Journal of Molecular Neuroscience (2021) 71:1338–1355
https://doi.org/10.1007/s12031-021-01825-7

The Potential Role of miRNAs as Predictive Biomarkers in Neurodevelopmental Disorders

Iman Imtiyaz Ahmed Juvale[1] · **Ahmad Tarmizi Che Has**[1]

Received: 25 January 2021 / Accepted: 2 March 2021 / Published online: 27 March 2021

Abstract

Neurodevelopmental disorders are defined as a set of abnormal brain developmental conditions marked by the early childhood onset of cognitive, behavioral, and functional deficits leading to memory and learning problems, emotional instability, and impulsivity. Autism spectrum disorder, attention-deficit/hyperactivity disorder, Tourette syndrome, fragile X syndrome, and Down's syndrome are a few known examples of neurodevelopmental disorders. Although they are relatively common in both developed and developing countries, very little is currently known about their underlying molecular mechanisms. Both genetic and environmental factors are known to increase the risk of neurodevelopmental disorders. Current diagnostic and screening tests for neurodevelopmental disorders are not reliable; hence, individuals with neurodevelopmental disorders are often diagnosed in the later stages. This negatively affects their prognosis and quality of life, prompting the need for a better diagnostic biomarker. Recent studies on microRNAs and their altered regulation in diseases have shed some light on the possible role they could play in the development of the central nervous system. This review attempts to elucidate our current understanding of the role that microRNAs play in neurodevelopmental disorders with the hope of utilizing them as potential biomarkers in the future.

Keywords Attention-deficit/hyperactivity disorder · Autism spectrum disorder · Down's syndrome · Fragile X syndrome · MicroRNA · Tourette syndrome

Introduction

The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines neurodevelopmental disorders (NDDs) as a range of abnormal brain developmental conditions characterized by an early childhood onset of cognitive, behavioral, and functional deficits that can result in memory and learning problems, emotional instability, and a lack of self-control (American Psychiatric Association 2013). Common NDDs include autism spectrum disorder (ASD), cerebral palsy (CP), attention-deficit/hyperactivity disorder (ADHD), Tourette syndrome (TS), fragile X syndrome (FXS), and Down's syndrome (DS) (American Psychiatric Association 2013). Children are being increasingly diagnosed with these disorders (Boyle et al. 2011). A recent population-based study in India reported NDDs to be a significant public health burden, with the probability of a clinical diagnosis being as high as 1:8 (Arora et al. 2018). There is a higher prevalence of comorbidities such as epilepsy (Reilly et al. 2014; Gillberg et al. 2017; Alabaf et al. 2019), asthma (Chen et al. 2013; Kotey et al. 2014), headaches (Parisi et al. 2014), migraines (Fasmer et al. 2011; Sullivan et al. 2014), autoimmune disorders (Zerbo et al. 2015; Frye et al. 2017), and gastrointestinal problems (Chaidez et al. 2014; Ferguson et al. 2017; Li et al. 2017) in individuals with NDDs. A higher mortality rate has also been observed among persons with NDDs (Dalsgaard et al. 2015; Hirvikoski et al. 2016; Schendel et al. 2016). A recent study in sub-Saharan Africa revealed that although child mortality rates have dropped from 3.4 million to 2.7 million between the years 1990 and 2016, the mortality rate for children aged < 5 years with NDDs has increased from 8.6 to 14.7 million (Olusanya et al. 2018). The prevalence of ASD in the USA has increased over time, with 1 in 150 being reported in 2000–2002, 1 in 59 reported in 2014, and 1 in 54 reported in 2016 (Maenner et al. 2020). Similarly, the incidence rate of DS in the USA has also increased from

✉ Ahmad Tarmizi Che Has
ahmadtarmizi@usm.my

[1] Department of Neurosciences, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia

49,923 in 1950 to 206,366 in 2010 (de Graaf et al. 2016). The global burden of ADHD and TS has been reported to be 5.29% (Smith 2017) and 0.3–1% respectively (Cath et al. 2011). Comparatively, FXS has a global incidence rate of 1/4000 in males and 1/8000 in females (Peprah 2011); for in-depth population-based reports, refer to Peprah (2011). Studies have also shown that siblings of individuals with CP have a higher chance of developing NDDs and have higher mortality rates (Tollånes et al. 2016). A lack of education combined with the stigma and fear surrounding these disorders often results in children with NDDs being abandoned or institutionalized, which can cause further trauma and exacerbate psychiatric symptoms (Dumaret and Rosset 1993; Solomon and Peltz 2008). Unless tested for during pregnancy, expectant mothers are often unaware that their fetus has an NDD and are unprepared for raising such an individual. On the other hand, couples may worry about having a severely affected child with NDD and may choose to terminate the pregnancy upon detection; for example, the termination rate in Denmark following a prenatal diagnosis of DS is high (> 95%) (Lou et al. 2018). However, these tests are not always reliable (Sainz et al. 2012; Alldred et al. 2017; Santorum et al. 2017; Wiechec et al. 2017); benign variations in maternal DNA have been shown to increase false-positive screening results (Snyder et al. 2015). Similarly, these tests have also been known to generate false-negative results, which could in turn have negative psychological effects on the parents and their child (Hall et al. 2000; Simonsen et al. 2013; Simionescu and Stanescu 2020). One factor that may often be overlooked by parents is that NDDs tend to vary in their severity, range, and duration of symptoms. Hence, a positive diagnosis does not always mean that the fetus will develop the most severe form of the condition. Therefore, better counseling and a more robust screening procedure are necessary to ensure that parents can make informed decisions.

The Need for an Early Diagnostic Biomarker

While some NDDs such as DS have prenatal screening options, several other NDDs are diagnosed much later after birth. Individuals with DS or FXS may exhibit certain facial phenotypes specific to their condition, which increases the likelihood of early detection (Cornejo et al. 2017; Ciaccio et al. 2017). However, this is not true for NDDs such as ADHD, ASD, and TS that lack specific diagnostic tests and rely heavily on a behavioral diagnosis (Wilens and Spencer 2010; Randall et al. 2018; Novotny et al. 2018). Studies have shown that compared with males, females with ASD have a higher risk of remaining undiagnosed or being diagnosed later into adulthood, with some individuals diagnosed after the age of 40 years (Lehnhardt et al. 2015; Bargiela et al. 2016; Young et al. 2018; Leedham et al. 2019; Green et al. 2019). The diagnosis of ADHD is often contentious, with some studies claiming ADHD to be an overly diagnosed and over-treated condition, whereas other researchers propose the opposite (Hamed et al. 2015). Patients with ASD are often misdiagnosed with ADHD in their early years only to be correctly diagnosed much later in their adolescence (Kentrou et al. 2018). In the case of TS, although the usual age at symptom onset is around 3 years, individuals are typically not diagnosed until they are aged 8 years (Mol Debes et al. 2008; Shilon et al. 2008). This late diagnosis usually has a negative impact on individuals with NDDs as they can go through life being misunderstood, self-critical, and often suffer from psychosocial difficulties, identity crises, addiction, and poor mental health, leading to suicidal ideations (Huntley et al. 2012; Agnew-Blais et al. 2018; Leedham et al. 2019). Therefore, there is a vital need for early diagnosis and intervention for individuals with NDDs. An early diagnosis would provide more adjustment time for families to educate and prepare themselves for raising an individual with special needs. This would also ensure that lifestyle changes are made according to the child's needs, including the use of applied behavior analysis, and other interventions such as the Early Start Denver Model, Picture Exchange Communication Systems, Discrete Trial Training, and Pivotal Response Treatment are used to educate children with NDDs instead of relying on the conventional education system (Yu et al. 2020). Early childhood intervention and treatment have been shown to reduce symptoms and complications of NDDs in adulthood, ensuring an overall better quality of life (Angulo-Barroso et al. 2008; Dawson et al. 2012; O'Neill et al. 2012; McPhilemy and Dillenburger 2013; Anderson et al. 2014; Sullivan et al. 2014; Ornoy and Spivak 2019; Smith et al. 2020). However, the current diagnostic tools are not precise enough to detect NDDs in their early stages, thus prompting the search for a more accurate and reliable biomarker that can aid in confirming the diagnosis and facilitate personalization of treatment regimens. MicroRNA (miRNA) has recently been discovered to play a role in several NDDs. This review aims to highlight its potential role as a biomarker.

miRNA: an Overview

miRNAs are small non-coding RNAs (~ 22 nucleotides in length) that are involved in the regulation of gene expression through RNA interference or gene silencing (O'Brien et al. 2018). Their function is critical to survival, as each cell in the human body possesses identical copies of DNA and cells differentiate and mature in response to the set of genes that are expressed or silenced. The process of miRNA synthesis begins in the nucleus, where RNA polymerase II transcribes miRNA genes into a hairpin loop structure referred to as primary miRNA (Yin et al. 2015). The RNA-binding protein DiGeorge Syndrome Critical Region 8 (DGCR8) then detects specific motifs such as the N6-methyladenylated GGAC

