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Emerging Role of Non-coding RNAs in Autism Spectrum Disorder

Soudeh Ghafouri-Fard[1] · Rezvan Noroozi[2] · Serge Brand[3] · Bashdar Mahmud Hussen[4] · Reyhane Eghtedarian[5] · Mohammad Taheri[6,7] · Kaveh Ebrahimzadeh[8]

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Abstract

Autism spectrum disorders (ASD) embrace a diverse set of neurodevelopmental diseases with a multifaceted genetic basis. Non-coding RNAs (ncRNAs) are among putative loci with critical participation in the development of ASD. Expression of some lncRNAs, namely RP11-466P24.2, SYP-AS1, STXBP5-AS1, and IFNG-AS1 has been decreased in ASD, while AK128569, CTD-2516F10.2, MSNP1AS, RPS10P2-AS1, LINC00693, LINC00689, NEAT1, TUG1, and Shank2-AS lncRNAs have been over-expressed in ASD. Expression of several miRNAs which are implicated in the immunological developmental, immune responses, and protein synthesis as well as those participating in the regulation of PI3K/Akt/mTOR and EGFR signaling pathways is dysregulated in the context of ASD. In the present article, we describe investigations which appraised the role of lncRNAs, miRNAs, and circRNAs in the pathobiology of ASD.

Keywords Autism spectrum disorder · lncRNA · miRNA · circRNA

Introduction

Autism spectrum disorders (ASD) encompass a mixed set of neurodevelopmental diseases with a multifaceted genetic foundation. ASD is diagnosed by substantial debit in mutual social communications, reduced interactions, and limited monotonous actions, which are mostly apparent by the age of three (2013). The substantially high rate concordance among monozygotic twins and elevated risk of disorder for siblings of ASD cases suggest the presence of a remarkable genetic basis for ASD (Rosenberg et al. 2009; Ozonoff et al. 2011). Non-coding RNAs (ncRNAs) are among putative loci with critical participation in the development of ASD (Cogill et al. 2018). These transcripts exert regulatory impacts on the expression of several genes particularly those implicated in the neurodevelopmental processes (Roberts et al. 2014). These regulatory transcripts vary in the terms of size, biogenesis, and mechanism of action. While long non-coding RNAs (lncRNAs) are more than 200 nucleotides, microRNAs (miRNAs) are small-sized transcripts with sizes about 20–22 nucleotides (Esteller 2011). Through functioning as signal, molecular sponges, platforms, directors, or enhancer RNAs, lncRNAs affect genome structure or gene expression (Fang and Fullwood 2016). LncRNAs have some similar features with mRNAs among them are transcription by RNA polymerase II and existence of poly A tails and caps at the 3′ and 5′ ends, respectively (Kashi et al.

✉ Mohammad Taheri
mohammad_823@yahoo.com

✉ Kaveh Ebrahimzadeh
dr.kavehmay1980@gmail.com

1 Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

2 Malopolska Centre of Biotechnology, Jagiellonian University, Krakow, Poland

3 Psychiatric Clinics, Center for Affective, Stress and Sleep Disorders, University of Basel, Basel, Switzerland

4 Department of Pharmacognosy, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq

5 Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

6 Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

7 Institute of Human Genetics, Jena University Hospital, 07740 Jena, Germany

8 Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

2016). On the other hand, miRNAs are made through a multi-step route in the nucleus and cytoplasm and alter expression of their targets through binding with their 3′ untranslated regions. Therefore, they mainly alter expression of genes at post-transcriptional level (Macfarlane and Murphy 2010). Another newly appreciated group of ncRNAs consisted circular RNAs (circRNAs). These closed lncRNAs are constructed through covalent binding of the 5′ and 3′ ends (Yu and Kuo 2019). Assessment of transcript profile and co-expression network of transcripts in the evolving brain tissue has led to identification of some lncRNAs which are linked with the development of ASD. These lncRNAs are enriched in two separate clusters with over-expression in the prenatal and postnatal periods, respectively. The former cluster mostly included transcriptional regulators, whereas the latter comprised those being implicated in the synapse establishment (Cogill et al. 2018). Other groups of ncRNAs are also associated in the pathogenesis of ASD. In the present article, we explain investigations which appraised the role of lncRNAs, miRNAs, and circRNAs in the pathobiology of ASD.

LncRNAs and ASD

Ziats et al. profiled lncRNA and mRNA signatures in the post-mortem brain samples of ASD patients versus control samples of prefrontal cortex and cerebellum regions. They reported differential expression of tens of lncRNAs in ASD samples versus controls. These lncRNAs were mostly associated with neurodevelopmental processes and psychiatric disorders. Notably, lncRNA signature of ASD brains was more homogenous compared with controls (Ziats and Rennert 2013). Another high-throughput study conducted by Wang et al. showed differential expression of thousands of lncRNAs in the peripheral leukocytes of ASD cases compared to controls. These lncRNAs were functionally linked with neurological pathways such as synaptic vesicle trafficking, continuing depression, and persistent potentiation. Based on prominent dysregulation of synaptic lncRNAs and their associated mRNAs in ASD cases, synaptic vesicle transport and trafficking has putative role in the pathogenesis of ASD. Among dysregulated lncRNAs are those related with HOX genes. Most notably, two natural antisense transcripts (NATs), namely SHANK2-AS and BDNF-AS, have been identified that possibly modulate expression of the sense transcripts with well-known roles in the development of ASD (Wang et al. 2015b). Consistent with the possible role of NATs in the regulation of human transcripts, another study has reported under-expression of IFNG-AS1 while over-expression of IFNG in ASD cases compared with healthy children. The mentioned study also emphasized on the role of chronic inflammation in the pathophysiology of ASD (Fallah et al. 2020). MSNP1AS is an over-expressed lncRNA in the autopsy samples obtained from cerebral cortex of ASD cases, especially those having ASD-related 5p14.1 markers (Kerin et al. 2012b). Upregulation of MSNP1AS in human neural progenitor cells has led to reduction in neurite quantities and neurite dimension. Such morphological changes were accompanied by alterations in the expressions of a number of proteins implicated in protein biogenesis and chromatin configuration (DeWitt et al. 2016b). Encoded from an intronic region of the protein-coding MACROD2, RPS10P2-AS1 comprises a risk element for ASD, namely rs4141463. Expression of this lncRNA has been shown to be higher in temporal cortex of ASD cases, particularly in those with the ASD-linked rs4141463 genotype. Besides, RPS10P2-AS1 levels were elevated in human neural progenitor cells following exposure with air poisons. Such upregulation was accompanied by aberrant expression of neuronal genes (Bilinovich et al. 2019). Another high throughput study has shown dysregulation of a number of primate-specific lncRNAs in ASD in addition to under-expression of the alternative splicing of activity-related neuron-specific exons (Parikshak et al. 2016). A candidate-gene study has appraised expression levels of NEAT1, TUG1, and PANDA in the peripheral blood samples of ASD cases compared with healthy children showing over-expression of first two lncRNAs in the ASD cases (Sayad et al. 2019). Features of downregulated and upregulated lncRNAs in ASD are presented in Tables 1 and 2, respectively.

