DOI 10.47176/sjmshm.5.4.1

Original Article

SRPH

SJMSHM, 2023; 5(4): 1-6

miR-181-5p, miR-19-3p, miR-144-3p, miR-101-39.2, miR-218-5p Target Autism Genes and Regulate Axon Guidance, cAMP and MAPK Signalling Pathway

Javad Amini[1*] and Elham Feridouni[2]

[1]Department of Biology, Faculty of Basic Sciences, University of Zabol, Zabol, Iran.
[2]Department of Biological Sciences, Gonbad Kavous University, Gonbad Kavous, Iran.

***Corresponding Author:**
Aminijavad4@gmail.com

Received: 15 September, 2023
Accepted: 28 November, 2023
Published: 25 December, 2023

ABSTRACT

Autism spectrum disorder (ASD) is a term used to describe a constellation of Behavioral and mental disorders and social communication defects with the repetitive activity that is lifelong. Studies recently have shown the complex underpinnings of genetic and high heritability for autism. Due to the widespread behavioural symptoms of the disease in patients with neurodevelopmental disorders, it is difficult to diagnose correctly and quickly. Accordingly, the use of molecular methods and biomarkers such as microRNAs can be useful in diagnosing autism from other neurodevelopmental disorders. In this study, we used databases to find the microRNAs and their target genes that are most associated with the pathogenesis of ASD. The association between autism and other neurodevelopmental disorders was also examined. According to analyzes, microRNAs, miR-181-5p , miR-19-3p, miR-144-3p ,miR-101-39.2,miR-218-5p are most associated with autism.

Keywords: Autism, miR-181-5p, miR-19-3p, miR-144-3p, miR-101-39.2, miR-218-5p

Introduction

Autism spectrum disorders (ASD) are developmental disorders usually with an onset before the age of three. Individuals with autism spectrum disorders (ASD) develop differently. These differences are usually present in social interaction, communication, and sensory processing, and become visible through a wide variety of behavioural responses that differ from individuals without autism spectrum disorders [1]. ASD are very heterogenous due to complex underlying pathomechanisms triggered by various factors. Some children and adults with ASD are fully able to perform all activities of daily living, while others require substantial support to perform basic activities [2]. The Autism and Developmental Disabilities Monitoring (ADDM) Network is an active surveillance system that provides estimates of the prevalence of autism spectrum disorder (ASD) among children aged 8 years. According to the latest findings of the ADDM network, the overall ASD prevalence estimate of 16.8 per 1,000 children aged 8 years in 2014 is higher than previous estimates from the ADDM Network. With the prevalence of ASD reaching nearly 3% in some communities and representing an increase of 150% since 2000[3] ASD affects males at a much higher rate than females. The prevalence of autism in males is about four times that of females [4]. Gender also affects how symptoms occur in such a way that Males with autism tend to show external symptoms, such as aggression and hyperactivity, while females with autism tend to show less social communication in addition to restrictive and repetitive behaviours [5].

The aetiology of ASD is likely to be multifactorial, with both genetic and non-genetic factors playing a role. ASD can be syndromic or non-syndromic. Syndromic ASD is often associated with chromosomal abnormalities or monogenic alterations. Such examples

[DOI: 10.47176/sjmshm.5.4.1]

Publisher: Scientific Research Publishing House (SRPH), Shirvan, Iran
http://srpub.org
Email: sjmshm@srpub.org

include Rett syndrome, fragile X syndrome, and *MECP2* duplication syndrome [2]. Contrary to syndromic ASD, the aetiology of non-syndromic ASD is still relatively undefined due to its genetic heterogeneity. A collaboration of de novo mutations and prenatal plus postnatal environmental factors are likely to play a role [6].