region of the primary miRNA and binds to it (Alarcon et al. 2015). This is followed by DGCR8 coupling with a ribonuclease III enzyme called Drosha, which cleaves the primary miRNA into a smaller precursor miRNA (Denli et al. 2004). This precursor miRNA is then exported into the cytoplasm through a nuclear pore via the GTP-binding nuclear protein Ran/exportin-5 complex (Bohnsack et al. 2004). Upon its release into the cytoplasm, this precursor miRNA is recognized by another enzyme, the RNase III endonuclease Dicer, which further cleaves the terminal loop of this precursor to generate a shorter double-stranded mature miRNA (Liu et al. 2015). The protein Argonaute-2 (AGO-2) then associates with Dicer to bind to the mature miRNA, which initiates the unwinding of the double-stranded structure (Bossé and Simard 2010). This single guide strand binds to AGO-2 couples with other proteins to form the miRNA-induced silencing complex (RISC), which carries out the crucial function of gene silencing (Kawamata and Tomari 2010). Upon completion of transcription, this structure can interact with complementary sequences on the newly generated messenger RNA (mRNA) and can inactivate it either by cleaving the mRNA strand (Park and Shin 2014) or by hindering mRNA-ribosomal complex interaction (Antic et al. 2015) (all steps are illustrated in Fig. 1), thus inhibiting translation and protein generation. Studies have revealed that miRNAs regulate gene silencing by interacting with either the promoter region, the 5′ untranslated region (UTR), or the 3′ UTR of their target mRNA (Huntzinger and Izaurralde 2011; Xu et al. 2014; Ipsaro and Joshua-Tor et al. 2015). The interaction with the 5′ UTR results in gene silencing (Zhang et al. 2018), whereas the binding of miRNA to the promoter region results in the upregulation of transcription (Dharap et al. 2013). Although miRNAs are usually known for gene silencing, several studies have reported their paradoxical role in the upregulation of gene expression and translational activation (Vasudevan and Steitz 2007; Orom et al. 2008; Truesdell et al. 2012; Bukhari et al. 2016). For further information, readers can refer to the comprehensive reviews detailing the regulation and function of miRNAs by Gebert and MacRae (2019) and O'Brien et al. (2018). Numerous studies have confirmed the involvement of miRNAs in embryogenesis (Tang et al. 2007; Feng et al. 2015; Yuan et al. 2016), apoptosis (Chang et al. 2007; Asuthkar et al. 2012; Adams et al. 2016), cell adhesion, and intracellular signaling (Harris et al. 2008; Cuman et al., 2015; Lui et al. 2015; Cheng et al. 2020). miRNAs are highly expressed in the central nervous system and have been shown to play a role in synaptic plasticity and memory formation (Busto et al. 2015; Ryan et al. 2015; Kremer et al. 2018; Smith and Kenny 2018), axonal development of retinal ganglion cells (Marler et al. 2014; He et al. 2018; Mak et al. 2020), differentiation of oligodendrocytes (Dugas et al. 2010; Letzen et al. 2010; Buller et al. 2012; Santra et al. 2014) and astrocytes (Neo et al. 2014; Shenoy et al. 2015; Zhou et al. 2017), and the differentiation, proliferation, migration, and axonal growth of neural progenitor cells (Otaegi et al. 2011; Dajas-Bailador et al. 2012; Bian et al. 2013; Zhang et al. 2013; Radhakrishnan and Alwin Prem Anand 2016), thus highlighting their critical role in neurodevelopment. Due to its diverse physiological roles, the dysregulation of miRNA has been implicated in numerous diseases including cancer (Peng and Croce, 2016), with more recent studies reporting altered miRNA activity in NDDs.

miRNA Alterations in Neurodevelopmental Disorders

Autism Spectrum Disorder

The term ASD has been assigned to individuals suffering from a set of heterogenous NDDs characterized by social communication deficits and repetitive behavior, with intellectual function ranging from severely impaired to exceptionally gifted (Nakata et al. 2019). Studies have suggested various causes and risk factors for ASD, including genetics, drug usage (e.g. anti-depressants), and environmental factors (e.g., toxins, maternal infection) (Amaral 2017). Numerous studies based on children with ASD have reported alterations in their miRNA levels (Vasu et al. 2014; Hicks et al. 2016; Kichukova et al. 2017; Hicks et al. 2020; Sehovic et al. 2020). Their saliva samples revealed downregulation of miR-23a-3p, miR-32-5p, miR-140-3p, and miR-628-5p, and an upregulation of miR-7-5p (Sehovic et al. 2020). The predicted target genes for these miRNAs (*ZBTB20*, *GAS7*, *NTRK2*, and *SCN2A*) (Table 1) have previously been shown to be involved in critical neural processes and have also been linked to ASD (Garbett et al. 2008; Chandley et al. 2015; Zhang et al. 2016; Jones et al. 2018; Spratt et al. 2019). Expression levels of 14 other miRNAs were also shown to be altered in the serum of children with ASD, with expression levels of five miRNAs (miR-181b-5p, miR-320a, miR-572, miR-19b-3p, and miR-130a-3p) being significantly different enough to distinguish ASD individuals from the control group (Vasu et al. 2014). Furthermore, higher expression levels of serum miR-365a-3p, miR-619-5p, and miR-664a-3p were detected in children with ASD, along with the downregulation of miR-197-5p, miR-328-3p, miR-424-5p, miR-500a-5p, and miR-3135a (Kichukova et al. 2017). Studies have identified Fragile X Mental Retardation 1 (*FMR1*) and Forkhead Box Protein P2 (*FOXP2*) mRNAs to be common targets for several of these altered miRNAs (Table 1) (Hicks et al. 2016; Sehovic et al. 2020). *FMR1* is essential for the regulation of synapses, and alterations in its resulting protein can cause FXS (Wang et al. 2012), which is known to account for 20% of female and 40–60% of male patients with ASD (Chaste et al. 2012). Additionally,

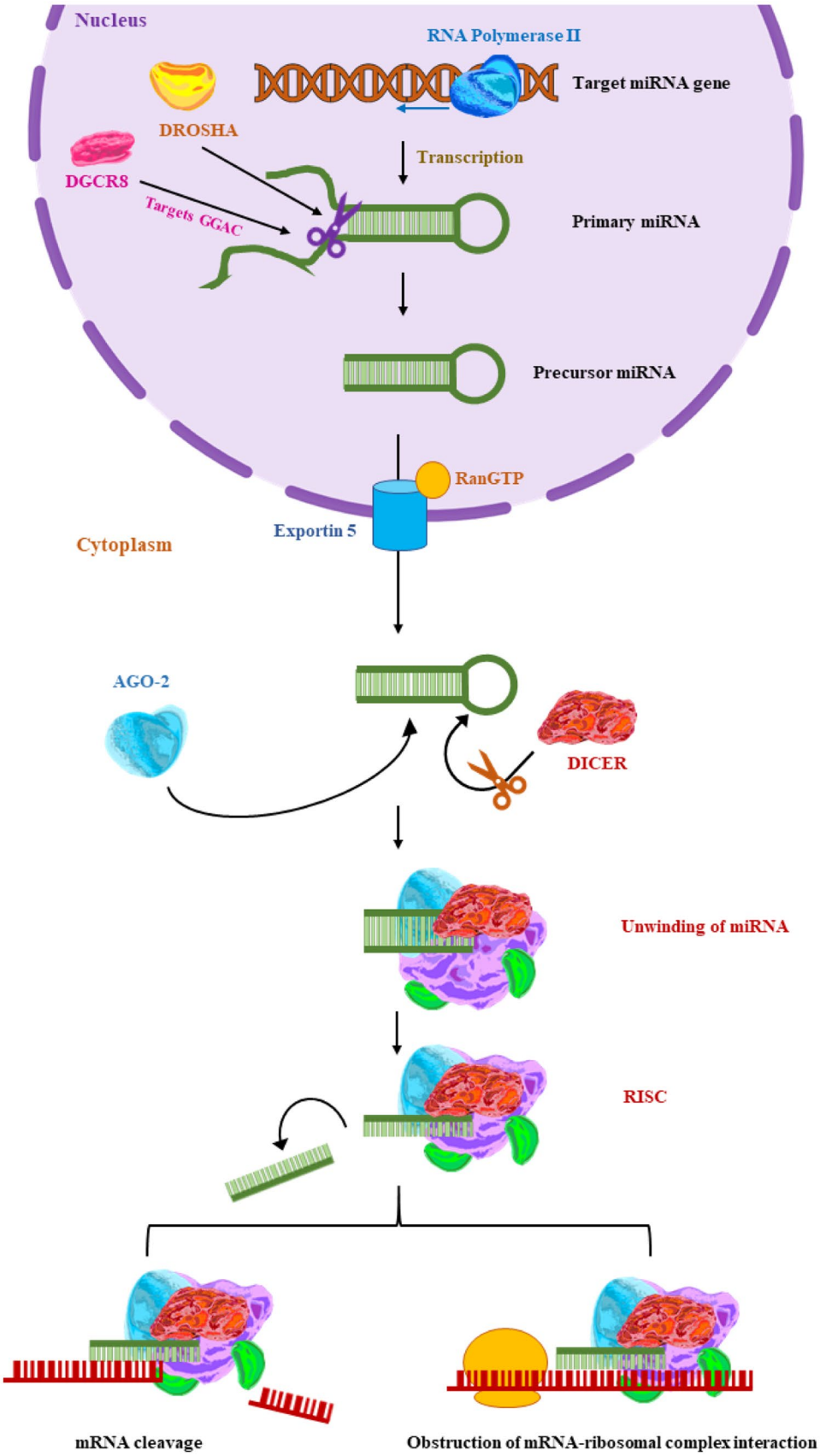

Fig. 1 The biosynthesis of microRNA (miRNA). The process begins in the nucleus of the cell where RNA Polymerase II transcribes the miRNA gene of interest to generate a primary miRNA. The primary miRNA is then cleaved by DiGeorge Syndrome Critical Region 8 (DGCR8) and Drosha to create a shorter precursor miRNA which is transported into the cytoplasm via Exportin 5 in a RanGTP-dependent manner. The terminal loop of this precursor miRNA undergoes further cleavage via Dicer resulting in the formation of a mature double stranded miRNA which proceeds to couple with Argonaute-2 (AGO-2), initiating the unwinding of the double stranded structure. This structure is recognized by several other proteins that associate with it to form the miRNA-induced silencing complex (RISC). The RISC carries out gene silencing either through messenger RNA (mRNA) cleavage or translational repression

Table 1 Alterations in the expression levels of miRNAs and their corresponding target genes in neurodevelopmental disorders