Association between lncRNA genetic variants and susceptibility to ASD has also been assessed. Safari et al. have genotyped four HOTAIR polymorphisms, namely rs12826786, rs1899663, and rs4759314 in Iranian ASD patients and healthy controls. They recognized association between T allele of the rs12826786 and susceptibility to ASD. TT genotype of this SNP enhanced risk of ASD compared with the other genotypes. Yet, no association was detected between the other SNPs and susceptibility to ASD. Moreover, distribution of HOTAIR haplotypes was similar among cases and controls (Safari et al. 2020).

Peripheral expression levels of lncRNAs have the potential to be used as markers for the purpose of ASD diagnosis. A single investigation has reported the diagnostic accuracy of NEAT1 in distinguishing between ASD and normal children to be 0.75. Diagnostic power of PANDA and TUG1 has been less than NEAT1 (Sayad et al. 2019). Table 3 demonstrates the specificity and sensitivity values of these three lncRNAs in ASD.

miRNAs and ASD

Hick et al. have quantified miRNA signature in saliva samples of ASD patients, children with typical development, and those with developmental delay. They reported differential expression of 14 miRNAs between three study subgroups. Different panels of miRNAs were identified that could distinguish ASD cases

Table 1 Summary of lncRNA functions whose expression has been reduced in autism spectrum disorder (ASD)

LncRNAs	Specimens	Cell line	Interaction	Signaling pathways	Roles	Reference
RP11-466P24.2 SYP-AS1 STXBP5-AS1	25 age- and sex-matched ASD and control children	Peripheral leukocytes		Chemokine signaling, T cell receptor, leukocyte transendothelial migration, and adherens junction	This study revealed the differences in the expression of synaptic lncRNAs and mRNAs and further highlighted the importance of synaptic vesicle transportation in delivery of synaptosomal proteins between presynaptic and postsynaptic membranes in ASD	(Wang et al. 2015b)
IFNG-AS1	50 ASD children and 50 age- and sex-matched controls	Peripheral blood	IFNG	IFNG/IFNG-AS1 pathway	A functional disruption in IFNG/IFNG-AS1 regulation might affect the chronic inflammatory aspect of ASD	(Fallah et al. 2020)
CCAT1	30 ASD cases and 41 controls	Peripheral blood	IRF5, P2×4r		Downregulation of CCAT1 could cause overexpression of IRF5 in which was involved in the induction of immune related conditions. Dysregulation of this transcription factor could affect the expression levels of P2×4r that involved in the pathophysiology of ASD	(Taheri et al. 2021b)
SNHG6	30 ASD cases and 41 controls	Peripheral blood		VDR-related pathway	Dysregulation of a number of VDR-related genes and lncRNAs may contribute to ASD pathogenesis	(Ghafouri-Fard et al. 2021)

Table 2 Summary of lncRNAs whose expression has been augmented in autism spectrum disorder (ASD)

LncRNAs	Specimens	Cell line	Interaction	Signaling pathways	Roles	Reference
RP11-38L15.3 STX16-NPEPL1 AC005606.14 STX8 RP1-78O14.1 RP5-839B4.7 RP11-501J20.5 AK128569 CTD-2516F10.2	25 age- and sex-matched ASD and control children	Peripheral leukocytes		Apoptosis, chemokine signaling, synaptic vesicle cycle, and insulin secretion	This study revealed the differences in expression of synaptic lncRNAs and mRNAs and further highlighted the importance of synaptic vesicle transportation in delivery of synaptosomal proteins between presynaptic and postsynaptic parts	(Wang et al. 2015b)
MSNP1AS	The human neural progenitor cell lines SK-N-SH cells and ReNcell CX cells	SK-N-SH cells and ReNcell CX cells		Neuronal differentiation	Overexpression of MSNP1AS affects neuronal differentiation through protein synthesis and chromatin structure	(DeWitt et al. 2016b)
RPS10P2-AS1	10 ASD cases and 10 controls	Brain samples	ZNF865, RDH13, RNU4-1, RNU4-2, RPS16, RPLP1, IFI6, MX1, IFI44L, SLC7A11, and ASNS		RPS10P2-AS1 might be a key player in neuron development and reaction to environmental stimulants	(Bilinovich et al. 2019)
LINC00693 LINC00689	31 ASD patients and 33 age- and sex-matched healthy controls	Cortex samples		miRNA or FMRP interactions	The mentioned lncRNAs are normally down-regulated in individuals' normal development but are upregulated in ASD and have interaction with microRNA processing complexes	(Parikshak et al. 2016)
MSNP1AS	10 ASD cases and 10 age- and sex-matched healthy controls	Cortex samples	Moesin	Neuronal differentiation	Overexpression of MSNP1AS lncRNA regulates neuronal differentiation via protein synthesis and altering chromatin structure	(Kerin et al. 2012a; DeWitt et al. 2016a)
MSNP1AS	Human hippocampal neurons	Neuronal cells	Moesin	RhoA, Rac1 and PI3K/Akt Pathways	MSNP1AS plays a role in inhibition of moesin protein expression. This lncRNA is able to activate and suppress RhoA pathway, and Rac1 and PI3K/Akt pathways, respectively	(Luo et al. 2020)

Table 2 (continued)

LncRNAs	Specimens	Cell line	Interaction	Signaling pathways	Roles	Reference
NEAT1 TUG1	30 ASD cases and 41 controls	Peripheral blood	miR497 miR-9	miR497/BDNF pathway	This study revealed the contribution of these dysregulated lncRNAs in ASD through altering apoptotic or neurogenic pathways	(Sayad et al. 2019)
Shank2-AS	40 ASD patients and age- and sex-matched healthy controls	Peripheral blood	Shank2		Dysregulated Shank2-AS contributes to ASD development through regulation of Shank2 expression which alters neuron's structure and growth	(Luo et al. 2018)
MEG3	30 ASD cases and 41 controls	Peripheral blood	miR-181b		Overexpression of Meg3 contributes to regulation of 12/15-LOX expression and affect ischemia outcome in brain nerve cells	(Taheri et al. 2021a)
CCAT2	30 ASD cases and 41 controls	Peripheral blood	*MYC*		Overexpression of CCAT2 contributes to the dysregulation of *MYC* and might be affected the overexpression of *MYC*	(Taheri et al. 2021b)
IFNG	50 ASD cases and 50 controls	Peripheral blood		IFNG/IFNG-AS1	It is hypothesized that chronic immune dysfunction involves in ASD development and severity. There might be a correlation between the age of ASD children and IFNG/IFNG-AS1 expression levels as important regulators of inflammation	(Fallah et al. 2020)
CYP27B1	30 ASD cases and 41 controls	Peripheral blood		VDR-related pathway	Dysregulation of a number of VDR-related genes and lncRNAs may contribute to ASD pathogenesis	(Ghafouri-Fard et al. 2021)

Table 3 Diagnostic value of LncRNAs in autism spectrum disorder (ASD)

