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AAK1 Circular Regulates Neuronal Development by Interacting with miR-132, miR-146a and miR484

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ABSTRACT

Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders characterized by communication and social interaction impairment. Circular RNAs were discovered to be extremely enriched in the mammalian brain, to be highly conserved in sequence, and it has been demonstrated that circular RNAs deregulate in ASD postmortem brains. In the present study, we attempted to answer the question of which circular RNA can inhibit pathogenic ASD miRNAs. ASD miRNAs were downloaded from HMDD and three including miR-132, miR-146a and miR484 were selected. Their pathogenic role in ASD was determined experimentally. miRNAs gene targets predicted by miRDB and AAK1 were obtained as a common target gene. circular RNA origin from exons so, miRNAs could bind to their circular gene targets. AAK1 circular RNAs downloaded from circAtlas 2.0 and results blasted by NCBI BLAST. Finally, 10 circular RNA was obtained for AAK1.

Keywords: Autism, Circular RNA, AAK1, miR-132, miR-146a and miR484

Introduction

Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders characterized by communication and social interaction impairment, as well as restricted repetitive and stereotyped behaviours [1]. Autism spectrum disorders (ASDs) are lifelong and often devastating conditions that severely impair social functioning and self-sufficiency, wreaking havoc on the lives of the affected individuals' entire families. ASDs are defined by persistent deficits in social communication and interaction, as well as restricted and repetitive behaviours, interests, and activities, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [2].

Circular RNAs (circRNAs) are endogenous biomolecules that are covalently closed and have no 5' end caps or 3' poly(A) tails. These RNAs are classified as non-coding RNA (ncRNA) molecules [3]. Our understanding of the expression profiles and biological roles of circRNAs has advanced dramatically in recent years. circRNAs are particularly enriched and expressed more abundantly in the brain than their linear counterpart transcripts. They have a high level of activity at neuronal synapses. These characteristics make circRNAs particularly important for understanding brain health, disease, and neuropsychiatric disorders [4]. As a result of the lack of exposed ends that could be targeted by 3' or 5' exoribonucleases, circRNAs are estimated to be 2.5 to 5 times more stable than linear transcripts [5]. circRNAs were found to be extremely enriched in the mammalian brain, to be highly conserved in sequence, to be frequently expressed as circRNAs in both human and mouse brains, and to be occasionally detected in Drosophila brains. circRNAs were found to be upregulated in general during neuronal differentiation, to be highly enriched in synapses, and to be frequently differentially expressed when compared to their mRNA isoforms [6]. A study on postmortem brains from individuals with ASD has shown that in ASD, 60 circRNAs and three coregulated modules were disrupted [7]. ASD circRNAs can regulate the TGF-

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beta signalling pathway, Notch signalling pathway, MAPK signalling pathway and long-term depression take part in the pathogenesis of autism [8]. CircRNA has also been shown to regulate transcription or splicing, act as a sponge for miRNA, interact with RNA-binding proteins, and translate protein [9]. Researchers have discovered that microRNAs (miRNAs) could be one of the possible causes of ASD [10].

MiRNAs are small non-coding RNAs that regulate gene expression. They are frequently associated with biological processes and have been implicated in neurodevelopment.

The aim of this study find circRNAs that can sponge ASD pathogenic miRNAs so, these circRNAs can play a beneficial role against the ASD symptoms. In the present study, we evaluated ASD miRNAs and their interaction of them with circRNAs finally circRNAs candied which potential for interaction and sponge ASD miRNAs.

Materials and Methods

ASD's miRNAs

The HMDD database is an experimentally validated database of human miRNA diseases It gathered 32281 entries with experimentally supported miRNA–disease associations [11]. ASD's miRNAs were downloaded from HMDD v3.2 then miRNAs were selected because they have an experimentally pathogenic role in ASD.

miRNA target prediction

miRDB is a web-based database that predicts functional microRNA targets [12].

Circular RNA prediction

circAtlas 2.0 predicts circular RNAs based on an analysis of 1070 RNA-seq samples from 19 different tissues. It has collected over one million circular RNAs from six different organisms [13]. circAtlas 2.0 was employed for circular RNA prediction.

Results

ASD's miRNAs

19 miRNAs were obtained from HMDD v3.2 database after that, 3 miRNAs including miR-132, miR-146a and miR484 were selected which experimentally approved their function in the ASD.

miRNA target prediction

Gene target prediction for miR-132, miR-146a and miR484 were performed by miRDB database. Just AAK1 was a common gene target for miR-132, miR-146a and miR484 so, it was used for circular RNA prediction. The Methyl CpG binding protein 2 gene (MeCP2 gene) encodes a transcriptional repressor that is abundant in mammalian neurons. MeCP2 regulates neuronal differentiation, neural development, and synaptic plasticity. MiR-132 binds to the 3'UTR of MeCP2 and inhibits its expression at the post-transcriptional level [14]. Overexpression of miR-146a promotes neurite outgrowth and branching, as well as differentiation into neuronal-like cells. Analysis of transcriptome expression revealed that 10% of the transcriptome was deregulated and organized into two modules important for cell cycle control and neuronal differentiation [15]. Mature miR-484 was found to be expressed during active cortical neurogenesis, and overexpression of miR-484 in vivo reduced proliferation while increasing neural progenitor differentiation [16].