miRNAs are known to play a critical role in neurodevelopment, metabolism, neuroplasticity, apoptosis, and other fundamental neurobiological processes [7]. They constitute a class of small non-coding RNAs composed of 20-22 nucleotides. miRNAs are post-transcriptional regulators; they bind to the 3' untranslated region (UTR) of messenger RNAs (mRNAs) to inhibit the translation or degradation of mRNA. a single miRNA can target approximately 200 transcripts, and more than one miRNA can act upon a single mRNA target.[8] Importantly, almost %70 of experimentally-detectable miRNAs are expressed in the human nervous system. [9] evidence suggests that alterations in miRNA expression or function are associated with the cognitive deficits and neurodevelopmental abnormalities observed in autism, schizophrenia and other forms of intellectual dysfunction [10, 11]. microRNAs are abundant in the developing brain and are dysregulated in children with ASD. Patterns of miRNA expression are altered in the brain, blood, saliva, and olfactory precursor cells of ASD subjects [12, 13, 14]. Approximately 11% of copy number variant (CNV) loci found in individuals with ASD harbour miRNAs, and CNVs on chromosomes 1, 2 and 22 are associated with miRNA overexpression (MicroRNA Expression Profiles in Autism Spectrum Disorder: Role for miR-181 in Immunomodulation).

This study uses bioinformatics to look for microRNAs that can target genes involved in the pathogenesis of ASD from signalling pathways associated with developmental neurodegeneration. The availability and extracellular stability of miRNAs make them an ideal candidate for biomarker discovery.

Materials and Methods

Autism-associated genes

SFARI gene is an online database that collected Autism genes in four categories including Syndromic, Category 1,2 and 3 [15]. All Autism genes were downloaded from the SFARI gene and they were used for miRNAs identification.

miRNA prediction

The web tool MIENTURNET aided in the prediction of miRNAs that target the identified influential genes (MicroRNA ENrichment TURned NETwork). To predict the interaction of miRNA on the target gene, this tool considers both computational and experimental evidence from the TargetScan and miRTarBase websites [16]. So, we employed MIENTURNET for miRNA prediction.

Gene enrichment analysis and disease-related analysis

KEGG pathway enrichment analysis for miRNAs target genes was performed using the Enrichr database [17]. DisGeNet disease-associated genes analysis was also performed using the Enrichr database.

Results

Autism-associated genes

1032 genes were obtained from the SFARI gene database. 150, 477, 198 and 26 genes were from S, score 3, score 2 and score 1 category respectively.

miRNA-target enrichment

219 miRNAs were obtained from MIENTURNET and 169 of them were significant (P-value < 0.05). the highest ASD genes-miRNAs interactions devoted to miR-181-5p, miR-19-3p, miR-101-3p.2, miR-218-5p and miR-144-3p. miR-181-5p targets 14, 86, 30 and 40 genes from category of S, 1,2 and 3 respectively.

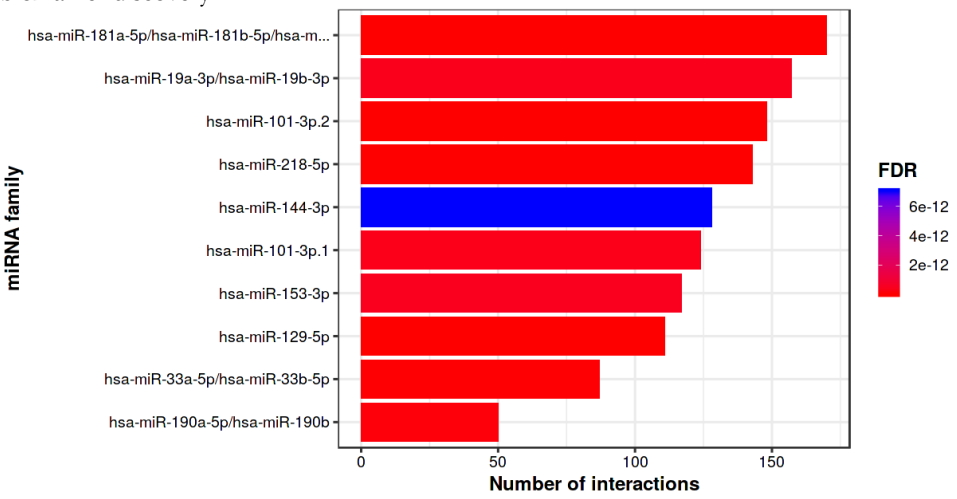


Figure 1. miRNA-target enrichment. miRNAs were sorted base on the number of interactions. The highest interaction devoted to miR-181-5p, miR-19-3p, miR-101-3p, miR-218-5p and miR-144-3p respectively.