LncRNA	Specimens	Distinguishing ability	Area under curve	Sensitivity	Specificity	Reference
NEAT1	30 ASD patients and 41 age- and sex-matched healthy controls	ASD and healthy individuals	0.759	70	75.61	(Sayad et al. 2019)
PANDA			0.628	90	36.59	
TUG1			0.733	76.67	65.85	
CCAT1	30 ASD patients and 41 age- and sex-matched healthy controls	ASD and healthy individuals	0.663	53.33	82.93	(Taheri et al. 2021b)
CCAT2			0.779	86.67	73.17	
MEG3	30 ASD patients and 41 age- and sex-matched healthy controls	ASD and healthy individuals	0.792	83.33	70.73	(Taheri et al. 2021a)
DISC2	30 ASD patients and 41 age- and sex-matched healthy controls	ASD and healthy individuals	0.763	83.33	73.17	(Tamizkar et al. 2021)
LOC101928237			0.9	90	82.93	
LRRC2-AS1			0.929	86.67	100	
PRKAR2A-AS1			0.794	86.67	78.05	
SNHG6	30 ASD patients and 41 age- and sex-matched healthy controls	ASD and healthy individuals	0.94	60	73.17	(Ghafouri-Fard et al. 2021)
CYP27B1			0.78	93.33	70.73	
VDR			0.52	90	29.27	

from children without ASD with appropriate accuracy, whose expressions were linked with social affect, or stereotypic behavior, respectively. Thus, salivary miRNA profiling has been proposed as a non-invasive method for ASD diagnosis (Hicks et al. 2020). Vaccaro et al. have identified different patterns of seven miRNAs in the blood samples of ASD cases versus controls. These miRNAs mainly target genes which contribute to the development of immune system, immune reactions, and protein biogenesis. Notably, MeCP2 gene which participates in the pathogenesis of Rett syndrome is a target of one of these miRNAs, explaining the presence of ASD-related symptoms in Rett syndrome (Vaccaro et al. 2018). Nakata et al. have quantified miRNA signature in peripheral blood of a subgroup of ASD cases versus healthy subjects. They reported substantial downregulation of miR-6126 in ASD cases in association with the seriousness of social abnormalities. This miRNA possibly targets a number of genes participating in the synaptic functions and oxytocin signaling pathways (Nakata et al. 2019). Nt et al. have measured peripheral expression of miR-328-3p and miR-3135a in ASD cases and matched controls. They recognized downregulation of these miRNAs in ASD patients. These miRNAs were predicated to regulate expression of genes with functions in synaptic pathways and neurodegenerative disorders including Alzheimer, Huntington, and Parkinson disorders (Nt et al. 2018). Wu et al. have shown upregulation of hsa-miR-21-3p and downregulation of its target genes in autopsy brain tissues of ASD cases. Moreover, expression of hsa_can_1002-m was decreased in ASD. The latter miRNA has been shown to modulate activity of EGFR and FGFR signaling pathways which participate in the development of brain and immune system (Wu et al. 2016). Nguyen et al. have assessed expression of miR-146a in the temporal lobe samples of patients with ASD. They demonstrated that over-expression of this miRNA in ASD brains happened early in the childhood. In vitro experiments revealed the impact of miR-146a upregulation in enhancement neurite outgrowth. Therefore, miR-146a has a dynamic participation in primary neuronal developmental processes in ASD (Nguyen et al. 2018). Finally, Mor et al. have reported upregulation of miR-142-5p, miR-142-3p, miR-451a, miR-144-3p, and miR-21-5p in the brain tissues of ASD patients. Besides, they demonstrated hypomethylation of the promoter of the miR-142 gene in these specimens. Dysregulated miRNAs have been predicted to affect expression of genes contributing to the synaptic processes. Moreover, miR-451a and miR-21-5p have been shown to target the oxytocin receptor gene whose expression has been enhanced in the assessed brain specimens. miR-21-5p has been suggested to decrease expression of oxytocin receptor gene in the brain sections of ASD patients (Mor et al. 2015). Serum profiling of miRNAs in ASD children has also demonstrated downregulation of miR-19a-3p, miR-361-5p, miR-3613-3p, miR-150-5p, miR-126-3p, and miR-499a-5p in these subjects compared with normal children. Notably, expression of these miRNAs have been lower in the clinically normal parents of these ASD subjects and in their siblings compared with genetically unrelated healthy subjects. Consistently, expression of these miRNAs have been shown to be decreased in the blood, hypothalamus, and sperm of two animal models of ASD (Ozkul et al. 2020b). Another similar study has revealed differential expression of 13 miRNAs between ASD cases and healthy children, five of them showing appropriate predictive value for recognition of ASD cases (Vasu et al. 2014). Figure 1 shows the underlying mechanism of miR-199a-5p, miR-92a-2-5p, and miR-193a roles in ASD.

Tables 4 and 5 provide a summary of investigations which identified decreased or increased levels of miRNAs in ASD, respectively.

miRNA expression profiling has facilitated ASD diagnosis. miR-328-3p has a suitable diagnostic value in this regard (Table 6).

circRNAs and ASD

CircRNAs are a group of stable lncRNAs with high expression in neural tissues of mammalian species (Rybak-Wolf et al. 2015). A genome-wide expression assessment of these transcripts in autopsied brains samples obtained from ASD cases and controls showed altered expression of 60 circRNAs in ASD patients. Integrative assessment of circRNA, miRNA, and mRNA patterns has resulted in the recognition of thousands of interactions between these three kinds of transcripts among them have been ASD risk genes and those coding inhibitory postsynaptic density molecules. One overexpressed circRNA, namely, circARID1A, has been shown to affect expression of a number of ASD risk genes in neurons through acting as a sponge for miR-204-3p. The large set of ASD-related circRNA and their interactions with ASD risk genes implies the role of circRNAs in the development of ASD (Chen et al. 2020b).

Discussion

The crosstalk between mRNAs, miRNAs, lncRNAs, and circRNAs indicates the existence of a network which plays a critical role in brain development (Yuan et al. 2018). Several studies, particularly genome-wide investigations, have demonstrated abnormal expression of ncRNAs in brain to peripheral blood samples of ASD children as compared with normally developing kids. The latter types of studies also indicate the putative biomarker role of these transcripts. This finding has practical significance in the diagnosis of ASD considering the difficulties in the assessment of children particularly under 3 years old. Dysregulated ncRNAs in ASD tissues have been enriched in immune-related pathways, synaptic vesicle trafficking protein biogenesis, and chromatin

