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Analysis of the role of TBR1 variants Glu223Gln and His681Gln in the development of ADHD

Elaine Vanterpool
Oakwood University, evanterpool@oakwood.edu

Josel Bryant
Oakwood University

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Josel Bryant and Elaine Vanterpool, PhD
Oakwood University
Department of Biological Sciences
Huntsville AL, 35896

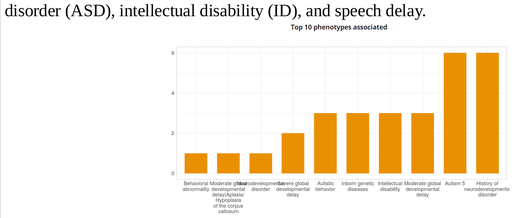
ABSTRACT

Attention-deficit/ hyperactivity disorder (ADHD) is a mental health condition characterized by constant instances of inattention and/or hyperactivity that interfere with an individual's performance and development. ADHD symptoms can manifest as early as the age of 3 and can continue into adulthood. The purpose of this study is to contribute to research concerning ADHD and the genetic variants associated with the disease. The public archive, Simple ClinVar, detected the genes associated with ADHD, including TBR1. TBR1 was revealed to be associated with 25 potentially pathogenic mutations. Significantly, of the 25 missense mutations detected, 8 possessed the phenotype for Autism 5 and autistic behavior, while 7 possessed the phenotype for neurodevelopmental disorder. With the addition of prediction tools such as PolyPhen-2 and SIFT, designated mutations were analyzed to determine their pathogenicity and role in affecting protein function. SWISS-MODEL, a protein structure homology-modeling server, assembled information about the protein structure. The T-Box Brain Transcription Factor, a gene primarily expressed in the brain, is a member of the T-box family with common features including DNA-binding and transcriptional regulatory activity, a role in development, and conserved expression patterns. Missense mutations from E223Q and H681Q were observed and interpreted. Mutation E223Q was predicted to be probably damaging with a score of 0.997 and to affect protein function with a score of 0.00. In contrast, the mutation H681Q was found to be possibly damaging with a score of 0.932, and affected protein function with a score of 0.02. Establishing a connection between TBR1 and ADHD is a critical step in lessening the cases of delayed diagnosis due to information gaps.

INTRODUCTION

Attention deficit hyperactivity disorder, a neurodevelopmental disorder that presents with inattention, hyperactivity, and impulsivity, is classified into three subtypes: predominantly inattentive, predominantly hyperactive-impulsive, and combined. While the causes of ADHD are diverse they include aberrant neural development, affecting neurogenesis, synaptogenesis, myelination, and neuronal and glial proliferation and migration.

As a condition that affects brain function, it is coherent that the disorder has some association with TBR1, a neuron-specific transcription factor involved in brain development. TBR1 is commonly associated with a neurodevelopmental disorder (NDD) combining features of autism spectrum disorder (ASD), intellectual disability (ID), and speech delay.



The central purpose of this study is to analyze abnormalities that occur during neurogenesis that correlate with ADHD. TBR1 expression plays important regulatory roles in developing many brain structures such as the embryonic amygdala, hippocampus, olfactory bulb, and the deep cerebellar nuclei. Thus, evaluating the association between ADHD and TBR1 will have significant results.

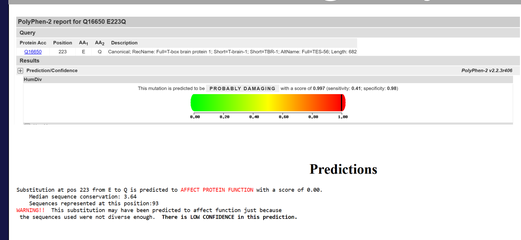
METHODS

The methods utilized in this study include Simple ClinVar, PolyPhen-2, SIFT, and SWISS Modeling.

- Simple ClinVar was used to determine the genes affiliated with ADHD. Filtering the search to missense mutations that had pathogenic, likely pathogenic, uncertain/conflicting, and likely benign clinical significance allowed further exploration of the mutations in the selected gene, TBR1, that contribute to ADHD.
- PolyPhen-2 and SIFT were used to analyze the pathogenicity of the TBR1 mutations E223Q and H681Q and their effect on protein function.
- Swiss Modeling was used to visualize the structure/homology of the proteins TBR1 codes for.
- The datasets provided by the National Library of Medicine were used to establish the location of gene expression, and the conserved domains, and obtain the protein FASTA used in PolyPhen-2 and SIFT to specify the TBR1 gene being studied.