[DOI: 10.47176/sjmshm.5.4.1]

The most interaction was devoted to miR-181-5p. Based on MIENTURNET results miR-181-5p targets 170 ASD genes and 86 of its target genes were from score 3.

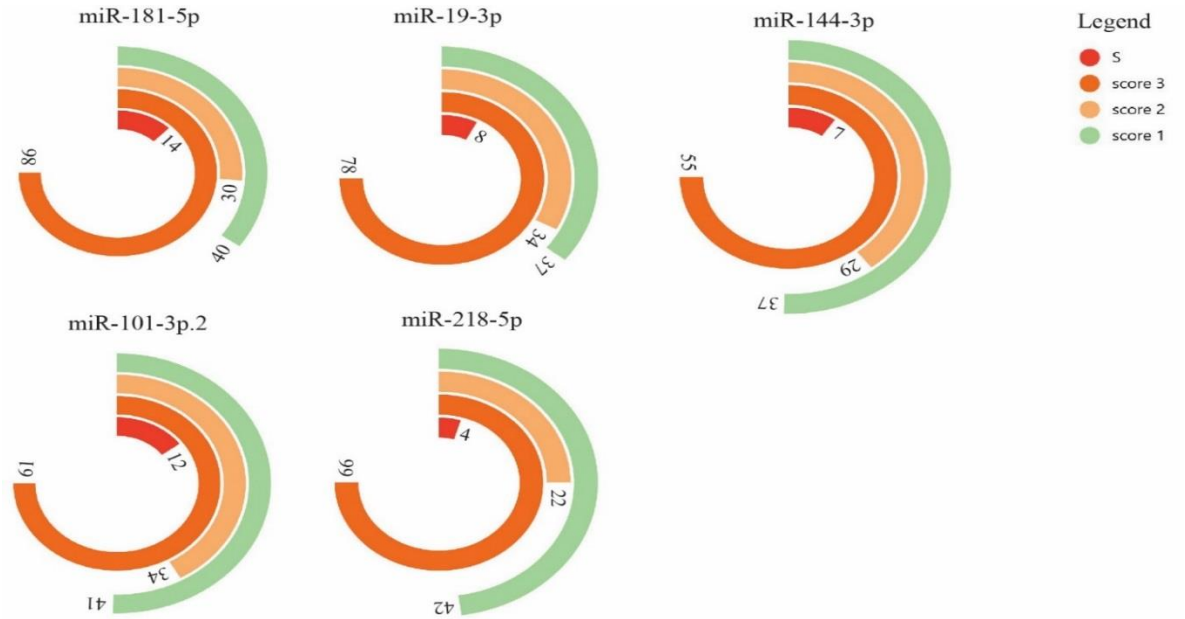
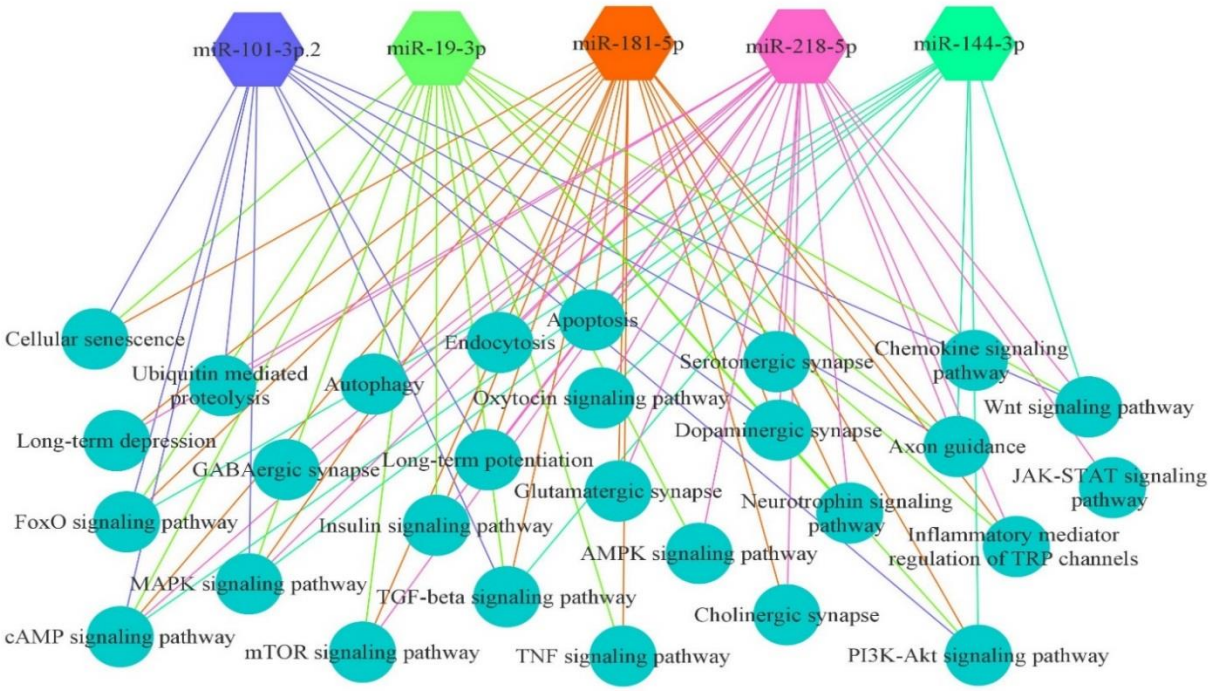