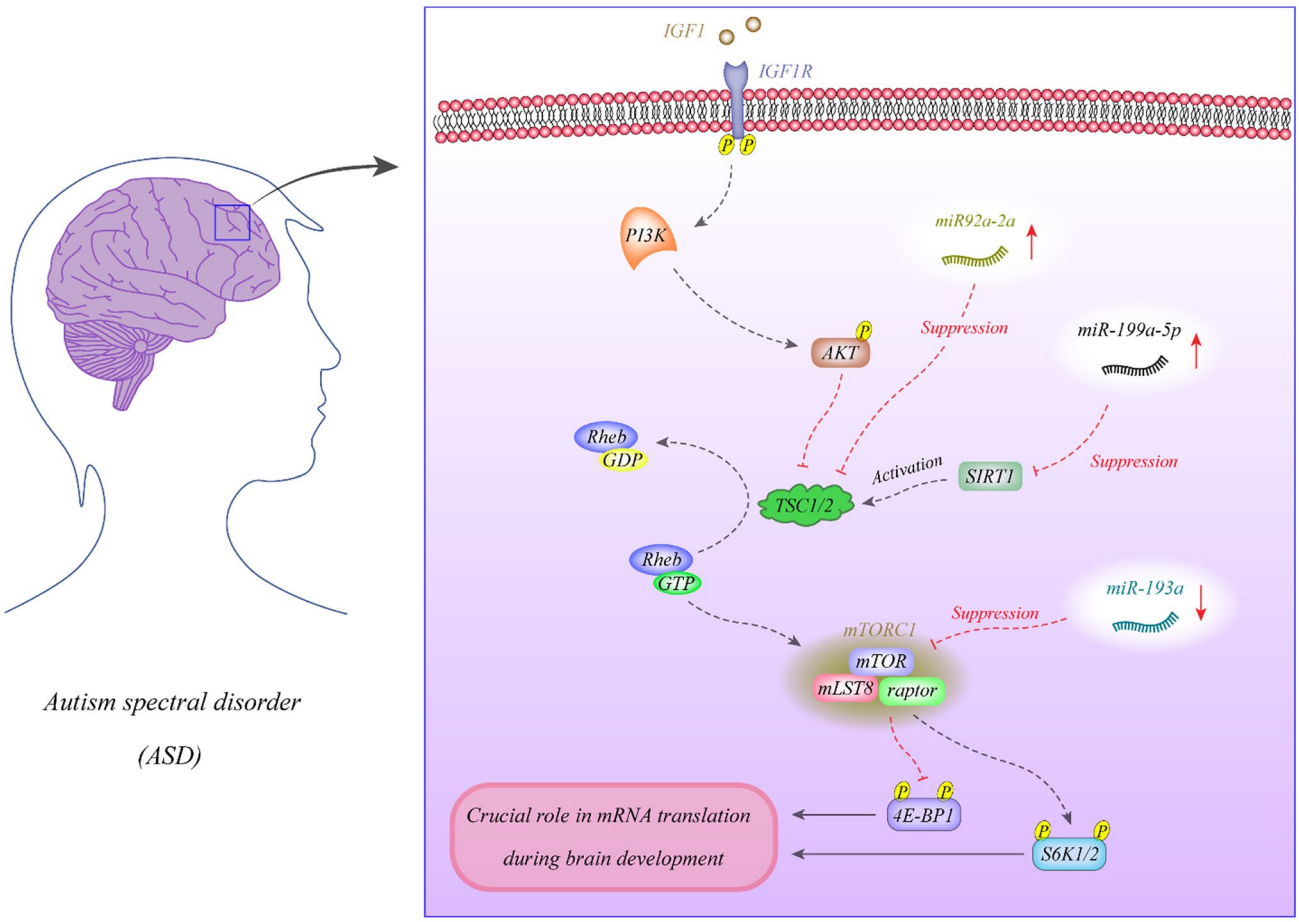

Fig. 1 SIRT1 can regulate mTOR through modulating TSC1/2. miR-199a-5p is increased in ASD patients leading to reduction of SIRT1. miR-92a-2-5p has an inhibitory role on TSC1. Expression of this miRNA is increased in ASD patients. Finally, expression of miR-193 is decreased in ASD. This miRNA could inhibit mTOR (Vaccaro et al. 2018)

Table 4 Information about of miRNAs whose expression has been reduced in autism spectrum disorder (ASD)

microRNA	Specimens	Source	Targets/regulators	Signaling pathways	Roles	Reference
miR-28–3p miR-148a-5p miR-151a-3p miR-125b-2–3p miR-7706	187 ASD children, 125 children with typical development, and 69 cases of developmental delay	Saliva			Salivary miRNA patterns are changed in ASD and have an association with disease severity and their quantification is a non-invasive method to identify ASD status	(Hicks et al. 2020)
miR-19-b-1-5p	7 ASD male patients and 4 non-ASD male controls	Blood		Immunological developmental, immune response, and protein synthesis	The mentioned miRNAs are dysregulated permanently since embryonic development of ASD patients and their assessment may be a good factor for prognosis of the disease	(Vaccaro et al. 2018)
miR-27a-3p miR-193a-5p			SIRT1 and HDAC2	Immunological developmental, immune response, protein synthesis, PI3K/Akt-TSC: mTOR signaling pathways		
miR-204-3p	48 ASD individuals and 49 non-ASD controls	Brain	NLGN1, STAG1, HSD11B1 and VIP	circARID1A-miR-204-3p axis	Several ASD genes (NLGN1, STAG1, HSD11B1, VIP, and UBA6) were altered by circARID1A in human neurons	(Chen et al. 2020b)

Table 4 (continued)

microRNA	Specimens	Source	Targets/regulators	Signaling pathways	Roles	Reference
miR-6126 miR-6780a-5p miR-1227-5p miR-3156-5p miR-4716-3p miR-144-3p miR-3127-5p miR-5581-5p miR-6756-5p miR-6767-5p miR-7977 miR-4486 miR-6734-5p miR-4653-3p miR-6085 miR-874-3p	30 ASD patients and 30 normal controls	Blood	ANK3, CACNA2D1, NRXN3 and PCDH9		miR-6126 have the potential to be the most accurate blood indicator of ASD status in high-functioning adult patients	(Nakata et al. 2019)
miR-328-3p miR-3135a	30 ASD patients and 30 age- and sex-matched normal controls	Serum	APP, SLC8A1 and BACE1		miR-328-3p and miR-3135a might be promising novel biomarkers for ASD	(Nt et al. 2018)

Table 4 (continued)

microRNA	Specimens	Source	Targets/regulators	Signaling pathways	Roles	Reference
miR-19a-3p miR-361-5p miR-3613-3p miR-150-5p	45 ASD children, 33 individuals of their unaffected siblings, 74 individuals of their unaffected parents, 21 healthy controls, and 16 healthy control parents	Serum	Pten, Fmr1, and Foxp2 STAT6, TWIST1, VEGFA, and SND1 CREB1, STAT1, TP53, IGF2, and NOTCH3		The mentioned microRNAs may serve as early biomarkers in diagnosis of autistic children	(Ozkul et al. 2020b)
miR-126-3p			SIRT1, SOX2, SPRED1, and FOXO3			
miR-499a-5p			Cadps2, Foxp2, Fmr1, and Gabrb3			
miR-151a-3p miR-181b-5p miR-320a miR-328 miR-433 miR-489 miR-572 miR-663a	55 ASD patients and 55 age- and sex-matched healthy controls	Serum		TGF-beta, MAPK, Hedgehog, mTOR, and Wnt signaling pathways	The mentioned lncRNAs may serve as non-invasive and promising novel biomarkers in identification of ASD	(Vasu et al. 2014)
hsa_can_1002-m	55 ASD cases and 42 controls	Brain	EPS8, DDAH1, and RUNX1	EGFR and FGFR	It is postulated that increased brain cell proliferation in primates is restricted through negative regulatory mechanisms, namely microRNAs. Failure of these mechanisms leads to uncontrolled proliferation and brain functional and developmental disruption	(Wu et al. 2016)

