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# Analysis of FOXC2 variant implicated in diabetes

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# Analysis of FOXC2 variant implicated in diabetes

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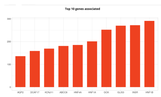
## ABSTRACT

Diabetes is a chronic health condition that affects the way individuals' bodies choose to breakdown food. In a healthy individual the body breaks down the food you eat into glucose, releasing it into the bloodstream. When the glucose levels become too high, the body then signals the pancreas to release insulin, which allows the blood sugar to be used as energy. Now in individuals who are suffering from diabetes, their bodies can't make enough insulin, and as a result blood sugar levels rise expeditiously. The purpose of this study is to determine the variants implicated in one of the major leading killers in the world, known as diabetes. The variant identified to be associated with diabetes was FOXC2. FOXC2, which stands for forkhead box C2, is a gene member apart of the forkhead box family. In addition, this gene is also considered a transcription factor, giving it control over the activity of other genes. Through analysis of FOXC2, 13 missense mutations were identified, three of which were studied throughout this study. Additional analysis tools, SIFT and PolyPhen-2 were utilized to predict the impacts amino acid substitutions have on the function of human proteins. SWISS modeling was used to to get a sense of how the protein structure looked three-dimensionally. The three missense mutations identified were Leu487Pro, Ala189Glu, and Tyr41Phe. Leu487Pro and Tyr41Phe were predicted to be tolerated with a score of 0.97, whereas Ala189Glu was predicted to be tolerated with a score of 0.007. All these mutations were predicted to have a high chance of affecting protein function, with a score of 0.0. Gene expression was predominantly identified in the lymphatic endothelial cell, reason being why cancer patients with diabetes are more prone to resistance against

## INTRODUCTION

Diabetes is a chronic disease that affects much of the population, being one of the most common killers worldwide. This disease occurs when the pancreas can't produce enough insulin. In other cases, this disease can also occur when the body isn't able to productively use the insulin produced. This can be detrimental to one's blood glucose level, causing it to rise substantially. Once one's blood glucose level rises too high for the body to maintain, the buildup of glucose in the blood causes hyperglycemia, which in turn can be deadly. There are three types of diabetes: type 1, type 2, and gestational diabetes. The most common is type 2 diabetes, which is acquired genetically, reason being why individuals with a family history of diabetes should watch on what they consume. Individuals with type 2 diabetes make insulin, but the amount of insulin is less than what the body is accustomed to. The body produces less insulin due to the body's acquired resistance to it. Type 1 diabetes is very similar to type 2 diabetes, only difference being that the pancreas makes absolutely no insulin. Gestational diabetes is seen among pregnant women. Women diagnosed with gestational diabetes can't produce enough insulin to maintain blood glucose levels, but these levels return to normal once they've given birth.

In order to identify courses of action to be taken to prevent this disease, and if not prevent make it manageable, the genes associated with this disease should be analyzed. Diseases are interesting in a way that they aren't caused by one specific gene expression, but by the way all the genes choose to work together. If a mutation in one gene causes an overexpression, this can affect the expression of another gene, in turn causing a domino effect. Additionally, genes such as , may be associated in a disease but may not entirely be the cause, it instead may give rise to other diseases.



## METHODS

- SWISS modeling was used to get a sense of how the protein structure looked three-dimensionally.
- Simple-Clinvar was used in this study to identify the presence of FOXC2 in diabetes.
- SIFT and Polypehn-2 were used to help predict the impacts amino acid substitutions have on the function of human proteins.
- Polyphen-2 was used to the predict the effect of missense variants through amino acid substitution.
- SIFT was used to predict the affect amino acid substitution has on protein function.

## RESULTS

### Gene Identification

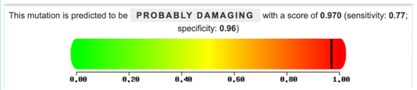
- FOXC2, which stands for forkhead box C2, is a gene that's a member of the forkhead box family. In addition, this gene is also considered a transcription factor, giving it control over the activity of other genes.
- Its key role is in the regulation of lymphatic endothelial cell differentiation during embryogenesis. In addition, this gene also plays an important role in the formation of smooth muscle layers and morphogenesis of lymphatic valves, which still takes place during embryogenesis.

### Protein Homology

### Prediction of Pathogenicity: SIFT and Polyphen-2

The three missense mutations identified were Leu487Pro, Ala189Glu, and Tyr41Phe.

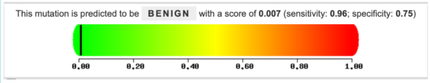
- Leu487Pro missense mutation is uncertain. Polyphen-2 predicts this missense mutation will probably be damaging due to its score of 0.97.
- SIFT predicts Leu487Pro to be tolerated with a score of 0.00.




**Predictions**

```
Substitution at pos 487 from L to P is predicted to AFFECT PROTEIN FUNCTION with a score of 0.00.
    Median sequence conservation: 3.73
    Sequences represented at this position:8
WARNING!! This substitution may have been predicted to affect function just because
 the sequences used were not diverse enough.  There is LOW CONFIDENCE in this prediction.
```

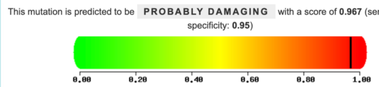
- Ala189Glu missense mutation is likely benign. Polyphen-2 predicts this missense mutation will be benign due to its score 0.007.
- SIFT predicts Ala189Glu to be tolerated with a score of 0.93.




**Predictions**

```
Substitution at pos 189 from A to E is predicted to be TOLERATED with a score of 0.93.
    Median sequence conservation: 3.39
    Sequences represented at this position:32
```

- Tyr41Phe missense mutation is pathogenic. Polyphen-2 predicts this missense mutation will probably be damaging due to its score 0.967.
- SIFT predicts Tyr41Phe to be tolerated with a score of 0.02.

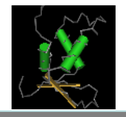



**Predictions**

```
Substitution at pos 41 from Y to F is predicted to AFFECT PROTEIN FUNCTION with a score of 0.02.
    Median sequence conservation: 3.46
    Sequences represented at this position:17
WARNING!! This substitution may have been predicted to affect function just because
 the sequences used were not diverse enough.  There is LOW CONFIDENCE in this prediction.
```

### Protein Homology

The only conserved domain found was the FH domain. This domain is named for the Drosophila forkhead protein, which is a transcription factor responsible for promoting terminal development. The FH domain is structured containing two flexible "wings" in the C-terminal region.



## DISCUSSION AND CONCLUSION

- Individuals who suffer from diabetes typically don't have healthy diets. These unhealthy diets increase FOXC2 levels, which surprisingly enough counteract most of the symptoms associated with obesity. These symptoms include hypertriglyceridemia and induced insulin resistance. Essentially stating that increased FOXC2 levels improve the chances of protection against type 2 diabetes.
- FOXC2 is an emerging oncogene linked to cancer progression. Its drug resistance makes it difficult for therapies such as chemotherapeutics to succeed. Some factors that drive cancer chemoresistance include its promotion of epithelial-mesenchymal transition, induction of multidrug transporter, deregulation of cell survival signaling pathways, and activation of oxidative stress response. FOXC2 is linked to cancer due to the factors that drive its resistance to chemoresistance, making this gene an oncogene.

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HudsonAlpha Institute for Biotechnology
CODE
Characterizing Our DNA Exceptions