processes such as signaling pathways, cytoskeletal organization, and the movement of vesicles within a cell. Its domains include the GTPase Domain, the switch Regions and the Effector Binding sites.

•A Missense mutation at position fifty-nine from Valine to Glycine (Val59Gly) is a pathogenic mutation. It was predicted to be damaging with a score of 0.740. An interesting finding is that RABL3 has a low rating (RPKM=1) in the pancreas. However, the significance of its role in cell function could potentially explain why mutations in the protein complex may contribute to pancreatic cancer. An understanding of the connection of RABL3 and Pancreatic cancer can lead to an earlier diagnosis for pancreatic cancer. Advances in this research can also lead to preventative medicine for this deadly disease.

INTRODUCTION

Rab is apart of the GTPase family, these proteins have a large role in cell transportation and cytoskeleton modulation.
Missense mutations substitute one protein for another which can lead to problems with the function of a complex.
RPKM (Reads Per Kilobase Million) is a metric used to quantify gene expression levels.
Valine is a neutral hydrophobic amino acid.
Glycine is the simplest amino acid with a side chain consisting of just a single hydrogen atom, it is hydrophobic and neutrally charged.

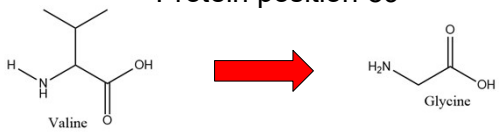
METHODS

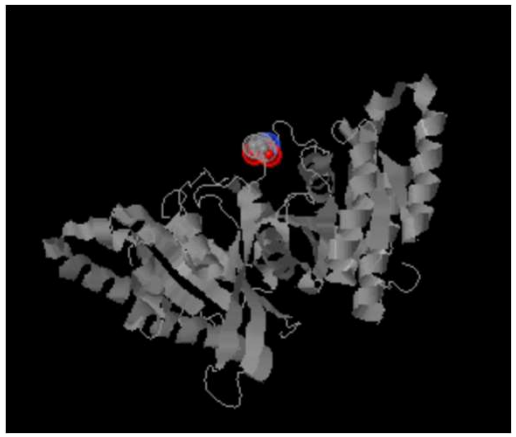
- **Data Collection and Analysis**
  - Utilized ClinVar database for pancreatic cancer research.
  - Conducted gene mapping, phenotype analysis, and mutation investigation.
  - Obtained FASTA files for gene identification and tagging.
  - Mutation Prediction
  - Employed PolyPhen2 to predict functional effects of mutations on human physiology.
  - Utilized SIFT to forecast alterations in protein function resulting from mutations.
  - Used Swiss and NCBI databases to study 3D models. Focused on RABL3 gene, a member of the Ras family of GTPases.
  - Analyzed domains including GTPase Domain, switch Regions, and Effector Binding sites.
- **Pathogenic Mutation Identification**
  - Identified a pathogenic missense mutation (Val59Gly) within RABL3.
  - Predicted to be damaging with a score of 0.740.
  - Expression Analysis
  - Investigated RABL3 expression levels in pancreatic tissue (RPKM=1).

RESULTS

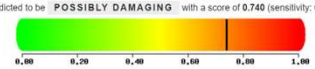
Protein position 59

A missense mutation causes Glycine to be placed where valine is normally.



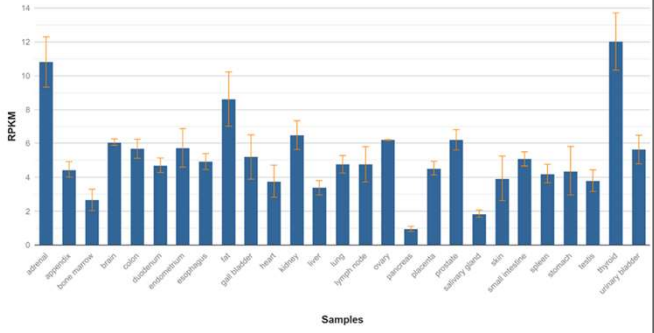


This mutation is predicted to be POSSIBLY DAMAGING with a score of 0.740 (sensitivity: 0.85; specificity: 0.92)



The mutation has a score of 0.740 or 74% in terms of damage.

In the pancreas RABL3 has a low RPKM of 1.



DISCUSSION AND CONCLUSION

The results support a missense mutation in RABL3 substituting Valine for Glycine being a likely cause for pancreatic cancer. Although RABL3 has a low expression rate in the pancreas, Its importance in cell signaling and cytoskeletal stability makes it a critical gene for cell regulation.

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