Table 4 (continued)

microRNA	Specimens	Source	Targets/regulators	Signaling pathways	Roles	Reference
miR-873	SH-SY5Y cell line	SH-SY5Y cell line	ACE, HTR6, ACHE, DRD4, GRIN1, MECP2, TCF7L2, and GRIN2D		Since miR-873 regulates genes related to changes in neuronal morphology and cell differentiation, it might contribute to ASD pathology	(Lu et al. 2020)
miR-576-3p miR-193a-5p miR-27a-5p miR-379-5p miR-134-5p miR-574.-3p miR-382-5p miR-7-5p miR-103a-3p miR-378a-3p miR-3614-5p miR-873-3p miR-433-3p	105 ASD cases and 35 healthy controls	Serum		Neuronal development, synaptic plasticity, cell proliferation/differentiation	Dysregulation of serum miRNA levels shows changes in IL-1ß/IL-10 ratios in PBMo and mitochondrial respiration in PBMCs	(Jyonouchi et al. 2019)
miR-500a-5p miR-197-5p miR-424-5p miR-664a-3p	30 ASD cases and 30 healthy controls	Serum			The mentioned microRNAs may serve as suitable non-invasive biomarkers to diagnose ASD	(Kichukova et al. 2021)
miR-1290	Neuronal stem cells (NSCs)	iPSC-derived neural stem cell	MECP2, NLG3, DCX, DLG3, and CNTNAP2		miR-1290 regulation represents a vital role during neuronal differentiation in early brain development	(Moore et al. 2019)
miR-19a-3p miR-361-5p miR-3613-3p miR-150-5p miR-126-3p miR-499a-5p	45 ASD cases and 144 healthy controls	Serum				(Ozkul et al. 2020a)

Table 5 List of microRNAs whose expression has been upregulated in autism spectrum disorder (ASD)

microRNA	Numbers of clinical samples (tissues, serum, etc.)	Assessed cell line	Targets/regulators	Signaling pathways	Function and comments	Reference
miR-665 miR-4705 miR-620 miR-1277–5p	187 ASD children, 125 children with typical development, and 69 cases of developmental delay	Saliva			Salivary miRNAs are altered in ASD and have an association with disease severity and their quantification is a non-invasive method to identify ASD status	(Hicks et al. 2020)
miR-34c-5p miR-145-5p	7 ASD male patients and 4 non-ASD male controls	Blood		Immunological development, immune response, and protein biogenesis	The mentioned miRNAs are dysregulated permanently since embryonic development of ASD patients and their assessment may be a good factor for prognosis of the disease	(Vaccaro et al. 2018)
miR-92a-2-5p			SIRT1 and HDAC2	Immunological development, immune response, protein biogenesis, PI3K/Akt-TSC: mTOR signaling pathways		
miR-199a-5p			MeCP2, SIRT1 and HDAC2			
miR-4515 miR-328-3p	30 ASD patients and 30 normal controls	Blood				(Nakata et al. 2019)
miR-101-3p miR-106b-5p miR-130a-3p miR-195-5p miR-19b-3p	55 ASD patients and 55 age- and sex-matched healthy controls	Serum		TGF-beta, MAPK, Hedgehog, mTOR, and Wnt signaling pathways	The mentioned lncRNAs may serve as non-invasive and promising novel biomarkers in identification of ASD	(Vasu et al. 2014)
miR-21-3p	55 ASD cases and 42 controls	Brain	DLGAP1, SV2B, TSC1, and FBXO11		miR-21-3p targets neuronal genes whose expression is decreased in ASD	(Wu et al. 2016)
miR-146a	Freshly frozen brain samples from ASD cases ($n=5$) and normal controls ($n=4$)	Brain	ICAM1, FAS, IRAK2, CFH, CDKN1A, TLR4, L1CAM, and CARD10	hNSC differentiation	This study highlighted miR-146a overexpression which occurs early in human brain development	(Nguyen et al. 2018)
miR-142-5p miR-142-3p miR-144-3p miR-451a miR-21-5p	12 ASD cases and 12 healthy controls	Brain	OXTR	Synaptic function	This study revealed the association of epigenetic mechanisms and miRNA dysregulation in the brain which participate in ASD	(Mor et al. 2015)
miR-206 miR-184 miR-223-5p miR-4732-5p miR 193b-5p	105 ASD cases and 35 healthy controls	Serum		Neuronal development, synaptic plasticity, cell proliferation/differentiation	Dysregulation of serum miRNA levels shows changes in IL-1ß/IL-10 ratios in PBMo and mitochondrial respiration in PBMCs	(Jyonouchi et al. 2019)
miR-424-5p miR-500a-5p miR-197-5p miR-664-3p	30 ASD cases and 30 healthy controls	Serum			The mentioned microRNAs may serve as suitable non-invasive biomarkers to diagnose ASD	(Kichukova et al. 2021)

Table 6 Diagnostic value of microRNAs in autism spectrum disorder (ASD)

microRNA	Specimens	Distinguishing ability	Area under curve	Sensitivity	Specificity	Reference
miR-3135a	30 ASD patients and 30 age- and sex-matched normal controls	ASD patients and normal individuals	0.828	76.3%	88.9%	(Nt et al. 2018)
miR-328-3p			0.858	78.9%	88.9%	
miR-28–3p, miR-151-a-3p, miR-148a-5p, and miR-125b-2–3p	187 ASD children, 125 children with typical development, and 69 cases of developmental delay	ASD patients and normal individuals	0.694	89.2%	32.0%	(Hicks et al. 2020)
hsa-miR-101-3p	55 ASD patients and 55 age- and sex-matched healthy controls	ASD patients and normal individuals	0.686	66.7%	72.2%	(Vasu et al. 2014)
hsa-miR-106b-5p			0.648	43.4%	81.8%	
hsa-miR-130a-3p			0.852	85.5%	72.7%	
hsa-miR-151a-3p			0.756	98.1%	40.8%	
hsa-miR-181b-5p			0.868	85.4%	78%	
hsa-miR-195-5p			0.675	55.6%	72.7%	
hsa-miR-19b-3p			0.822	79.6%	80%	
hsa-miR-320a			0.906	84.6%	87%	
hsa-miR-328			0.767	82.7%	64.6%	
hsa-miR-433			0.723	52%	85.7%	
hsa-miR-489			0.803	90.2%	68.1%	
hsa-miR-572			0.822	83.3%	74.5%	
hsa-miR-663a			0.743	84.9%	61.7%	
miR-424-5p	30 ASD patients and 30 age- and sex-matched healthy controls	ASD patients and normal individuals	0.756	88.9	75.0	(Kichukova et al. 2021)
miR-500a-5p			0.796	77.8	92.9	
miR-197-5p			0.825	86.1	78.6	
miR-664-3p			< 0.7	25.0	100	

configuration, introducing these pathways as possible candidates for therapeutic interventions in ASD.

