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Analysis of the R100Q and P206S variants' implications in bipolar disorder

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ABSTRACT

Bipolar disorder is a psychiatric disorder that has a heritability rate of 0.7-0.8. There is much unknown regarding the genetic mutations associated with this disorder. The serotonergic system has been proven to be involved in the development of BD, and several genes have been studied for their involvement. Understanding the gene variants involved in this highly heritable disease and their impact on the human body is crucial to understanding how the genes implicated in this disorder interact to produce this phenotype. To discover and analyze these genes Simple Clinvar, Polyphen 2, SIFT, and SWISS modeling as well as the National Library of Medicine were used. The TPH2 gene, which comparatively was highly expressed in the brain, was identified in Simple Clinvar as being implicated in bipolar disorder for its critical involvement in the biosynthesis of serotonin. Out of the ten variants identified for this gene, two variants were selected for further analysis. While the R100Q variant was predicted to be benign and tolerated in protein function, the P206S variant was predicted to be possibly damaging and to have an effect on protein function. TPH is a rate-limiting enzyme that is implicated in other psychological disorders such as depression and suicidal behavior. The TPH2 isoform is commonly expressed in the raphe nuclei neuron that contains serotonergic neuronal components. There is very little information known on the effects of polymorphisms of TPH2. However, research suggests that mutations to this gene that decrease its activity negatively affect behavior and possibly survival. If more research is done on the P206S variant, it can potentially be discovered how it can impact bipolar disorder and modify its treatment.

INTRODUCTION

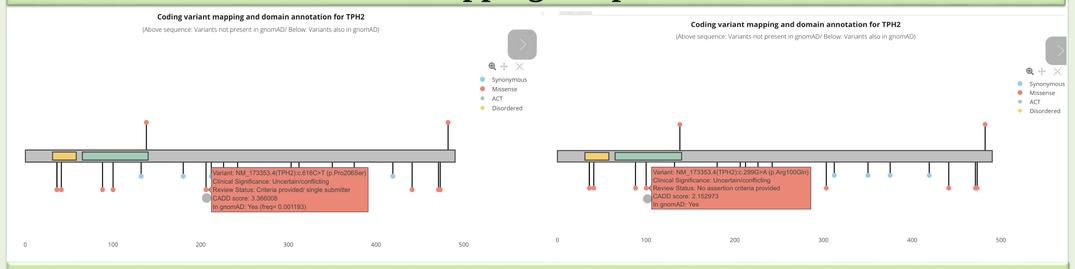
Bipolar disorder is a psychiatric disorder that has a heritability rate of 0.7-0.8 (Harrison et al., 2018). A child of a parent who has bipolar disorder is ten times as likely to experience it in their lifetime. Individuals with bipolar disorder experience episodes of elevated mood described as mania, followed by depression. In between these fluctuations, they can experience normal moods (euthymia). Most individuals have longer periods of depression than mania, although the duration of mood episodes varies between persons, as well as the number of episodes. It has been difficult to find causative genes for this disorder due to many genes with small effects, as well as gene-gene interactions being involved (Choi et al., 2010). The serotonergic system has been shown to be involved in the development of BD, and several genes have been studied for their involvement.

METHODS

Simple Clinvar was used to identify the genes implicated in bipolar disorder as well as phenotypes, missense mutations, and the protein mapping for the TPH2 gene. The National Library of Medicine was used to discover more information about the gene and related phenotypes, to find relevant literature, to obtain the FASTA format of the amino acid sequence, and to identify conserved domains. Polyphen 2 utilized the FASTA sequence to analyze relevant variants for the likelihood of pathogenicity. SIFT was used to analyze the likelihood of the variants selected to affect protein function. Swiss Model Pro was used to obtain models of the gene.