Figure 2. Gene targets categories. The highest interactions were devoted to miR-181-5p and miR-19-3p. miR-181-5p and miR-19-3p target 86 and 78 genes from the score 3 categories (based on the SFARI gene database).

Cellular pathway

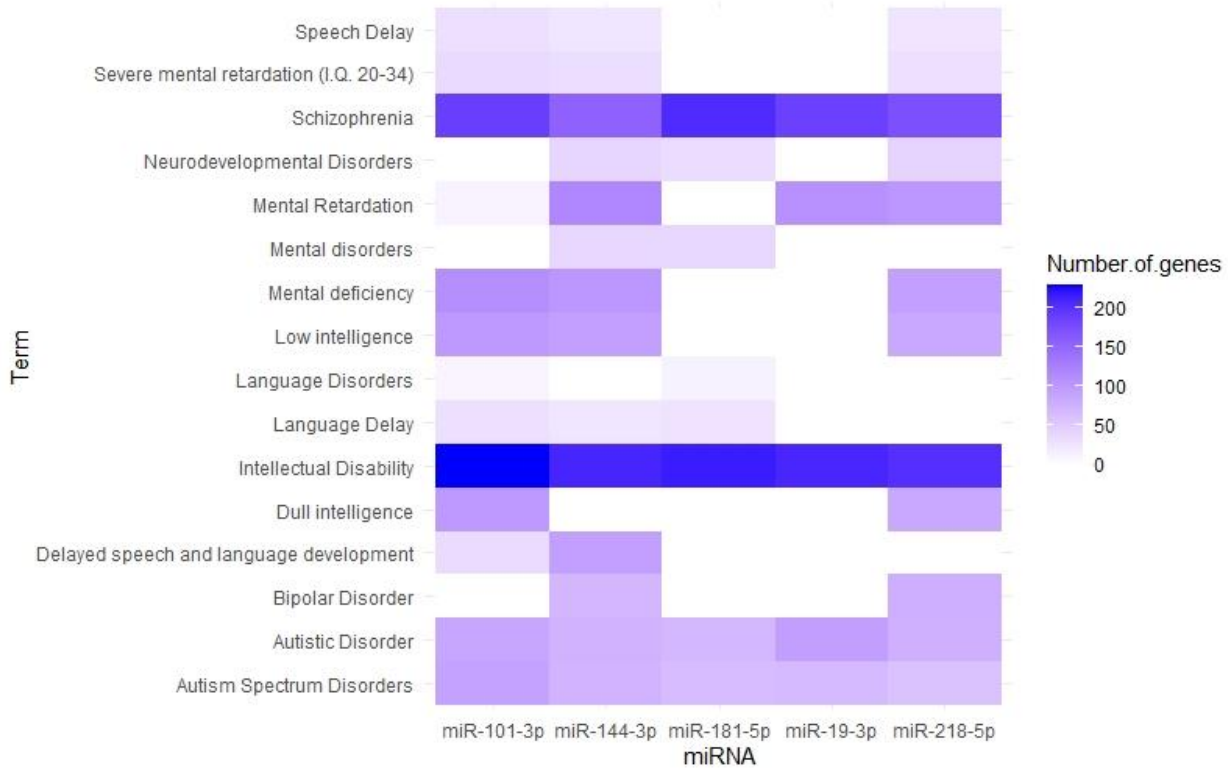
Totally 28 significant cellular pathways were obtained from enrichment analysis. miR-218 target the highest number of pathways, it targets 22 cellular pathways. Axon guidance, cAMP signalling pathway and MAPK signalling pathway targe by all five miRNAs.