Spatio-temporal expression of miRNAs in brain is crucial for the development of the central nervous system (Cho et al. 2020, Chen and Qin 2015, Yapijakis 2020, Davis et al. 2015). Dysregulated miRNAs are related with several neurological and psychological disorders (Yoshino et al. 2020; Brennan and Henshall 2020; Hu et al. 2019; Siedlecki-Wullich et al. 2019). Animal model studies showed that the synaptogenesis is influenced by miRNAs controlling neurotransmitter release or targeting synaptic proteins like neuroligin and neurexin as two candidate genes which are strongly associated with ASD (Simon et al. 2008; Hu et al. 2012, Südhof 2008). miRNAs have special position in the diagnosis of ASD. These transcripts have distinct signature in saliva or serum samples of ASD patients, therefore can be used as non-invasive methods for ASD diagnosis. In addition to miRNA profiling, multi-"omic" profiling methods have been suggested as practical methods for enhancement of accuracy of diagnosis, facilitating their application in the clinical settings (Hicks et al. 2020).

Besides, tissue-specific expression of lncRNAs especially the restricted expression of some of them in the brain suggested lncRNAs as the other contributors in the brain development (Derrien et al. 2012). LncRNA expression profiling suggested the aberrant expression of lncRNAs as critical determinant of different neurological disorders (Ding et al. 2020). Particularly, an evolutionarily conserved mRNA/lncRNA co-expression network, enriched for coding genes involved in synaptic functions, confirms the role of lncRNAs in the etiology of ASD as a synaptopathy (Won et al. 2013; Necsulea et al. 2014; Quesnel-Vallieres et al. 2019). In addition to the mentioned evidence regarding dysregulation of lncRNAs in ASD brains as well as the results of functional studies, the higher abundance of lncRNAs in human brain than mRNAs suggests that lncRNAs are putative partakers in the development of ASD (16). Loci that confer risk of ASD might affect gene expression patterns in the cortical region. Notably, various genetic abnormalities can result in phenotypic convergence at numerous physiopathological levels in the context of ASD (17). Most notably, among several differentially expressed lncRNAs in ASD blood samples, the upregulated *SHANK2-AS* as an intronic antisense for *SHANK2* gene is of great interest (Wang et al. 2015a). Several studies reported rare causative mutations in this gene which categorize it

as a syndromic candidate gene for ASD (Berkel et al. 2010; Sanders et al. 2012; Monteiro and Feng 2017). The functional analysis also confirms the effects of such mutations on protein localization, synaptic function, and cognitive behavior in mice models (Berkel et al. 2012; Leblond et al. 2012; Zaslavsky et al. 2019). Therefore, detected upregulation of the *SHANK2-AS*, which leads to altered expression of Shank2 in ASD patients and results in abnormal neuronal structure and growth, may highlight the underlying epigenetic mechanisms involved in the etiology of the ASD (Wang et al. 2015a; Luo et al. 2019).

The other form of non-coding RNAs are circRNAs which are produced as a by-product of the splicing process by circularization of exons into a covalently closed loop. These transcripts have spatiotemporal dynamic expression in the brain from embryonic stages to adulthood (Venø et al. 2015; Mehta et al. 2020). Most circRNAs are enriched in the synapses suggesting their role in the synaptic plasticity and brain function (Hanan et al. 2017) and explaining their link with ASD development (Chen et al. 2020a). Appraisal of association between genetic polymorphism of lncRNAs, miRNAs, and circRNAs and risk of ASD through genome-wide studies would facilitate identification of genetic abnormalities which lead to similar phenotypes.

Conclusion

Preliminary results have indicated the association between altered ncRNA signatures in ASD and some neurodegenerative conditions suggesting the possible shared mechanisms for these disorders. Comparative high-throughput sequencing studies in these disorders might facilitate identification of such common molecular basis.

Abbreviations ASD: Autism spectrum disorders (ASD); ncRNAs: Non-coding RNAs; miRNAs: MicroRNAs; circRNAs: Circular RNAs; NATs: Natural antisense transcripts

Author Contribution SGF wrote the draft and revised it. MT designed and supervised the study. SB and KE edited the final version and collected the data. RN, BMH, and RE collected the data and designed the figure and tables. All the authors read and approved the submitted version.

Declarations

Ethics Approval and Consent to Participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent of Publication Not applicable.

Competing Interest The authors declare they have no conflict of interest.

References

Berkel S, Marshall CR, Weiss B, Howe J, Roeth R, Moog U, Endris V, Roberts W, Szatmari P, Pinto D (2010) Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. Nat Genet 42:489

Berkel S, Tang W, Trevino M, Vogt M, Obenhaus HA, Gass P, Scherer SW, Sprengel R, Schratt G, Rappold GA (2012) Inherited and de novo SHANK2 variants associated with autism spectrum disorder impair neuronal morphogenesis and physiology. Hum Mol Genet 21:344–357

Bilinovich SM, Lewis K, Grepo N, Campbell DB (2019) The long noncoding RNA RPS10P2-AS1 is implicated in autism spectrum disorder risk and modulates gene expression in human neuronal progenitor cells. Front Genet 10:970

Brennan GP, Henshall DC (2020) MicroRNAs as regulators of brain function and targets for treatment of epilepsy. Nat Rev Neurol 16:506–519

Chen W, Qin C (2015) General hallmarks of microRNAs in brain evolution and development. RNA Biol 12:701–708

Chen Y-J, Chen C-Y, Mai T-L, Chuang C-F, Chen Y-C, Gupta SK, Yen L, Wang Y-D, Chuang T-J (2020a) Genome-wide, integrative analysis of circular RNA dysregulation and the corresponding circular RNA-microRNA-mRNA regulatory axes in autism. Genome Res 30:375–391

Cho KH, Xu B, Blenkiron C, Fraser M (2020) Emerging roles of miRNAs in brain development and perinatal brain. Neurological Outcomes in Preterm Infants–Current Controversies and Therapies for Brain Injury

Cogill SB, Srivastava AK, Yang MQ, Wang L (2018) Co-expression of long non-coding RNAs and autism risk genes in the developing human brain. BMC Syst Biol 12:91–91

Davis GM, Haas MA, Pocock R (2015) MicroRNAs: not "fine-tuners" but key regulators of neuronal development and function. Front Neurol 6:245

Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG (2012) The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res 22:1775–1789

DeWitt JJ, Grepo N, Wilkinson B, Evgrafov OV, Knowles JA, Campbell DB (2016a) Impact of the autism-associated long noncoding RNA MSNP1AS on neuronal architecture and gene expression in human neural progenitor cells. Genes 7(10):76