Neurodevelopmental disorder	microRNAs altered	Affected genes	References
Autism spectrum disorder	miR-23a-3p, miR-32-5p, miR-140-3p, miR-628-5p, and miR-7-5p	Zinc finger and BTB domain containing 20 (*ZBTB20*), Growth arrest-specific protein 7 (*GAS7*), Neurotrophic receptor tyrosine kinase 2 (*NTRK2*), Sodium voltage-gated channel alpha subunit 2 (*SCN2A*) Fragile X mental retardation 1 (*FMR1*) and Forkhead box protein P2 (*FOXP2*)	Hicks et al. (2016) and Sehovic et al. (2020)
	miR-486-3p	AT-rich interaction domain 1B (*ARID1B*)	Yu et al. (2018)
	miR34c-5p, miR92a-2-5p, miR-145-5p, miR199a-5p, miR27a-3p, miR19-b-1-5p, and miR193a-5p	Methyl CpG binding protein 2 (*MECP2*), Histone deacetylase 2 (*HDAC2*), Sirtuin 1 (*SIRT1*)	Vaccaro et al. (2018)
Attention-deficit/hyperactivity disorder	miR-101-3p	Solute Carrier Family 12 Member 2 (*SLC12A2*), Kinesin Family Member 1A (*KIF1A*), Ankyrin 2 (*ANK2*), Ran-binding protein 9 (*RANBP9*)	Barbato et al. (2014), Lippi et al. (2016), and Zadehbagheri et al. (2019)
	miR-130a-3p	Methyl CpG binding protein 2 (*MECP2*)	Zhang et al. (2016) and Zadehbagheri et al. (2019)
	miR-138-5p	Glycogen synthase kinase-3β (*GSK-3β*), Retinoic acid receptor alpha (*RARA*)	Siegel et al. (2009), Schröder et al. (2014), Wang et al. (2015), and Zadehbagheri et al. (2019)
	miR-195-5p	Death receptor 6 (*DR-6*), Beta-site APP cleaving enzyme 1 (*BACE1*), Amyloid precursor protein (*APP*)	Ai et al. (2013), Chen et al. (2017), and Zadehbagheri et al. (2019)
	miR-106b-5p	Cyclin D1 (*CCND1*), E2F Transcription Factor 1 (*E2F1*), Cyclin dependent kinase inhibitor 1A (*CDKN1A*), Phosphatase and tensin homolog (*PTEN*), RB transcriptional corepressor 1 (*RB1*), RB transcriptional corepressor like 1 (*RBL1*), and RB Transcriptional Corepressor Like 2 (*RBL2*)	Trompeter et al. (2011) and Zadehbagheri et al. (2019)
	miRNA-let-7d	Tyrosine Hydroxylase (*TH*)	Wu et al. (2010) and Weaver et al. (2012)
	miR-652-3p, miR-148b-3p, and miR-942-5p	Beta-1,4-galactosyltransferase 2 (*B4GALT2*), Solute Carrier Family 6 Member 9 (*SLC6A9*), transducin-like enhancer of split 1 (*TLE1*), Ankyrin 3 (*ANK3*), Trio rho guanine nucleotide exchange factor (*TRIO*), TATA-box binding protein associated factor 1 (*TAF1*), and Spectrin repeat containing nuclear envelope protein 1 (*SYNE1*)	Nuzziello et al. (2019)
	miR-3171	Solute Carrier Family 1 Member 3 (*SLC1A3*)	Huang et al. (2019)

Table 1 (continued)

Neurodevelopmental disorder	microRNAs altered	Affected genes	References
Tourette syndrome	miR-189	Slit and Trk-like family member 1 (*SLITRK1*)	Abelson et al. (2005) and O'Roak et al. (2010)
	miR-429	Zinc finger E-box binding homeobox 1 (*ZEB1*), Zinc finger E-box binding homeobox 2 (*ZEB2*), SRY-box transcription factor 2 (*SOX2*), and E2F transcription factor 3 (*E2F3*)	Korpal et al. (2008), Ragusa et al. (2010), Eipper-Mains et al. (2011), Peng et al. (2012), and Rizzo et al. (2015)
	miRNA-106b and miRNA-198b	Nicotinic acetylcholine receptor alpha 7 subunit (*CHRNA7*) and Netrin 4 (*NTN4*)	Pagliaroli et al. (2017)
Fragile X syndrome	miR-125, miR-132, miR-19b, miR-302b*, miR-323-3p, miR-34b, miR-340, miR-302, and miR-148a	Fragile X mental retardation 1 (*FMR1*)	Lin et al. (2006), Yi et al. (2010), Lin (2015), and Liu et al. (2015)
	mir-382	RE-1 silencing transcription factor (*REST*)	Halevy et al. (2015)
Down's syndrome	miR-504, miR-320c, miR-1298, miR-1297, miR-891b, and miR-513a-3p	BACE2, CBS, RUNX1, and CRYAA	Lim et al. (2015a)
	miR-155	Complement factor H (*CFH*) and Methyl CpG binding protein 2 (*MECP2*)	Griffiths et al. (2009), Elton et al. (2010), Keck-Wherley et al. (2011), Li et al. (2012), and Lu et al. (2013)
	miR-802	Methyl CpG binding protein 2 (*MECP2*)	Elton et al. (2010), Keck-Wherley et al. (2011), and Lu et al. (2013)
	miR-138-5p	Enhancer of zeste homolog 2 (*EZH2*)	Shi et al. (2016)

FOXP2 has been previously implicated in speech development and language disorders (Kurt et al. 2012); thus, both *FMR1* and *FOXP2* are strong candidates for generating ASD phenotypes. Children with ASD have also been shown to have specifically altered miRNAs compared with peers with non-ASD NDDs (Hicks et al. 2020). A test that screens for these miRNAs could therefore be more accurate in diagnosing ASD and distinguishing it from other NDDs relative to behavioral analysis alone. Another study identified overexpression of serum miR-486-3p in individuals with ASD resulting in the downregulation of AT-Rich Interaction Domain 1B (ARID1B) protein expression (Table 1) (Yu et al. 2018). ARID1B is crucial for neuronal differentiation and maturation (Ka et al. 2016; Ronzoni et al. 2016), and an insufficiency of this protein can lead to alterations in the expression levels of c-Fos and Arc resulting in the abnormal development of dendrites and synapses (Yu et al. 2018). These neural aberrations have previously been linked to cognitive deficits and autistic behavior (Curatolo et al. 2014; Tang et al. 2014). In addition, mutations in *ARID1B* have also been associated with the development of ASD (Pinto et al. 2014; D'Gama et al. 2015; Alvarez-Mora et al. 2016). The upregulation of miR-23a and downregulation of miR-106b have also been correlated with ASD and its associated comorbidities (Abu-Elneel et al. 2008; Sarachana et al. 2010). Altered pre-miRNA and miRNA expression levels have also been also detected in the superior temporal sulcus (miR-4753-5p and miR-1) and in the primary auditory cortex (miR-664-3p, miR-4709-3p, miR-4742-3p and miR-297) of patients with ASD (Ander et al. 2015). The target genes of these miRNAs have been reported to be functionally involved in the cell cycle, various neural processes, immune pathways, and canonical signaling pathways such as the PI3K-Akt signaling pathway, all of which have been associated with the development of ASD (Ander et al. 2015). Similarly, another study reported that patients with ASD exhibited higher expression levels of miR34c-5p, miR92a-2-5p, miR-145-5p, and miR199a-5p, as well as lower expression levels of miR27a-3p, miR19-b-1-5p, and miR193a-5p (Vaccaro et al. 2018). These miRNAs were shown to regulate *SIRT1*, *HDAC2* (Table 1), immune system development and response, and the PI3K/Akt/TSC/mTOR signaling pathways (Vaccaro et al. 2018). Previous studies have reported similar expression levels of these miRNAs in patients with Alzheimer's disease (AD) (Wang et al. 2014). Additionally, *MECP2*, a common target of miR-199a-5p (Table 1), has also been linked to Rett syndrome (RS), which could explain the similarities observed between ASD and RS (Vaccaro et al. 2018). A recent study identified overlapping expression levels of miR-19a-3p, miR-361-5p, miR-3613-3p, miR-150-5p, miR-126-3p, and miR-499a-5p in both animal and human models of ASD (Ozkul et al. 2020). Several studies have also observed altered miRNA function in association with ASD: miR-34b and miR-103a-3p (Huang et al. 2015), hsa-miR-21-3p and hsa_can_1002-m (Wu et al. 2016), miR-6126 (Nakata et al. 2019), miR486-3p (Popov et al. 2012), and miR-142-5p, miR-142-3p, miR-451a, miR-144-3p, and miR-21-5p (Mor et al. 2015). The genes regulated by these miRNAs have all been predicted to be directly or indirectly involved in the pathophysiology of ASD and its associated comorbidities. Age-dependent alterations in miRNA expression levels have also been observed in patients with ASD (Stamova et al. 2015); this could explain the lack of a coherent trend in previous studies.

Attention-Deficit/Hyperactivity Disorder

Commonly observed in children, ADHD is a complex NDD characterized by hyperactivity and an inability to pay attention or control impulses, which can hinder educational progress and cause symptoms that persist into adulthood (Wu et al. 2015). This disorder can present with comorbidities such as ASD and other behavioral disorders in association with common risk factors such as genetics, early childhood trauma, prenatal or postnatal exposure to lead, and premature birth (Thapar et al. 2013). Children with ADHD have been shown to have higher serum expression levels of hsa-miR-101-3p, hsa-miR-130a-3p, hsa-miR-138-5p, and hsa-miR-195-5p as well as lower expression levels of hsa-miR-106b-5p (Zadehbagheri et al. 2019). Hsa-miR-101 is responsible for various neurological processes and in particular neuronal excitation, synapse formation, and dendritic growth. By supervising the expression levels of *NKCC1*, *KIF1A*, and *ANK2* (Table 1), it can modulate gamma aminobutyric acid (GABA) signaling and protect the brain from hyperexcitability and memory impairment (Lippi et al. 2016). In hippocampal neurons, this miRNA is known to regulate Ran-binding protein (*RANBP9*) (Table 1) expression levels and hence control the metabolism of the amyloid precursor protein (APP), which plays a critical role in AD (Barbato et al. 2014; Zadehbagheri et al. 2019). Hsa-miR-130a controls neurite outgrowth and dendritic density by repressing the *MECP2* gene (Table 1), a dysfunction that can lead to RS and ASD (Zhang et al. 2016). It has been suggested that ADHD and ASD may share a common molecular mechanism (Zadehbagheri et al. 2019). hsa-miR-138-5p has been shown to monitor dendritic spine formation in hippocampal neurons (Siegel et al. 2009) by upregulating glycogen synthase kinase-3β (*GSK-3β*) (Table 1) and downregulating retinoic acid receptor alpha (*RARA*) (Table 1). This enhances the phosphorylation of tau protein, which is involved in synaptic plasticity and memory formation (Schröder et al. 2014; Wang et al. 2015). Animal model studies have revealed that hsa-miR-195-5p inhibits dendritic degeneration and