[DOI: 10.47176/sjmshm.5.4.1]

Related diseases

All 5 miRNAs can target several genes from ASD related genes. All miRNAs target more than 200 genes from intellectual disability and schizophrenia. They also, target autistic disorders and autism spectrum disorders.



Discussion

Autism spectrum disorders (ASD) are complex, highly heritable neurodevelopmental diseases characterized by individuals with a combination of behavioural and cognitive impairments. These include impaired or diminished social communication skills, repetitive behaviours, and restricted sensory processing or interests [18]. Many large-scale genome-wide association studies (GWAS), as well as whole-exome sequencing (WES) and whole-genome sequencing (WGS), show the complex genetic underpinnings of ASD [19, 20, 21]. the diagnosis of ASD relies heavily on psychometric assessments. Given that the symptoms of the disease appear differently in each person, the use of molecular evidence such as miRNAs is essential for the early diagnosis of ASD.

Posttranscriptional mechanisms such as microRNAs (miRNAs) regulate gene expression without altering the genetic code. They regulate approximately two-thirds of human mRNAs [22]. For example, in mice with fragile X-associated tremor/ataxia syndrome (FXTAS), the fragile X mental retardation (FMR1) transcript is targeted by miR-221, miR-101, and miR-129-5p [23]. It has been studied recently that Some rare and highly-penetrant gene variants and copy number variation (CNV) regions have been dysregulated by microRNAs including miR-181b, miR-486 in signalling pathways may a role in ASD [24].

Examining the findings in the database, we identified the microRNAs and their target genes that were most associated with autism. Examining the findings, we identified the microRNAs and their target genes that were most associated with autism. MicroRNA 181-5p and its family members target more than 150 genes Also predicted for microRNAs 101-3p.2, 19-3p, 218-5p, 144-3p more than 100 genes.

Overall, the SFARI (Simons Foundation Autism Research Initiative) gene database, a database of autism candidate genes, lists about 1000 genes associated with ASD. Genes entered into the database are scored based on their strength of association with ASD risk, and are sorted into four different categories: S syndromic, category 1, category 2, and category 3 [https://gene.sfari.org/about-human-gene/ // https://gene.sfari.org/database/gene-scoring/]. It has been shown that five microRNAs target genes in all four categories. Only one mutation has been reported for third-line genes and Half of the genes associated with autism are in this category, hence the number of genes predicted for microRNAs is more in this category than in other categories.