DeWitt JJ, Grepo N, Wilkinson B, Evgrafov OV, Knowles JA, Campbell DB (2016b) Impact of the autism-associated long noncoding RNA MSNP1AS on neuronal architecture and gene expression in human neural progenitor cells. Genes (Basel) 7

Ding Y, Wang X, Pan J, Ji M, Luo Z, Zhao P, Zhang Y, Wang G (2020) Aberrant expression of long non-coding RNAs (lncRNAs) is involved in brain glioma development. Arch Med Sci 16:177

Esteller M (2011) Non-coding RNAs in human disease. Nat Rev Genet 12:861–874

Fallah H, Sayad A, Ranjbaran F, Talebian F, Ghafouri-Fard S, Taheri M (2020) IFNG/IFNG-AS1 expression level balance: implications for autism spectrum disorder. Metab Brain Dis 35:327–333

Fang Y, Fullwood MJ (2016) Roles, functions, and mechanisms of long non-coding RNAs in cancer. Genomics Proteomics Bioinformatics 14:42–54

Ghafouri-Fard S, Eghtedarian R, Hussen B, Motevaseli E, Arsang-Jang S, Taheri M (2021) Expression analysis of VDR-related LncRNAs in autism spectrum disorder. JMol Neurosci 71

Hanan M, Soreq H, Kadener S (2017) CircRNAs in the brain. RNA Biol 14:1028–1034

Hicks SD, Carpenter RL, Wagner KE, Pauley R, Barros M, Tierney-Aves C, Barns S, Greene CD, Middleton FA (2020) Saliva microRNA differentiates children with autism from peers with typical and atypical development. J Am Acad Child Adolesc Psychiatry 59:296–308

Hu Z, Gao S, Lindberg D, Panja D, Wakabayashi Y, Li K, Kleinman JE, Zhu J, Li Z (2019) Temporal dynamics of miRNAs in human DLPFC and its association with miRNA dysregulation in schizophrenia. Transl Psychiatry 9:1–17

Hu Z, Hom S, Kudze T, Tong X-J, Choi S, Aramuni G, Zhang W, Kaplan JM (2012) Neurexin and neuroligin mediate retrograde synaptic inhibition in C. elegans. Science 337:980–984

Jyonouchi H, Geng L, Toruner GA, Rose S, Bennuri SC, Frye RE (2019) Serum microRNAs in ASD: association with monocyte cytokine profiles and mitochondrial respiration. Front Psychiatry 10:614

Kashi K, Henderson L, Bonetti A, Carninci P (2016) Discovery and functional analysis of lncRNAs: methodologies to investigate an uncharacterized transcriptome. Biochim Biophys Acta Gene Regul Mech 1859:3–15

Kerin T, Ramanathan A, Rivas K, Grepo N, Coetzee GA, Campbell DB (2012a) A noncoding RNA antisense to moesin at 5p14.1 in autism. Sci Transl Med 4:128ra40

Kerin T, Ramanathan A, Rivas K, Grepo N, Coetzee GA, Campbell DB (2012b) A noncoding RNA antisense to moesin at 5p14. 1 in autism. Sci Transl Med 4:128ra40

Kichukova T, Petrov V, Popov N, Minchev D, Naimov S, Minkov I, Vachev T (2021) Identification of serum microRNA signatures associated with autism spectrum disorder as promising candidate biomarkers. Heliyon 7:e07462

Leblond CS, Heinrich J, Delorme R, Proepper C, Betancur C, Huguet G, Konyukh M, Chaste P, Ey E, Rastam M (2012) Genetic and functional analyses of SHANK2 mutations suggest a multiple hit model of autism spectrum disorders. PLoS Genet 8:e1002521

Lu J, Zhu Y, Williams S, Watts M, Tonta MA, Coleman HA, Parkington HC, Claudianos C (2020) Autism-associated miR-873 regulates ARID1B, SHANK3 and NRXN2 involved in neurodevelopment. Transl Psychiatry 10:418

Luo T, Liu P, Wang XY, Li LZ, Zhao LP, Huang J, Li YM, Ou JL, Peng XQ (2019) Effect of the autism-associated lncRNA Shank2-AS on architecture and growth of neurons. J Cell Biochem 120(2):1754–1762

Luo T, Liu P, Wang XY, Li LZ, Zhao LP, Huang J, Li YM, Ou JL, Peng XQ (2019) Effect of the autism-associated lncRNA Shank2-AS on architecture and growth of neurons. J Cell Biochem 120:1754–1762

Luo T, Ou JN, Cao LF, Peng XQ, Li YM, Tian YQ (2020) The Autism-Related lncRNA MSNP1AS Regulates Moesin Protein to Influence the RhoA, Rac1, and PI3K/Akt Pathways and Regulate the Structure and Survival of Neurons. Autism Research 13(12):2073–2082

Macfarlane L-A, Murphy PR (2010) MicroRNA: biogenesis, function and role in cancer. Curr Genomics 11:537–561

Mehta SL, Dempsey RJ, Vemuganti R (2020) Role of circular RNAs in brain development and CNS diseases. Prog Neurobiol 186:101746

Monteiro P, Feng G (2017) SHANK proteins: roles at the synapse and in autism spectrum disorder. Nat Rev Neurosci 18:147

Moore D, Meays BM, Madduri LSV, Shahjin F, Chand S, Niu M, Albahrani A, Guda C, Pendyala G, Fox HS, Yelamanchili SV (2019) Downregulation of an evolutionary young miR-1290 in an iPSC-derived neural stem cell model of autism spectrum disorder. Stem Cells Int 2019:8710180

Mor M, Nardone S, Sams DS, Elliott E (2015) Hypomethylation of miR-142 promoter and upregulation of microRNAs that target the oxytocin receptor gene in the autism prefrontal cortex. Mol Autism 6:46

Vasu MM, Anitha A, Thanseem I, Suzuki K, Yamada K, Takahashi T, Wakuda T, Iwata K, Tsujii M, Sugiyama T, Mori N (2014) Serum microRNA profiles in children with autism. Mol Autism 5:40

Nakata M, Kimura R, Funabiki Y, Awaya T, Murai T, Hagiwara M (2019) MicroRNA profiling in adults with high-functioning autism spectrum disorder. Mol Brain 12:82

Necsulea A, Soumillon M, Warnefors M, Liechti A, Daish T, Zeller U, Baker JC, Grützner F, Kaessmann H (2014) The evolution of lncRNA repertoires and expression patterns in tetrapods. Nature 505:635–640

Nguyen LS, Fregeac J, Bole-Feysot C, Cagnard N, Iyer A, Anink J, Aronica E, Alibeu O, Nitschke P, Colleaux L (2018) Role of miR-146a in neural stem cell differentiation and neural lineage determination: relevance for neurodevelopmental disorders. Mol Autism 9:38

Nt P, Ds M, Mm N, In M, Ti V (2018) Investigation of circulating serum microRNA-328-3p and microRNA-3135a expression as promising novel biomarkers for autism spectrum disorder. Balkan J Med Genet 21:5–12