neuronal death by downregulating *APP*, death receptor 6 (*DR-6*), and *BACE1* (Table 1) in the hippocampal and cortical brain regions (Ai et al. 2013; Chen et al. 2017). On the other hand, hsa-miR-106b orchestrates cell cycle arrest during neuronal lineage differentiation by modulating cyclin D1 (*CCND1*), *E2F1*, *CDKN1A* (p21), *PTEN*, *RB1*, *RBL1* (p107), and *RBL2* (p130) (Table 1) expression levels (Trompeter et al. 2011). Previous studies have also reported polymorphisms in the gene for hsa-miR-106b to be linked to ASD (Toma et al. 2015). Significantly higher serum levels of miRNA-let-7d have been detected in children with ADHD relative to their healthy counterparts (Wu et al. 2015; Cao et al. 2019). miRNA-let-7d plays a crucial role in cellular differentiation and pluripotency, somatic reprogramming, neurogenesis, and synaptic plasticity (Andolfo et al. 2010; Wong et al. 2012; Wu et al. 2015); animal model studies have identified that overexpression of this miRNA in the rat prefrontal cortex results in suppression of the *TH* gene (Table 1), which is essential for dopamine metabolism (Wu et al. 2010; Weaver et al. 2012). Altered expression levels of miR-652-3p, miR-148b-3p, and miR-942-5p were also detected in patients with ADHD in association with the downregulation of their target genes (*B4GALT2*, *SLC6A9*, *TLE1*, *ANK3*, *TRIO*, *TAF1*, and *SYNE1*) (Table 1) (Nuzziello et al. 2019). These genes are crucial for neuron survival (Dastidar et al. 2012), cognitive functioning (Iqbal et al. 2013), neuronal migration (Zong et al. 2015), axon guidance (Zong et al. 2015), memory formation (Nuzziello et al. 2019), and regulation of glutamate and $GABA_A$ receptors at the postsynaptic membrane (Zhang et al. 2017; Rathje et al. 2019). Several other miRNAs have also been reported to alter the expression of ADHD-associated genes such as *SNAP-25*, *BDNF*, *DAT1*, *HTR2C*, and *HTR1B* (Wu et al. 2010; Németh et al. 2013; Sánchez-Mora et al. 2013; Kandemir et al. 2014; Ye et al. 2016; Wu et al. 2017; Srivastav et al. 2018; Tian et al. 2019; Huang et al. 2019). Recent studies have linked the *SLC1A3* gene with ADHD susceptibility (Turic et al. 2005; Huang et al. 2019). This gene encodes the excitatory amino acid transporter 1 (EAAT1), which is essential for astrocytic glutamate reuptake upon synapse, preventing spill-over into neighboring synapses; it is predominantly found in the cerebellum, which has a role in motor movements (Parkin et al. 2018). Mutations in this gene can alter the hsa-miR-3171 (Table 1) binding site (Huang et al. 2019). Knockdown of the EAAT1 analogue in mice has been shown to generate ADHD phenotypes (Karlsson et al. 2008; Karlsson et al. 2009). Furthermore, methylphenidate, the conventional drug used to treat ADHD, has been proven to control the striatal levels of EAAT1 (Cavaliere et al. 2012), further emphasizing the crucial regulatory role of miRNAs in NDDs.

Tourette Syndrome

Characterized by the early childhood onset of involuntary motor and vocal tics, TS can be present with other comorbid disorders such as obsessive-compulsive disorder, anxiety, ASD, ADHD, behavioral disorders, and learning disabilities (Pagliaroli et al. 2020). However, unlike other NDDs, little is currently known about the molecular mechanisms underlying TS. Several studies have detected genetic variants of the Slit protein and Trk-like family member 1 (*SLITRK1*) gene in brains of individuals affected by TS (Abelson et al. 2005; O'Roak et al. 2010). Similar expression levels of mutant *SLITRK1* mRNA (containing var321) and hsa-miR-189 have been noted in the neocortex, hippocampus, and cerebellum of TS mice models (Abelson et al. 2005). *SLITRK1* is crucial for dendritic growth in neurons, and its expression levels are regulated by miR-189 (Table 1) (Abelson et al. 2005). However, the var321 mutation upregulates the miR-189 silencing function, which results in the neuro-morphological abnormalities seen in patients with TS (Abelson et al. 2005; O'Roak et al. 2010). Several studies have detected polymorphisms in the *SLITRK1* gene that contributes to the TS phenotype (Miranda et al. 2009; Karagiannidis et al. 2012; Inai et al. 2015); however, other studies have reported no *SLITRK1* gene variants in certain populations (Deng et al. 2006; Fabbrini et al. 2007; Zimprich et al. 2008; Yasmeen et al. 2013), suggesting genetic heterogeneity in TS. Lower expression levels of miR-429 have also been reported in patients with TS relative to healthy controls (Rizzo et al. 2015). miR-429 belongs to the miR-200 family that is known to modulate the epithelial-mesenchymal transition by silencing *ZEB1* and *ZEB2* (Table 1) (Korpal et al. 2008; Ragusa et al. 2010). These miRNAs have been shown to induce differentiation of midbrain dopaminergic neurons as well as ventral midbrain and hindbrain neural progenitor cells by regulating *SOX2* and *E2F3* (Table 1) expression levels (Peng et al. 2012). Animal model studies have also reported that miR-429 plays a crucial role in dendrite formation and synaptic plasticity (Eipper-Mains et al. 2011; Rizzo et al. 2015), thus further supporting the morphological alterations observed in brains of individuals with TS (Steeves et al. 2008; Patel et al. 2011; Tossell et al. 2011; Rizzo et al. 2015). miR-429 shares the same genetic locus (1p36.33) as several copy number variants have been implicated in ASD (Vaishnavi et al. 2013; Marrale et al. 2014). Genetic variants of the nicotinic acetylcholine receptor alpha 7 subunit (*CHRNA7*) gene and Netrin 4 (*NTN4*) gene (Table 1) have also been reported to alter the seed sequence of miRNA-106b and miRNA-198b, resulting in a five-fold reduction in their expression levels in brains of individuals affected by TS (Pagliaroli et al. 2017). CHRNA7 is essential for the release of various neurotransmitters (Sinkus et al. 2015) and for cognitive processes (Wallace and Porter 2011; Lendvai

et al. 2013; Wallace and Bertrand 2013), whereas NTN4 has been shown to play a role in cell migration, tissue morphogenesis, angiogenesis, and apoptosis (Xu et al. 2017). Lower expression levels of CHRNA7 have also been previously reported in ASD brains, suggesting a possible link between the two (Allen-Brady et al. 2010; Yasui et al. 2011). Similarly, a more recent study reported genetic variants of the LIM homeobox 6 (*LHX6*), inner mitochondrial membrane peptidase subunit 2 (*IMMP2L*), and arylacetamide deacetylase (*AADAC*) genes were associated with altered miRNA function in patients with TS (Pagliaroli et al. 2020). LHX6 is critical for the regulation of striatal and cortical interneurons (Grigoriou et al. 1998; Liodis et al. 2007; Zhao et al. 2008; Kreitzer et al. 2009) as well as the differentiation and formation of neural and lymphoid cells (Tepper et al. 2007). The protein encoded by *IMMP2L* ensures that transit proteins in the mitochondria are correctly processed, thus indirectly regulating apoptosis (Pagliaroli et al. 2020). Although not much is known about the function of the AADAC protein in the brain, studies have detected AADAC expressed in the hippocampus, corpus callosum, and caudate nucleus, which are regions commonly affected in TS (Plessen et al. 2009). The mutant AADAC also occurs in close proximity to the binding site of miR-4263, which has been reported to play a role in the differentiation of embryonic and neural stem cells (Goff et al. 2009; Pagliaroli et al. 2020), thus suggesting a possible role in TS.

Fragile X Syndrome

FXS is a common X-linked inherited intellectual disorder that arises due to hypermethylation of the upstream CpG islands and CGG repeats in the 5′ UTR of the *FMR1* gene, resulting in the downregulation of fragile mental retardation protein (FMRP) expression, which is an essential translational regulator during synapsis (Jin et al. 2004a; Wang et al. 2012). FXS has been shown to be a monogenic cause of ASD (Wang et al. 2012). FMRP can reversibly block ribosomal progression on mRNA during translation, thus regulating the levels of several presynaptic and postsynaptic proteins that have been associated with ASD (Darnell et al. 2011). Early studies in Drosophila have revealed that the miRNA protein AGO-1 predominantly regulates FMRP function during neurodevelopment and synaptogenesis (Jin et al. 2004b), whereas modulation via the bantam miRNA has been shown to be involved in primordial germ cell differentiation and maintenance (Yang et al. 2009). miR-125 and miR-132 (Table 1) are known to interact with FMRP to regulate group 1 metabotropic glutamate receptors (mGluR1) and *N*-methyl-d-aspartate receptor (NMDAR) signaling during normal neurodevelopment (Lin 2015). An in vivo study in zebrafish that utilized anti-*FMR1* miRNA detected synaptic deformities and increased long-term depression (LTD) via mGluR1 (Lin et al. 2006). Another zebrafish study reported that miRNA overexpression resulted in hypermethylation of the *FMR1* 5′-r(CGG) region causing neurite deformations and synaptic dysfunction, suggesting a crucial role in FXS (Chang et al. 2008). The 3′ UTR of the *FMR1* gene was also shown to be targeted by miR-19b, miR-302b*, and miR-323-3p (Table 1), causing gene repression and generating the FXS phenotype (Yi et al. 2010). A knockout study in mice revealed overexpression of several pre-miRNAs and miRNAs, with miR-34b, miR-340, and miR-148a (Table 1) shown to significantly downregulate reporter gene expression levels through the Met 3′ UTR (Liu et al. 2015). The miRNA miR-302 has been shown to play a physiological role by inhibiting *FMR1* translation and regulating neurodevelopment during the early stages of embryogenesis (Lin 2015). Following the blastocyst stage, miR-302 expression levels are downregulated, thus freeing *FMR1* to synthesize FMRP and initiate neural development. However, in FXS, there is an accumulation of mutated miRNAs that results in hypermethylation of the promoter regions of the *FMR1* gene, causing gene repression and a lack of FMRP production (Lin 2015). During spermatogenesis, the accumulation of these mutated miRNAs results in the downregulation of FMRP expression, causing hyperproliferation of Sertoli cells and spermatogenic defects (Ramaiah et al. 2019). These miRNAs have also been reported to modulate the levels of the eukaryotic translational initiation factor (eIF4E) and the cytoplasmic FMR1 interacting protein 1 (CYFIP1) that, when coupled with FMRP, create a translational regulatory complex (Ramaiah et al. 2019). A more recent in vitro study reported that the genes involved in the differentiation of neurons and axon guidance were abnormally expressed in FXS-derived neurons (Halevy et al. 2015). These genes were shown to be targeted by the RE-1 silencing transcription factor (*REST*), which was overexpressed in FXS cells. A further investigation revealed lower expression levels of hsa-mir-382 in these cells, and the subsequent reintroduction of an hsa-mir-382 (Table 1) analog resulted in *REST* suppression and upregulation of its target genes, thus highlighting the importance of miRNAs in normal neurodevelopment. In addition, recent urine samples from children with FXS revealed the overexpression of several miRNAs involved in the regulation of developmental processes, homeostasis, and neuronal function (Putkonen et al. 2020). Of these miRNAs, miR-125a was shown to have a significantly higher expression level compared with the control group. miR-125a has been associated with normal mGluR1 regulation, thereby hindering synaptic plasticity in FXS (Putkonen et al. 2020). This further supports the notion that miRNAs can be used as potential biomarkers for FXS.