[DOI: 10.47176/sjmshm.5.4.1]

miRNAs can induce significant degradation of mRNA targets despite imperfect mRNA-miRNA base-pairing. MicroRNAs might also silence their targets by sequestering mRNAs in discrete cytoplasmic foci known as mRNA processing bodies or P bodies, which exclude the translation machinery [25]. This mRNA destabilization may alter several downstream pathways and induce several noticeable effects. A study has shown that differentially expressed target genes of differently expressed miRNAs can play a role in different vital neural pathways [12]. Our enriched analysis identified 28 neurologically relevant pathways and target genes for the five microRNAs and their families (miR-181-5p, miR-19-3p, miR-144-3p, miR-101-3p.2, miR-218-5p) most associated with neuropsychiatric disorders and ASD pathogenesis. miR-181a-5p targets AKT3, a key regulator of the PI3K-AKT-mTOR signalling pathway [26]. Bone marrow mesenchymal stem cells alleviate severe acute pancreatitis and reduce inflammatory responses and apoptosis by secreting miR-181a-5p to target the PTEN/Akt/TGF-β1 signalling pathway [27].

miR-144 may role of regulating mammalian social behaviour by the Oxytocin pathway [28]. up-regulating miR-144 expression in the PKC/MAPK/AKT signalling pathway causing abnormal modulation of nerve-related genes to trigger neurodevelopmental toxicity in brief [29, 30].

A microRNA may target several genes in different cellular pathways. [Target genes were predicted for five microRNAs, miR-218-5p, miR-19-3p, miR101-3p.2, miR181-5p, miR-101-3p, in neurodevelopmental disorders. It was found that they can target more than 200 genes in both schizophrenia and intellectual disability. These results suggest a genetic overlap between schizophrenia and intellectual disability and autism. These illnesses have complex inheritance and other studies have shown overlap an overlap between the genetic loci and even alleles that predispose to the different phenotypes [30, 31] alterations in specific miRNAs are only an epiphenomenon of the disease and they could be ideal biomarker candidates, given the increased stability and durability of miRNAs. However, due to the high overlap of the target genes of a microRNA in some neurodevelopmental diseases, it is better to use behavioural assessment methods and diagnostic devices along with molecular methods for a more accurate diagnosis.

References

1. Grabrucker AM Editor. Autism Spectrum Disorders. Exon Publications Copyright© 2021, Brisbane (AU). 2021.
2. Sauer AK, et al. Autism Spectrum disorders: Etiology and pathology. *Exon Publications,* 2021; 1-15.
3. Baio J, et al. Prevalence of autism spectrum disorder among children aged 8 years-autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *MMWR Surveillance Summaries,* 2018; 67(6): 1.
4. Halladay AK, et al. Sex and gender differences in autism spectrum disorder: summarizing evidence gaps and identifying emerging areas of priority. *Mol Autism,* 2015; 6(1): 1-5.
5. Frazier TW, et al. Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection. *J Am Acad Child Adolesc Psychiatr.* 2014; 53(3): 329-340. e3.
6. Lu J, et al. Rethinking autism: the impact of maternal risk factors on autism development. *Am J Translat Res.* 2022; 14(2): 1136.
7. Schepici G, et al. Autism spectrum disorder and miRNA: An overview of experimental models. *Brain Sci.* 2019; 9(10): 265.
8. Aw S, Cohen SM. Time is of the essence: microRNAs and age-associated neurodegeneration. *Cell Res.* 2012; 22(8): 1218-1220.
9. Cao X, et al. Noncoding RNAs in the mammalian central nervous system. *Ann Rev Neurosci.* 2006; 29: 77-103.
10. Xu B, et al. MicroRNA dysregulation in neuropsychiatric disorders and cognitive dysfunction. *Neurobiol Dis.* 2012; 46(2): 291-301.
11. Vaishnavi V, Manikandan M, Munirajan AK. Mining the 3' UTR of autism-implicated genes for SNPs perturbing microRNA regulation. *Genom Proteom Bioinform.* 2014; 12(2): 92-104.
12. Mundalil Vasu M, et al. Serum microRNA profiles in children with autism. *Mol Autism,* 2014; 5: 40.
13. Popov NT, et al. Micro RNA HSA-486-3P gene expression profiling in the whole blood of patients with autism. *Biotech Biotechnol Equip.* 2012; 26(6): 3385-3388.
14. Weber JA, et al. The microRNA spectrum in 12 body fluids. *Clin Chem.* 2010; 56(11): 1733-1741.
15. Abrahams BS, et al. SFARI Gene 2.0: a community-driven knowledgebase for the autism spectrum disorders (ASDs). *Mol Autism,* 2013; 4(1): 36.
16. Licursi V, et al. MIENTURNET: an interactive web tool for microRNA-target enrichment and network-based analysis. *BMC Bioinform.* 2019; 20(1): 545.
17. Xie Z, et al. Gene set knowledge discovery with enrichr. *Curr Protoc.* 2021; 1(3): e90.
18. Morimoto Y, et al. Atypical sensory characteristics in autism spectrum disorders, in autism spectrum disorders. Grabrucker AM Editor. Copyright: The Authors: Brisbane (AU). *Exon Publications,* 2021.
19. Frye RE, et al. MicroRNA expression profiles in autism spectrum disorder: role for miR-181 in immunomodulation. *J Pers Med.* 2021; 11(9).
20. Werling DM, et al. An analytical framework for whole-genome sequence association studies and its implications for autism spectrum disorder. *Nat Genet.* 2018; 50(5): 727-736.