Ozkul Y, Taheri S, Bayram KK, Sener EF, Mehmetbeyoglu E, Oztop DB, Aybuga F, Tufan E, Bayram A, Dolu N, Zararsiz G, Kianmehr L, Beyaz F, Doganyigit Z, Cuzin F, Rassoulzadegan M (2020a) A heritable profile of six miRNAs in autistic patients and mouse models. Sci Rep 10:9011

Ozkul Y, Taheri S, Bayram KK, Sener EF, Mehmetbeyoglu E, Öztop DB, Aybuga F, Tufan E, Bayram A, Dolu N, Zararsiz G, Kianmehr L, Beyaz F, Doganyigit Z, Cuzin F, Rassoulzadegan M (2020b) A heritable profile of six miRNAs in autistic patients and mouse models. Sci Rep 10:9011

Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, Bryson S, Carver LJ, Constantino JN, Dobkins K, Hutman T, Iverson JM, Landa R, Rogers SJ, Sigman M, Stone WL (2011) Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. Pediatrics 128:e488–e495

Parikshak NN, Swarup V, Belgard TG, Irimia M, Ramaswami G, Gandal MJ, Hartl C, Leppa V, Ubieta LT, Huang J, Lowe JK, Blencowe BJ, Horvath S, Geschwind DH (2016) Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism. Nature 540:423–427

Quesnel-Vallieres M, Weatheritt RJ, Cordes SP, Blencowe BJ (2019) Autism spectrum disorder: insights into convergent mechanisms from transcriptomics. Nat Rev Genet 20:51–63

Roberts TC, Morris KV, Wood MJA (2014) The role of long non-coding RNAs in neurodevelopment, brain function and neurological disease. Philos Trans R Soc Lond Ser B Biol Sci 369:20130507

Rosenberg RE, Law JK, Yenokyan G, McGready J, Kaufmann WE, Law PA (2009) Characteristics and concordance of autism spectrum disorders among 277 twin pairs. Arch Pediatr Adolesc Med 163:907–914

Rybak-Wolf A, Stottmeister C, Glažar P, Jens M, Pino N, Giusti S, Hanan M, Behm M, Bartok O, Ashwal-Fluss R, Herzog M, Schreyer L, Papavasileiou P, Ivanov A, Öhman M, Refojo D, Kadener S, Rajewsky N (2015) Circular RNAs in the mammalian brain are highly abundant, conserved, and dynamically expressed. Mol Cell 58:870–885

Safari M, Noroozi R, Taheri M, Ghafouri-Fard S (2020) The rs12826786 in HOTAIR lncRNA Is Associated with Risk of Autism Spectrum Disorder. J Mol Neurosci 70:175–179

Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, Ercan-Sencicek AG, Dilullo NM, Parikshak NN, Stein JL (2012) De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature 485:237–241

Sayad A, Omrani MD, Fallah H, Taheri M, Ghafouri-Fard S (2019) Aberrant expression of long non-coding RNAs in peripheral blood of autistic patients. J Mol Neurosci 67:276–281

Siedlecki-Wullich D, Català-Solsona J, Fábregas C, Hernández I, Clarimon J, Lleó A, Boada M, Saura CA, Rodríguez-Álvarez J, Miñano-Molina AJ (2019) Altered microRNAs related to synaptic function as potential plasma biomarkers for Alzheimer's disease. Alzheimers Res Ther 11:46

Simon DJ, Madison JM, Conery AL, Thompson-Peer KL, Soskis M, Ruvkun GB, Kaplan JM, Kim JK (2008) The microRNA miR-1 regulates a MEF-2-dependent retrograde signal at neuromuscular junctions. Cell 133:903–915

Südhof TC (2008) Neuroligins and neurexins link synaptic function to cognitive disease. Nature 455:903–911

Taheri M, Tamizkar KH, Omrani S, Arsang-Jang S, Ghafouri-Fard S, Omrani MD (2021a) MEG3 lncRNA is over-expressed in autism spectrum disorder. Metab Brain Dis

Taheri M, Younesi Z, Moradi S, Tamizkar KH, Razjouyan K, Arsang-Jang S, Ghafouri-Fard S, Neishabouri SM (2021b) Altered expression of CCAT1 and CCAT2 lncRNAs in autism spectrum disorder. Gene Rep 23:101172

Tamizkar KH, Ghafouri-Fard S, Omrani MD, Pouresmaeili F, Arsang-Jang S, Taheri M (2021) Altered expression of lncRNAs in autism spectrum disorder. Metab Brain Dis 36:983–990

Vaccaro TD, Sorrentino JM, Salvador S, Veit T, Souza DO, De Almeida RF (2018) Alterations in the microRNA of the blood of autism spectrum disorder patients: effects on epigenetic regulation and potential biomarkers. Behav Sci (Basel) 8

Venø MT, Hansen TB, Venø ST, Clausen BH, Grebing M, Finsen B, Holm IE, Kjems J (2015) Spatio-temporal regulation of circular RNA expression during porcine embryonic brain development. Genome Biol 16:245

Wang Y, Zhao X, Ju W, Flory M, Zhong J, Jiang S, Wang P, Dong X, Tao X, Chen Q (2015) Genome-wide differential expression of synaptic long noncoding RNAs in autism spectrum disorder. Transl Psychiatry 5:e660

Wang Y, Zhao X, Ju W, Flory M, Zhong J, Jiang S, Wang P, Dong X, Tao X, Chen Q, Shen C, Zhong M, Yu Y, Brown WT, Zhong N (2015b) Genome-wide differential expression of synaptic long noncoding RNAs in autism spectrum disorder. Transl Psychiatry 5:e660

Won H, Mah W, Kim E (2013) Autism spectrum disorder causes, mechanisms, and treatments: focus on neuronal synapses. Front Mol Neurosci 6:19

Wu YE, Parikshak NN, Belgard TG, Geschwind DH (2016) Genome-wide, integrative analysis implicates microRNA dysregulation in autism spectrum disorder. Nat Neurosci 19:1463–1476

Yapijakis C (2020) Regulatory role of microRNAs in brain development and function. GeNeDis 2018. Springer

Yoshino Y, Roy B, Dwivedi Y (2020) Differential and unique patterns of synaptic miRNA expression in dorsolateral prefrontal cortex of depressed subjects. Neuropsychopharmacology 1–11

Yu C-Y, Kuo H-C (2019) The emerging roles and functions of circular RNAs and their generation. J Biomed Sci 26:29

Yuan Y, Jiaoming L, Xiang W, Yanhui L, Shu J, Maling G, Qing M (2018) Analyzing the interactions of mRNAs, miRNAs, lncRNAs and circRNAs to predict competing endogenous RNA networks in glioblastoma. J Neurooncol 137:493–502

Zaslavsky K, Zhang W-B, McCready FP, Rodrigues DC, Deneault E, Loo C, Zhao M, Ross PJ, el Hajjar J, Romm A (2019) SHANK2 mutations associated with autism spectrum disorder cause hyperconnectivity of human neurons. Nat Neurosci 22:556–564

Ziats MN, Rennert OM (2013) Aberrant expression of long noncoding RNAs in autistic brain. J Mol Neurosci 49:589–593