Down's Syndrome

DS or trisomy 21 is a chromosomal abnormality that arises due to an extra copy or fragment of the 21st chromosome. It is associated with severe comorbidities including cognitive deficits, mental retardation, immune system disorders, leukemia, congenital heart defects, hypotonia, dementia, and early onset AD (Lim et al. 2015a). Due to the high mortality rate associated with this disorder, expectant women are widely offered screening and diagnostic testing as optional components of prenatal care. The prevalence of DS has been directly linked to maternal age (Wu and Morris 2013). A recent genome-wide microarray study in DS placental samples reported overexpression of miRNA on chromosome 21 (miR-99a, miR-125b, and let-7c) as well as other chromosomes (miR-542-5p, miR-10b, miR-615, and miR-654) (Lim et al. 2015b). The placental samples also exhibited higher expression levels of mir-1973 and mir-3196, which have been suggested to modulate the genes involved in neurodevelopment. Another study reported up to 20 genes being upregulated in DS placental samples, with *BACE2*, *CBS*, *RUNX1*, and *CRYAA* showing significant associations with DS comorbidities (Lim et al. 2015a); miR-504, miR-320c, miR-1298, miR-1297, miR-891b, and miR-513a-3p (Table 1) have been reported to be involved in upregulation of these genes. This study also found miR-133b, miR-188-3p, and miR-1301 to be responsible for the downregulation of five other genes linked to complications of DS such as mental retardation, behavioral problems, and congenital abnormalities. Several human and animal model studies have reported altered miRNA expression levels in fetal samples affected by DS (Xu et al. 2013b; Lin et al. 2016; Arena et al. 2017; Karaca et al. 2018; Zbucka-Kretowska et al. 2019). A recent study in pregnant women with fetal DS reported elevated levels of hsa-miR-15a, hsa-let-7d, hsa-miR-142, hsa-miR-23a, hsa-miR-199, and hsa-miR-191, as well as lower levels of hsa-miR-1290, hsa-miR-1915, hsa-miR30e, hsa-miR-1260, hsa-miR-483, hsamiR-548, and hsa-miR-590, with their target genes being implicated in generating DS phenotypes (Zbucka-Kretowska et al. 2019). Another study reported higher levels of miR-125b-2, miR-155, and miR-3156 in the amniotic fluid of pregnant women with fetal DS relative to controls (Karaca et al. 2018). Overexpression of miR-99a-5p, miR-155-5p, and let-7c-5p has also been implicated in cardiac anomalies in fetal DS (Izzo et al. 2017). The prevalence of leukemia and immune system disorders in patients with DS could also be attributed to alterations in miRNA expression levels (Xu et al. 2013a; Shaham et al. 2015). Overexpression of miR-155, miR-802, miR-125b-2, let-7c, and miR-99a has been reported in DS with downregulation of their target mRNA (Elton et al. 2010; Elton et al. 2013; Siew et al. 2013; Alexandrov et al. 2018). The complement factor H (*CFH*) mRNA that is targeted by miR-155 (Table 1) is critical for neuroprotection, the immune response, complement opsonization, and leukocyte infiltration (Griffiths et al. 2009; Li et al. 2012). Thus, the overexpression of miR-155 may silence *CFH* function, possibly resulting in the pathological phenotype observed in patients with DS (Li et al. 2012). Both in vivo and in vitro studies have reported higher expression levels of miR-155 and miR-802 (Table 1) to result in decreased levels of methyl-CpG binding protein 2 (*MECP2*), causing developmental defects and neuronal malformations (Elton et al. 2010; Keck-Wherley et al. 2011; Lu et al. 2013). Lower levels of MECP2 in DS have also been associated with poor synaptic strength, which could result in cognitive deficits and reduced synaptic plasticity (Chao et al. 2007). Intellectual deficits due to the downregulation of enhancer of zeste homolog 2 (*EZH2*) by miR-138-5p (Table 1) have also been associated with DS (Shi et al. 2016). Therefore, altered miRNA function could play a significant role in neurodevelopment and DS-related comorbidities.

Conclusion

Although our current knowledge regarding the role of miRNAs in NDDs is limited, it is a promising area for future research. Several of the abovementioned studies detected altered miRNA expression levels using liquid biopsy samples (e.g., blood, urine, saliva) from patients with NDDs, thus eliminating the necessity for invasive procedures while also providing a more reliable diagnostic method than behavioral diagnosis alone. Northern blotting, in situ hybridization, reverse transcription qPCR, microarray, and next-generation sequencing are few of the existing assays that can detect altered miRNA levels in liquid biopsies (Dave et al. 2018). However, each method has its advantages and disadvantages (summarized by Dave et al. 2018), and researchers have yet to discover a full-proof miRNA-based screening test for NDDs. Currently, the Food and Drug Administration (FDA) has authorized a number of miRNA-based tests for cancer diagnosis which have been proven to be more sensitive and specific as compared with the conventional screening methods (Dave et al. 2018). Therefore, there is a possibility for miRNA to be used as a potential diagnostic marker for NDDs in the near future. The utilization of miRNAs to facilitate early diagnoses would ensure that individuals with NDDs are provided with the right kind of care beginning in their developmental years. They could be introduced to special enrichment classes designed for their condition, allowing them to learn and develop in a safe environment. An early diagnosis would also help prepare families and caretakers well in advance. Current treatment options for NDDs are limited. However, identification of target miRNAs could facilitate the development of new treatment options.

Availability of Data and Material

Data sharing is not applicable to this article as no new data were created or analyzed in this review work.

Author Contribution Iman Imtiyaz Ahmed Juvale: Designing and drafting the manuscript. Ahmad Tarmizi Che Has: Revising the manuscript critically and approving the manuscript to be published.

Funding This review work was funded by the Fundamental Research Grant Scheme (FRGS) 203/PPSP/6171233, sponsored by Ministry of Higher Education, Malaysia.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

References

Abelson J, Kwan K, O'Roak B, Baek D, Stillman A, Morgan T, Mathews C, Pauls D, Rasin M, Gunel M, Davis N, Ercan-Sencicek A, Guez D, Spertus J, Leckman J, Dure L, Kurlan R, Singer H, Gilbert D, Farhi A, Louvi A, Lifton R, Sestan N, State M (2005) Sequence variants in SLITRK1 are associated with Tourette's syndrome. Science 310(5746):317–320

Abu-Elneel K, Liu T, Gazzaniga FS, Nishimura Y, Wall DP, Geschwind DH, Lao K, Kosik KS (2008) Heterogeneous dysregulation of microRNAs across the autism spectrum. Neurogenetics 9:153–161

Adams CM, Hiebert SW, Eischen CM (2016) Myc induces miRNA-mediated apoptosis in response to HDAC inhibition in hematologic malignancies. Can Res 76(3):736–748

Agnew-Blais J, Polanczyk G, Danese A, Wertz J, Moffitt T, Arseneault L (2018) Young adult mental health and functional outcomes among individuals with remitted, persistent and late-onset ADHD. Br J Psychiatry 213(3):526–534

Ai J, Sun L-H, Che H, Zhang R, Zhang T-Z, Wu W-C, Su X-L, Chen X, Yang G, Li K (2013) MicroRNA-195 protects against dementia induced by chronic brain hypoperfusion via its anti-amyloidogenic effect in rats. J Neurosci 33:3989–4001

Alabaf S, Gillberg C, Lundström S, Lichtenstein P, Kerekes N, Råstam M, Anckarsäter H (2019) Physical health in children with neurodevelopmental disorders. J Autism Dev Disord 49(1):83–95

Alarcon CR, Lee H, Goodarzi H, Halberg N, Tavazoie SF (2015) N6-methyladenosine marks primary microRNAs for processing. Nature 519:482–485

Alexandrov PN, Percy ME, Lukiw WJ (2018) Chromosome 21-encoded microRNAs (mRNAs): impact on Down's syndrome and Trisomy-21 linked disease. Cell Mol Neurobiol 38(3):769–774

Alldred S, Takwoingi Y, Guo B, Pennant M, Deeks J, Neilson J, Alfirevic Z (2017) First trimester ultrasound tests alone or in combination with first trimester serum tests for Down's syndrome screening. Cochrane Database of Systematic Reviews

Allen-Brady K, Robison R, Cannon D, Varvil T, Villalobos M, Pingree C, Leppert MF, Miller J, McMahon WM, Coon H (2010) Genome-wide linkage in Utah autism pedigrees. Mol Psych 15:1006–1015