RESULTS

Protein Mapping-Simple Clinvar



Polyphen 2

PolyPhen-2 report for EAW97279.1 P206S

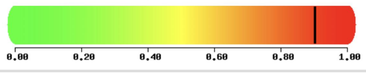
Query				
Protein Acc	Position	AA_1	AA_2	Description
EAW97279.1	206	P	S	tryptophan hydroxylase 2, isoform CRA_c [Homo sapiens]

Results

Prediction/Confidence — *PolyPhen-2 v2.2.3r406*

HumDiv

This mutation is predicted to be **POSSIBLY DAMAGING** with a score of **0.902** (sensitivity: **0.82**; specificity: **0.94**)



PolyPhen-2 report for EAW97279.1 R100Q

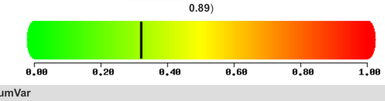
Query				
Protein Acc	Position	AA_1	AA_2	Description
EAW97279.1	100	R	Q	tryptophan hydroxylase 2, isoform CRA_c [Homo sapiens]

Results

Prediction/Confidence — *PolyPhen-2 v2.2.3r406*

HumDiv

This mutation is predicted to be **BENIGN** with a score of **0.321** (sensitivity: **0.90**; specificity: **0.89**)



HumVar

SIFT

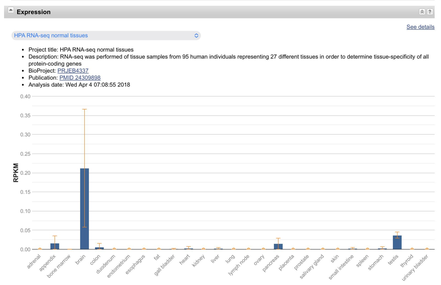
Predictions

```
Substitution at pos 206 from P to S is predicted to AFFECT PROTEIN FUNCTION with a score of 0.03.
    Median sequence conservation: 3.09
    Sequences represented at this position:24
```

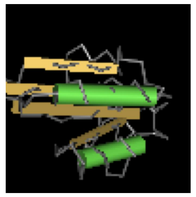
Predictions

```
Substitution at pos 100 from R to Q is predicted to be TOLERATED with a score of 0.27.
    Median sequence conservation: 3.09
    Sequences represented at this position:24
```

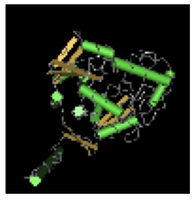
Gene Expression



Conserved Domains

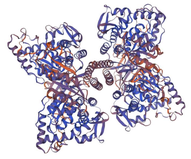


ACT domain

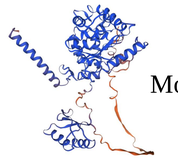


Biopterin_H Domain

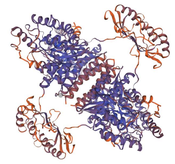
SWISS Pro Modeling



Model 1



Model 2



Model 3

DISCUSSION AND CONCLUSION

Tryptophan hydroxylase (TPH) is a rate-limiting enzyme responsible for catalyzing the biopterin-dependent monooxygenation of tryptophan to 5-hydroxytryptophan, which when decarboxylated becomes serotonin (Choi et al., 2010)(Lopez et al., 2007). The TPH2 gene located on chromosome 12q is the isoform of TPH that mostly is expressed in the raphe nuclei neuron of the brainstem, where serotonergic neurons are the main neuronal components. There have been several studies concerning the relationship between this gene and bipolar disorder. One study showed that in the dorsolateral prefrontal cortices of post-mortem bipolar disorder patients, there were higher levels of TPH2 (Choi et al., 2010). There is a significant association between mutations in TPH2 and bipolar disorder, and it has also been shown that there is a negative impact on behavior and survival in psychiatric affective disorders when mutations that decrease TPH2 activity occur (Lopez et al., 2007)(Popova & Kulikov, 2010). TPH2 has been studied concerning several psychological disorders, such as depression, suicidal behavior, and bipolar disorder. It has also been implicated in Attention deficit hyperactivity disorder 7. In this study, only the P206 mutation return results in SIFT and Polyphen as having the potential to be damaging and to affect protein function. Because bipolar disorder is highly associated with genetics it is important to study mutations that could be causative for it. If more research is done on the P206S mutation, it can potentially be discovered how it impacts bipolar disorder and this information can be used to modify its treatment.

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