RESULTS

Mutation Pathogenicity Predictions: PolyPhen-2 and SIFT



Figures 1 and 2. PolyPhen-2 and SIFT predictions for the pathogenic missense mutation at position 223 (Glu to Gln)

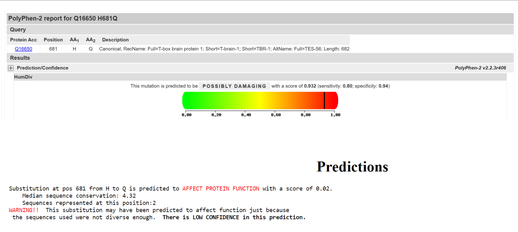


Figure 3 and 4. PolyPhen-2 and SIFT predictions for the uncertain/conflicting missense mutation at position 681 (His to Gln)

Protein Homology

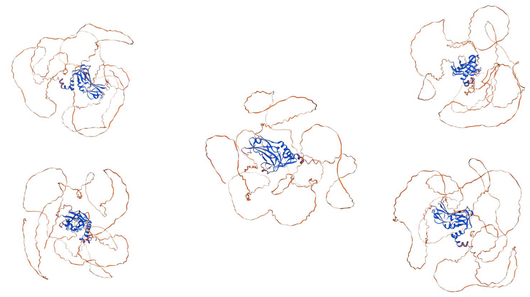
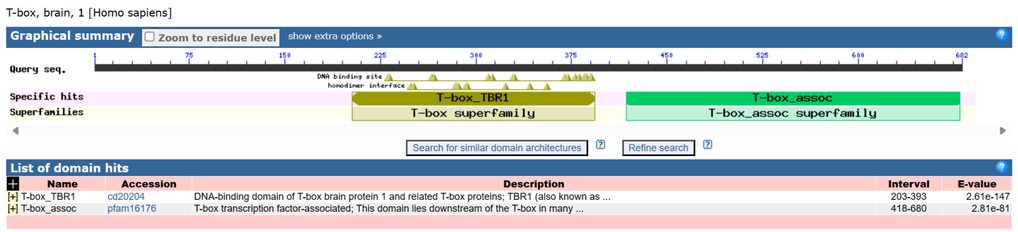


Figure 5. SWISS-Model. 3D structure homology-mode of the protein taken from five varying angles.

Conserved Domains



Domain 1: DNA-binding domain of T-box brain protein 1 and related T-box proteins
TBR1 (also known as T-brain-1 or TES-56) is a neuron-specific transcription factor of the T-box family and involved in forebrain development. It has been recognized as a high-confidence risk gene for autism spectrum disorders (ASD); it regulates the expression of ASD-related genes that are critical for cortical development.
Domain 2: T-box transcription factor-associated
This domain lies downstream of the T-box in many eukaryotic T-box proteins. The exact function is not known.

DISCUSSION AND CONCLUSION

- T-box brain transcription factor 1 encodes transcription factors involved in the regulation of numerous developmental processes. At the transcriptional level, TBR1 regulates the expression of several genes mutated in intellectual disability (ID) and autism spectrum disorders (ASD). Therefore, when analyzing the origins of neurodevelopmental disorders, it is essential to examine mutations in TBR1.
- Occasionally, symptoms of ADHD are mistaken for emotional or disciplinary problems or missed entirely in adolescents who mainly have symptoms of inattention, leading to a delay in diagnosis. It has been determined that the number of adults possessing ADHD has been increasing over the past 20 years. This can have detrimental effects on academic, personal, and career performance.
- By studying genes such as TBR1 and determining the correlation between mutations in this gene and ADHD, geneticists will be able to create connections that may lead to earlier and more frequent diagnoses of the disorder.
- Additionally, the study of TBR1 can offer insight into the biological mechanisms underlying conditions such as ADHD and the treatment needed to combat them. Selecting the appropriate treatment and dosage takes time, leading to delays in finding a suitable solution and, in some cases, termination of treatment. By making a connection between the mutation present and the effect that it will have on the individual the process can be expedited resulting in more patients receiving the treatment they require.

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