Alvarez-Mora M, Calvo Escalona R, Puig Navarro O, Madrigal I, Quintela I, Amigo J, Martinez-Elurbe D, Linder-Lucht M, Aznar Lain G, Carracedo A, Mila M, Rodriguez-Revenga L (2016) Comprehensive molecular testing in patients with high functioning autism spectrum disorder. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 784–785:46–52

Amaral DG (2017) Examining the causes of autism. Cerebrum : the Dana forum on brain science, 2017, cer-01–17

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, 5th edn. Arlington, VA

Ander B, Barger N, Stamova B, Sharp F, Schumann C (2015) Atypical miRNA expression in temporal cortex associated with dysregulation of immune, cell cycle, and other pathways in autism spectrum disorders. Mol Autism, 6(1)

Anderson D, Liang J, Lord C (2014) Predicting young adult outcome among more and less cognitively able individuals with autism spectrum disorders. J Child Psychol Psychiatry 55(5):485–494

Andolfo I, De Falco L, Asci R, Russo R, Colucci S, Gorrese M, Zollo M, Iolascon A (2010) Regulation of divalent metal transporter 1 (DMT1) non-IRE isoform by the microRNA Let-7d in erythroid cells. Haematologica 95(8):1244–1252

Angulo-Barroso R, Burghardt A, Lloyd M, Ulrich D (2008) Physical activity in infants with Down syndrome receiving a treadmill intervention. Infant Behav Dev 31(2):255–269

Antic S, Wolfinger MT, Skucha A, Hosiner S, Dorner S (2015) General and microRNA-mediated mRNA degradation occurs on ribosome complexes in Drosophila cells. Mol Cell Biol 35(13):2309–2320

Arena A, Iyer AM, Milenkovic I, Kovacs GG, Ferrer I, Perluigi M, Aronica E (2017) Developmental expression and dysregulation of miR-146a and miR-155 in Down's syndrome and mouse models of Down's syndrome and Alzheimer's disease. Curr Alzheimer Res 14(12):1305–1317

Arora NK, Nair MKC, Gulati S, Deshmukh V, Mohapatra A, Mishra D, Patel V, Pandey RM, Das BC, Divan G, Murthy GVS, Sharma TD, Sapra S, Aneja S, Juneja M, Reddy SK, Suman P, Mukherjee SB, Dasgupta R, Tudu P, Das MK, Bhutani VK, Durkin MS, Pinto-Martin J, Silberberg DH, Sagar R, Ahmed F, Babu N, Bavdekar S, Chandra V, Chaudhuri Z, Dada T, Dass R, Gourie-Devi M, Remadevi S, Gupta JC, Handa KK, Kalra V, Karande S, Konanki R, Kulkarni M, Kumar R, Maria A, Masoodi MA, Mehta M, Mohanty SK, Nair H, Natarajan P, Niswade AK, Prasad A, Rai SK, Russell PSS, Saxena R, Sharma S, Singh AK, Singh GB, Sumaraj L, Suresh S, Thakar A, Parthasarathy S, Vyas B, Panigrahi A, Saroch MK, Shukla R, Rao KVR, Silveira MP, Singh S, Vajaratkar V (2018) Neurodevelopmental disorders in children aged 2–9 years: population-based burden estimates across five regions in India. PLoS Med 15(7):e1002615

Asuthkar S, Velpula KK, Chetty C, Gorantla B, Rao JS (2012) Epigenetic regulation of miRNA-211 by MMP-9 governs glioma cell apoptosis, chemosensitivity and radiosensitivity. Oncotarget 3(11):1439–1454

Barbato C, Pezzola S, Caggiano C, Antonelli M, Frisone P, Ciotti MT, Ruberti F (2014) A lentiviral sponge for miR-101 regulates RanBP9 expression and amyloid precursor protein metabolism in hippocampal neurons. Front Cell Neurosci 8:37

Bargiela S, Steward R, Mandy W (2016) The experiences of late-diagnosed women with autism spectrum conditions: an investigation of the female autism phenotype. J Autism Dev Disord 46(10):3281–3294

Bian S, Hong J, Li Q, Schebelle L, Pollock A, Knauss JL, Garg V, Sun T (2013) MicroRNA cluster miR-17-92 regulates neural stem cell expansion and transition to intermediate progenitors in the developing mouse neocortex. Cell reports 3(5):1398–1406

Bohnsack MT, Czaplinski K, Gorlich D (2004) Exportin 5 is a RanGTP-dependent dsRNA-binding protein that mediates nuclear export of pre-miRNAs. RNA (New York, N.Y.), 10(2), pp.185–191

Bossé G, Simard M (2010) A new twist in the microRNA pathway: Not Dicer but Argonaute is required for a microRNA production. Cell Res 20:735–737

Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, Kogan MD (2011) Trends in the prevalence of developmental disabilities in US children, 1997–2008. Pediatrics 127(6):1034–1042

Bukhari S, Truesdell SS, Lee S, Kollu S, Classon A, Boukhali M, Jain E, Mortensen RD, Yanagiya A, Sadreyev RI, Haas W, Vasudevan S (2016) A specialized mechanism of translation mediated by FXR1a-associated microRNP in cellular quiescence. Mol Cell 61(5):760–773

Buller B, Chopp M, Ueno Y, Zhang L, Zhang R, Morris D, Zhang Y, Zhang Z (2012) Regulation of serum response factor by miRNA-200 and miRNA-9 modulates oligodendrocyte progenitor cell differentiation. Glia 60(12):1906–1914

Busto GU, Guven-Ozkan T, Fulga TA, Van Vactor D, Davis RL (2015) microRNAs that promote or inhibit memory formation in Drosophila melanogaster. Genetics 200(2):569–580

Cao P, Wang L, Cheng Q, Sun X, Kang Q, Dai L, Zhou X, Song Z (2019) Changes in serum miRNA-let-7 level in children with attention deficit hyperactivity disorder treated by repetitive transcranial magnetic stimulation or atomoxetine: an exploratory trial. Psychiatry Res 274:189–194

Cath D, Hedderly T, Ludolph A, Stern J, Murphy T, Hartmann A, Czernecki V, Robertson M, Martino D, Munchau A, Rizzo R (2011) European clinical guidelines for Tourette Syndrome and other tic disorders. Part I: assessment. European Child & Adolescent Psychiatry 20(4), pp. 155–171

Cavaliere C, Cirillo G, Bianco MR, Adriani W, De Simone A, Leo D, Perrone-Capano C, Papa M (2012) Methylphenidate administration determines enduring changes in neuroglial network in rats. Eur Neuropsychopharmacol 22(1):53–63

Chaidez V, Hansen RL, Hertz-Picciotto I (2014) Gastrointestinal problems in children with autism, developmental delays or typical development. J Autism Dev Disord 44(5):1117–1127

Chandley M, Crawford J, Szebeni A, Szebeni K, Ordway G (2015) NTRK2 expression levels are reduced in laser captured pyramidal neurons from the anterior cingulate cortex in males with autism spectrum disorder. Mol Autism 6:28. https://doi.org/10.1186/s13229-015-0023-2

Chang S-JE, Chang-Lin S, Chang DC, Chang CP, Lin S-L, Ying S-Y (2008) Repeat-associated microRNAs trigger fragile X mental retardation-like syndrome in Zebrafish. The Open Neuropsychopharmacology Journal 1:6–18

Chang TC, Wentzel EA, Kent OA, Ramachandran K, Mullendore M, Lee KH, Feldmann G, Yamakuchi M, Ferlito M, Lowenstein CJ, Arking DE, Beer MA, Maitra A, Mendell JT (2007) Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. Mol Cell 26(5):745–752

Chao HT, Zoghbi HY, Rosenmund C (2007) MeCP2 controls excitatory synaptic strength by regulating glutamatergic synapse number. Neuron 56(1):58–65

Chaste P, Betancur C, Gérard-Blanluet M, Bargiacchi A, Kuzbari S, Drunat S, Leboyer M, Bourgeron T, Delorme R (2012) High-functioning autism spectrum disorder and fragile X syndrome: report of two affected sisters. Molecular Autism 3(1):5

Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, Bai YM (2013) Asthma and attention-deficit/hyperactivity disorder: a nationwide population-based prospective cohort study. Journal of Child Psychology Psychiatry 54(11):1208–1214

Chen X, Jiang X-M, Zhao L-J, Sun L-L, Yan M-L, Tian Y, Zhang S, Duan M-J, Zhao H-M, Li, and W.-R., (2017) MicroRNA-195 prevents dendritic degeneration and neuron death in rats following chronic brain hypoperfusion. Cell death & disease 8:e2850

Cheng Y, Chen T, Song J, Teng Z, Wang C, Wang S, Lu G, Feng T, Qi Q, Xi Q, Liu S, Hao L, Zhang Y (2020) Pituitary miRNAs target GHRHR splice variants to regulate GH synthesis by mediating different intracellular signalling pathways. RNA Biol 19:1–13

Ciaccio C, Fontana L, Milani D, Tabano S, Miozzo M, Esposito S (2017) Fragile X syndrome: a review of clinical and molecular diagnoses. Ital J Pediatr 43(1):39. https://doi.org/10.1186/s13052-017-0355-y

Cornejo J, Pedrini H, Machado-Lima A, Nunes F (2017) Down syndrome detection based on facial features using a geometric descriptor. Journal of Medical Imaging 4(04):1

Cuman C, Van Sinderen M, Gantier MP, Rainczuk K, Sorby K, Rombauts L, Osianlis T, Dimitriadis E (2015) Human blastocyst secreted microRNA regulate endometrial epithelial cell adhesion. EBioMedicine 2(10):1528–1535

Curatolo P, Ben-Ari Y, Bozzi Y, Catania MV, D'Angelo E, Mapelli L, Oberman LM, Rosenmund C, Cherubini E (2014) Synapses as therapeutic targets for autism spectrum disorders: an international symposium held in Pavia on July 4th, 2014. Front Cell Neurosci 8:309. https://doi.org/10.3389/fncel.2014.00309

D'Gama A, Pochareddy S, Li M, Jamuar S, Reiff R, Lam A, Sestan N, Walsh C (2015) Targeted DNA sequencing from autism spectrum disorder brains implicates multiple genetic mechanisms. Neuron 88(5):910–917