Circular RNA prediction

A total of 102 circRNAs were found for AAK1 in different lengths from 42 to 1997 nucleotide. To find potential circRNA, we choose the 40 longest circRNAs because can target more miRNAs. for validation data, all 40 circRNAs were blasted with NCBI BLAST. 10 sequences from 40 circRNAs completely match AAK1. It seems that most AAK1 circular RNAs originate from exon 22. The longest circular RNA (has-AAK1_0079) is 724 nucleotide length and it also, origin from exon 22.

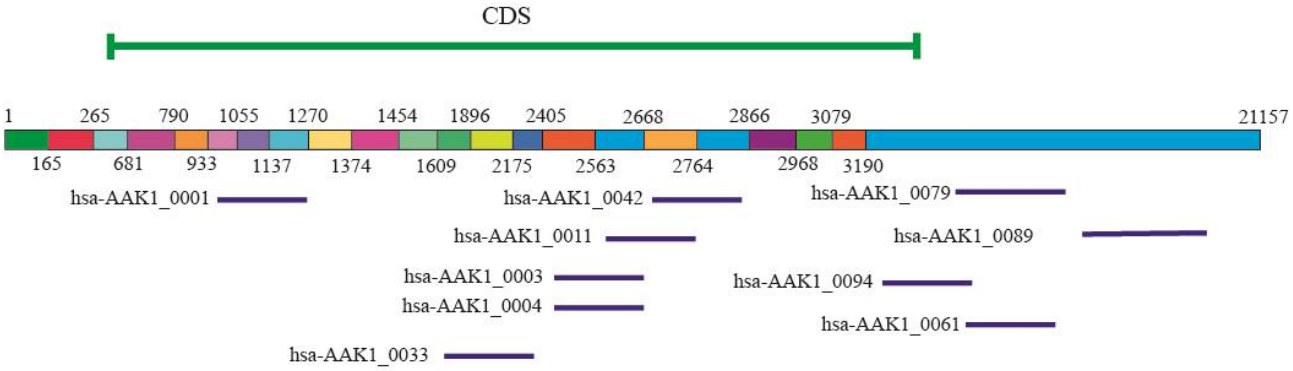

Figure 1. AAK1 gene contains 22 exons which are presented in different colours. Most AAK1 circular RNAs originate from exon 22.

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Table 1
AAK1 circular RNAs

Circular RNA	Start	End
hsa-AAK1_0079	11635	12358
hsa-AAK1_0089	16657	17325
hsa-AAK1_0011	2176	2764
hsa-AAK1_0001	682	1270
hsa-AAK1_0061	8097	8683
hsa-AAK1_0033	1897	2405
hsa-AAK1_0003	2175	2668
hsa-AAK1_0004	2176	2668
hsa-AAK1_0094	5030	5499
hsa-AAK1_0042	2406	2866

Discussion

Autism is a neurodevelopmental disorder marked by dysfunction in three key behavioural dimensions: repetitive behaviours, social deficits, and language abnormalities. Autism is classified as one of a group of disorders known as ASDs, which are distinguished by the severity of their symptoms [17]. According to the Centers for Disease Control and Prevention, one in every 54 children in the United States was diagnosed with ASD in 2016. ASD affects approximately one in every 160 children worldwide. The prevalence of ASD has risen in recent years as access to healthcare surveillance has improved. Autism prevalence increased by 78% in the United States between 2002 and 2008, according to the Autism and Developmental Disabilities Monitoring Network [18].

The study of epigenetics is more complicated than genetics because epigenetics of any tissue can change over time and vary depending on the tissues collected for the study. In an ideal world, autism research would involve studying the epigenome of brain tissue; however, such samples are scarce, and even when they are available, the phenotypes are not always well defined [19]. Although a wide range of gene expression dysregulation has been reported in autism spectrum disorder (ASD), the role of circRNAs in ASD is largely unknown [7].

Conclusion

In this study, we attempted to answer the question of which circular RNA can inhibit pathogenic ASD miRNAs. three ASD miRNA including miR-132, miR-146a and miR484 were obtained from HMDD. We found out that AAK1 is a common gene target for these miRNAs. so, AAK1 circular RNA could interact with miR-132, miR-146a and miR484 and play role in the pathogenicity of ASD.

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