[DOI: 10.47176/sjmshm.5.4.1]

21. Satterstrom FK, et al. Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell,* 2020; 180(3): 568-584.e23.
22. Friedman RC, et al. Most mammalian mRNAs are conserved targets of microRNAs. *Genom Res.* 2009; 19(1): 92-105.
23. Hicks SD, Middleton FA. A comparative review of microRNA expression patterns in autism spectrum disorder. *Front Psychiatr.* 2016; 7: 176.
24. Ghahramani Seno MM, et al. Gene and miRNA expression profiles in autism spectrum disorders. *Brain Res.* 2011; 1380: 85-97.
25. Eulalio A, Huntzinger E, Izaurralde E. Getting to the root of miRNA-mediated gene silencing. *Cell,* 2008; 132(1): 9-14.
26. Wang QG, et al. miR-320a in serum exosomes promotes myocardial fibroblast proliferation via regulating the PIK3CA/Akt/mTOR signaling pathway in HEH2 cells. *Exp Ther Med.* 2021; 22(2): 873.
27. Li HY, et al. Bone marrow-derived mesenchymal stem cells repair severe acute pancreatitis by secreting miR-181a-5p to target PTEN/Akt/TGF-β1 signaling. *Cell Signal,* 2020; 66: 109436.
28. Mor M, et al. Hypomethylation of miR-142 promoter and upregulation of microRNAs that target the oxytocin receptor gene in the autism prefrontal cortex. *Mol Autism,* 2015; 6: 46.
29. Diao W, et al. Triclosan targets miR-144 abnormal expression to induce neurodevelopmental toxicity mediated by activating PKC/MAPK signaling pathway. *J Hazard Mater.* 2022; 431: 128560.
30. Wang J, et al. Targeting MicroRNA-144/451-AKT-GSK3β axis affects the proliferation and differentiation of radial glial cells in the mouse hippocampal dentate gyrus. *ACS Chem Neurosci.* 2022; 13(7): 897-909.
31. Carroll LS, Owen MJ. Genetic overlap between autism, schizophrenia and bipolar disorder. *Genom Med.* 2009; 1(10): 102.

[DOI: 10.47176/sjmshm.5.4.1]

SJMSHM

Citation: Amini J, Feridouni E. miR-181-5p, miR-19-3p, miR-144-3p, miR-101-39.2, miR-218-5p Target Autism Genes and Regulate Axon Guidance, cAMP and MAPK Signalling Pathway. SJMSHM, 2023; 5(4): 1-6.

https://doi.org/10.47176/sjmshm.5.4.1