Dajas-Bailador F, Bonev B, Garcez P, Stanley P, Guillemot F, Papalopulu N (2012) microRNA-9 regulates axon extension and branching by targetingMap1b in mouse cortical neurons. Nat Neurosci 15:697–699

Dalsgaard S, Ostergaard SD, Leckman JF, Mortensen PB, Pedersen MG (2015) Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. Lancet 385(9983):2190–2196

Darnell J, Van Driesche S, Zhang C, Hung K, Mele A, Fraser C, Stone E, Chen C, Fak J, Chi S, Licatalosi D, Richter J, Darnell R (2011) FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism. Cell 146(2):247–261

Dastidar SG, Narayanan S, Stifani S, D'Mello SR (2012) Transducin-like enhancer of Split-1 (TLE1) combines with Forkhead box protein G1 (FoxG1) to promote neuronal survival. J Biol Chem 287(18):14749–14759

Dave V, Ngo T, Pernestig A, Tilevik D, Kant K, Nguyen T, Wolff A, Bang D (2018) MicroRNA amplification and detection technologies: opportunities and challenges for point of care diagnostics. Lab Invest 99(4):452–469

Dawson G, Jones E, Merkle K, Venema K, Lowy R, Faja S, Kamara D, Murias M, Greenson J, Winter J, Smith M, Rogers S, Webb S (2012) Early behavioral intervention is associated with normalized brain activity in young children with autism. J Am Acad Child Adolesc Psychiatry 51(11):1150–1159

de Graaf G, Buckley F, Skotko B (2016) Estimation of the number of people with Down syndrome in the United States. Genet Med 19(4):439–447

Deng H, Le W, Xie W, Jankovic J (2006) Examination of the SLITRK1 gene in Caucasian patients with Tourette syndrome. Acta Neurol Scand 114(6):400–402

Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ (2004) Processing of primary microRNAs by the microprocessor complex. Nature 432:231–235

Dharap A, Pokrzywa C, Murali S, Pandi G, Vemuganti R (2013) MicroRNA miR-324-3p induces promoter-mediated expression of RelA gene. PLoS ONE 8:e79467

Dugas JC, Cuellar TL, Scholze A, Ason B, Ibrahim A, Emery B, Zamanian JL, Foo LC, McManus MT, Barres BA (2010) Dicer1 and miR-219 Are required for normal oligodendrocyte differentiation and myelination. Neuron 65(5):597–611

Dumaret AC, Rosset DJ (1993) Trisomie 21 et abandon. Enfants nés et remis en vue d'adoption à Paris [Trisomy 21 and abandonment. Infants born and placed for adoption in Paris]. Arch Fr Pediatr, 50(10), pp. 851–7

Eipper-Mains JE, Kiraly DD, Palakodeti D, Mains RE, Eipper BA, Graveley BR (2011) microRNA-Seq reveals cocaine-regulated expression of striatal microRNAs. RNA 17:1529–1543

Elton TS, Sansom SE, Martin MM (2010) Trisomy-21 gene dosage over-expression of miRNAs results in the haploinsufficiency of specific target proteins. RNA Biol 7(5):540–547

Elton TS, Selemon H, Elton SM, Parinandi NL (2013) Regulation of the MIR155 host gene in physiological and pathological processes. Gene 532(1):1–12

Fabbrini G, Pasquini M, Aurilia C, Berardelli I, Breedveld G, Oostra BA, Bonifati V, Berardelli A (2007) A large Italian family with Gilles de la Tourette syndrome: clinical study and analysis of the SLITRK1 gene. Movement Disorders : Official Journal of the Movement Disorder Society 22(15):2229–2234

Fasmer OB, Halmoy A, Oedegaard KJ, Haavik J (2011) Adult attention deficit hyperactivity disorder is associated with migraine headaches. Eur Arch Psychiatry Clin Neurosci 261(8):595–602

Feng R, Sang Q, Zhu Y, Fu W, Liu M, Xu Y, Shi H, Xu Y, Qu R, Chai R, Shao R, Jin L, He L, Sun X, Wang L (2015) MiRNA-320 in the human follicular fluid is associated with embryo quality in vivo and affects mouse embryonic development in vitro. Sci Rep 5:8689

Ferguson BJ, Marler S, Altstein LL, Lee EB, Akers J, Sohl K, McLaughlin A, Hartnett K, Kille B, Mazurek M, Macklin EA, McDonnell E, Barstow M, Bauman ML, Margolis KG, Veenstra-VanderWeele J, Beversdorf DQ (2017) Psychophysiological associations with gastrointestinal symptomatology in autism spectrum disorder. Autism research : official journal of the International Society for Autism Research 10(2):276–288

Frye RE, Wynne R, Rose S, Slattery J, Delhey L, Tippett M, Kahler SG, Bennuri SC, Melnyk S, Sequeira JM, Quadros EV (2017) Thyroid dysfunction in children with autism spectrum disorder is associated with folate receptor α autoimmune disorder. J Neuroendocrinol 29(3). https://doi.org/10.1111/jne.12461

Garbett K, Ebert P, Mitchell A, Lintas C, Manzi B, Mirnics K, Persico A (2008) Immune transcriptome alterations in the temporal cortex of subjects with autism. Neurobiol Dis 30(3):303–311

Gebert LFR, MacRae IJ (2019) Regulation of microRNA function in animals. Nat Rev Mol Cell Biol 20:21–37

Gillberg C, Lundstrom S, Fernell E, Nilsson G, Neville B (2017) Febrile seizures and epilepsy: association with autism and other neurodevelopmental disorders in the child and adolescent twin study in Sweden. Pediatr Neurol 74:80–86

Goff LA, Davila J, Swerdel MR, Moore JC, Cohen RI, Wu H, Sun YE, Hart RP (2009) Ago2 immunoprecipitation identifies predicted microRNAs in human embryonic stem cells and neural precursors. PLoS ONE 4:e7192

Green RM, Travers AM, Howe Y, McDougle CJ (2019) Women and Autism Spectrum Disorder: Diagnosis and Implications for Treatment of Adolescents and Adults. Curr Psychiatry Rep 21(4):22. https://doi.org/10.1007/s11920-019-1006-3

Griffiths MR, Neal JW, Fontaine M, Das T, Gasque P (2009) Complement factor H, a marker of self protects against experimental autoimmune encephalomyelitis. J Immunol 182(7):4368–4377

Grigoriou M, Tucker AS, Sharpe PT, Pachnis V (1998) Expression and regulation of Lhx6 and Lhx7, a novel subfamily of LIM homeodomain encoding genes, suggests a role in mammalian head development. Development 125:2063–2074

Halevy T, Czech C, Benvenisty N (2015) Molecular mechanisms regulating the defects in fragile X syndrome neurons derived from human pluripotent stem cells. Stem Cell Reports 4(1):37–46

Hall S, Bobrow M, Marteau TM (2000) Psychological consequences for parents of false negative results on prenatal screening for Down's syndrome: retrospective interview study. BMJ (Clinical research ed) 320(7232):407–412

Hamed AM, Kauer AJ, Stevens HE (2015) Why the Diagnosis of Attention Deficit Hyperactivity Disorder Matters. Front Psychiatry 6:168. https://doi.org/10.3389/fpsyt.2015.00168

Harris TA, Yamakuchi M, Ferlito M, Mendell JT, Lowenstein CJ (2008) MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1. Proc Natl Acad Sci U S A 105(5):1516–1521

He Y, Li HB, Li X, Zhou Y, Xia XB, Song WT (2018) MiR-124 promotes the growth of retinal ganglion cells derived from muller cells. Cell Physiol Biochem 45:973–983

Hicks SD, Ignacio C, Gentile K, Middleton FA (2016) Salivary miRNA profiles identify children with autism spectrum disorder, correlate with adaptive behavior, and implicate ASD candidate genes involved in neurodevelopment. BMC Pediatr 16:52

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(2):296–308

Hirvikoski T, Mittendorfer-Rutz E, Boman M, Larsson H, Lichtenstein P, Bölte S (2016) Premature mortality in autism spectrum disorder. Br J Psychiatry 208(3):232–238

Huang F, Long Z, Chen Z, Li J, Hu Z, Qiu R, Zhuang W, Tang B, Xia K, Jiang H (2015) Investigation of gene regulatory networks associated with autism spectrum disorder based on MiRNA expression in China. PLoS ONE 10(6):e0129052

Huang X, Zhang Q, Chen X, Gu X, Wang M, Wu J (2019) A functional variant in SLC1A3 influences ADHD risk by disrupting a hsa-miR-3171 binding site: a two-stage association study. Genes Brain Behav 18(5):e12574

Huntley Z, Maltezos S, Williams C, Morinan A, Hammon A, Ball D, Marshall EJ, Keaney F, Young S, Bolton P, Glaser K, Howe-Forbes R, Kuntsi J, Xenitidis K, Murphy D, Asherson PJ (2012) Rates of undiagnosed attention deficit hyperactivity disorder in London drug and alcohol detoxification units. BMC Psychiatry 12:223. https://doi.org/10.1186/1471-244X-12-223

Huntzinger E, Izaurralde E (2011) Gene silencing by microRNAs: contributions of translational repression and mRNA decay. Nat Rev Genet 12:99–110

Inai A, Tochigi M, Kuwabara H, Nishimura F, Kato K, Eriguchi Y, Shimada T, Furukawa M, Kawamura Y, Sasaki T, Kakiuchi C, Kasai K, Kano Y (2015) Analysis of SLITRK1 in Japanese patients with Tourette syndrome using a next-generation sequencer. Psychiatr Genet 25:256–258

Ipsaro JJ, Joshua-Tor L (2015) From guide to target: molecular insights into eukaryotic RNA-interference machinery. Nat StructMol Biol 22:20–28

Iqbal Z, Vandeweyer G, van der Voet M, Waryah AM, Zahoor MY, Besseling JA, Roca LT, Vulto-van Silfhout AT, Nijhof B, Kramer JM, Van der Aa N, Ansar M, Peeters H, Helsmoortel C, Gilissen C, Vissers LE, Veltman JA, de Brouwer AP, Frank Kooy R, Riazuddin S, Schenck A, van Bokhoven H, Rooms L (2013) Homozygous and heterozygous disruptions of ANK3: at the crossroads of neurodevelopmental and psychiatric disorders. Hum Mol Genet 22(10):1960–1970

Izzo A, Manco R, de Cristofaro T, Bonfiglio F, Cicatiello R, Mollo N, De Martino M, Genesio R, Zannini M, Conti A, Nitsch L (2017) Overexpression of chromosome 21 miRNAs may affect mitochondrial function in the hearts of Down syndrome fetuses. Int J Genomics 2017:8737649

Jin P, Alisch RS, Warren ST (2004a) RNA and microRNAs in fragile X mental retardation. Nat Cell Biol 6:1048–1053

Jin P, Zarnescu D, Ceman S, Nakamoto M, Mowrey J, Jongens T, Nelson D, Moses K, Warren S (2004b) Biochemical and genetic interaction between the fragile X mental retardation protein and the microRNA pathway. Nat Neurosci 7(2):113–117

Jones K, Luo Y, Dukes-Rimsky L, Srivastava D, Koul-Tewari R, Russell T, Shapiro L, Srivastava A, Penzes P (2018) Neurodevelopmental disorder-associated ZBTB20 gene variants affect dendritic and synaptic structure. PLoS ONE 13(10):e0203760

Ka M, Chopra DA, Dravid SM, Kim WY (2016) Essential Roles for ARID1B in dendritic arborization and spine morphology of developing pyramidal neurons. J Neurosci 36:2723–2742

Kandemir H, Erdal ME, Selek S, Ay Öİ, Karababa IF, Kandemir SB, Ay ME, Yılmaz ŞG, Bayazıt H, Taşdelen B (2014) Evaluation of several micro RNA (miRNA) levels in children and adolescents with attention deficit hyperactivity disorder. Neurosci Lett 580:158–162

Karaca E, Aykut A, Ertürk B, Durmaz B, Güler A, Büke B, Yeniel AÖ, Ergenoğlu AM, Özkınay F, Özeren M, Kazandı M, Akercan F, Sağol S, Gündüz C, Çoğulu Ö (2018) MicroRNA expression profile in the prenatal amniotic fluid samples of pregnant women with Down syndrome. Balkan medical journal 35(2):163–166

Karagiannidis I, Rizzo R, Tarnok Z, Wolanczyk T, Hebebrand J, Nöthen MM, Lehmkuhl G, Farkas L, Nagy P, Barta C, Szymanska U, Panteloglou G, Miranda DM, Feng Y, Sandor P, Barr C, Paschou P (2012) Replication of association between a SLITRK1 haplotype and Tourette syndrome in a large sample of families. Mol Psychiatry 17:665–668

Karlsson R-M, Tanaka K, Saksida LM, Bussey TJ, Heilig M, Holmes A (2009) Assessment of glutamate transporter GLAST (EAAT1)-deficient mice for phenotypes relevant to the negative and executive/cognitive symptoms of schizophrenia. Neuropsychopharmacology 34(6):1578–1589

Karlsson R-M, Heilig M, Holmes A (2008) Loss of glutamate transporter GLAST (EAAT1) causes locomotor hyperactivity and exaggerated responses to psychotomimetics: rescue by haloperidol and mGlu2/3 agonist. Biol Psychiatry 64(9):810–814

Kawamata T, Tomari Y (2010) Making RISC Trends BiochemSci 35:368–376

Keck-Wherley J, Grover D, Bhattacharyya S, Xu X, Holman D, Lombardini ED, Verma R, Biswas R, Galdzicki Z (2011) Abnormal microRNA expression in Ts65Dn hippocampus and whole blood: contributions to Down syndrome phenotypes. Dev Neurosci 33(5):451–467

Kentrou V, de Veld D, Mataw K, Begeer S (2018) Delayed autism spectrum disorder recognition in children and adolescents previously diagnosed with attention-deficit/hyperactivity disorder. Autism 23(4):1065–1072

Kichukova TM, Popov NT, Ivanov IS, Vachev TI (2017) Profiling of circulating serum microRNAs in children with autism spectrum disorder using stem-loop qRT-PCR assay. Folia Med 59:43–52

Korpal M, Lee ES, Hu G, Kang Y (2008) The miR-200 family inhibits epithelial mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2. J Biol Chem 283:14910–14914

Kotey S, Ertel K, Whitcomb B (2014) Co-occurrence of autism and asthma in a nationally-representative sample of children in the United States. J Autism Dev Disord 44(12):3083–3088

Kreitzer AC (2009) Physiology and pharmacology of striatal neurons. Annual Rev Neurosci 32:127–147

Kremer EA, Gaur N, Lee MA, Engmann O, Bohacek J, Mansuy JI (2018) Interplay between TETs and microRNAs in the adult brain for memory formation. Sci Rep 8:1678

Kurt S, Fisher SE, Ehret G (2012) *Foxp2* mutations impair auditory-motor association learning. PLoS ONE 7(3):e33130

Leedham A, Thompson A, Smith R, Freeth M (2019) 'I was exhausted trying to figure it out': the experiences of females receiving an autism diagnosis in middle to late adulthood. Autism 24(1):135–146

Lehnhardt F, Falter C, Gawronski A, Pfeiffer K, Tepest R, Franklin J, Vogeley K (2015) Sex-related cognitive profile in autism spectrum disorders diagnosed late in life: implications for the female autistic phenotype. J Autism Dev Disord 46(1):139–154

Lendvai B, Kassai F, Szajli A, Nemethy Z (2013) Alpha 7 Nicotinic acetylcholine receptors and their role in cognition. Brain Res Bull 93:86–96

Letzen BS, Liu C, Thakor NV, Gearhart JD, All AH, Kerr CL (2010) MicroRNA expression profiling of oligodendrocyte differentiation from human embryonic stem cells. PLoS ONE 5:e10480

Li Q, Han Y, Dy ABC, Hagerman RJ (2017) The gut microbiota and autism spectrum disorders. Front Cell Neurosci 11:120

Li YY, Alexandrov PN, Pogue AI, Zhao Y, Bhattacharjee S, Lukiw WJ (2012) miRNA-155 upregulation and complement factor H deficits in Down's syndrome. NeuroReport 23(3):168–173

Lim J, Kim D, Lee D, Han J, Chung J, Ahn H, Lee S, Lim D, Lee Y, Park S, Ryu H (2015a) Genome-wide microRNA expression profiling in placentas of fetuses with Down syndrome. Placenta 36(3):322–328

Lim J, Lee D, Kim S, Kim H, Kim K, Han Y, Kim M, Choi J, Kim M, Ryu H, Park S (2015b) MicroRNAs as potential biomarkers for noninvasive detection of fetal trisomy 21. J Assist Reprod Genet 32(5):827–837

Lin H, Sui W, Li W, Tan Q, Chen J, Lin X, Guo H, Ou M, Xue W, Zhang R, Dai Y (2016) Integrated microRNA and protein expression analysis reveals novel microRNA regulation of targets in fetal down syndrome. Mol Med Rep 14(5):4109–4118

Lin S, Chang S, Ying S (2006) First in vivo evidence of microRNA-induced fragile X mental retardation syndrome. Mol Psychiatry 11(7):616–617

Lin SL (2015) 'microRNAs and Fragile X Syndrome', in Santulli G. (eds) microRNA: Medical Evidence. Advances in Experimental Medicine and Biology, vol 888. Springer, Cham, pp. 107–121

Liodis P, Myrto D, Marirena G, Cynthia AA, Yuchio Y, Vassilis P (2007) Lhx6 activity is required for the normal migration and specification of cortical interneuron subtypes. J Neurosci 27:3078–3089

Lippi G, Fernandes CC, Ewell LA, John D, Romoli B, Curia G, Taylor SR, Frady EP, Jensen AB, Liu JC (2016) MicroRNA-101 regulates multiple developmental programs to constrain excitation in adult neural networks. Neuron 92:1337–1351

Liu T, Wan RP, Tang LJ, Liu SJ, Li HJ, Zhao QH, Liao WP, Sun XF, Yi YH, Long YS (2015a) A microRNA profile in Fmr1 knockout mice reveals microRNA expression alterations with possible roles in fragile X syndrome. Mol Neurobiol 51(3):1053–1063

Liu Z, Wang J, Li G, Wang HW (2015b) Structure of precursor microRNA's terminal loop regulates human Dicer's dicing activity by switching DExH/D domain. Protein Cell 6(3):185–193

Lou S, Carstensen K, Petersen O, Nielsen C, Hvidman L, Lanther M, Vogel I (2018) Termination of pregnancy following a prenatal diagnosis of Down syndrome: a qualitative study of the decision-making process of pregnant couples. Acta Obstet Gynecol Scand 97(10):1228–1236

Lu HE, Yang YC, Chen SM, Su HL, Huang PC, Tsai MS, Wang TH, Tseng CP, Hwang SM (2013) Modeling neurogenesis impairment in Down syndrome with induced pluripotent stem cells from Trisomy 21 amniotic fluid cells. Exp Cell Res 319(4):498–505

Lui PY, Jin DY, Stevenson NJ (2015) MicroRNA: master controllers of intracellular signaling pathways. Cell Mol Life Sci 72:3531–3542

Maenner MJ, Shaw KA, Baio J, Washington A, Patrick M, DiRienzo M, Christensen DL, Wiggins LD, Pettygrove S, Andrews JG, Lopez M, Hudson A, Baroud T, Schwenk Y, White T, Rosenberg CR, Lee LC, Harrington RA, Huston M, Hewitt A, Esler A, Hall-Lande J, Poynter JN, Hallas-Muchow L, Constantino JN,

Fitzgerald RT, Zahorodny W, Shenouda J, Daniels JL, Warren Z, Vehorn A, Salinas A, Durkin MS, Dietz PM (2020) Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 Sites, United States, 2016. MMWR Surveill Summ., 69(SS-4), pp. 1–12

Mak H, Yung J, Weinreb R, Ng S, Cao X, Ho T, Ng T, Chu W, Yung W, Choy K, Wang C, Lee T, Leung C (2020) MicroRNA-19a-PTEN axis is involved in the developmental decline of axon regenerative capacity in retinal ganglion cells. Molecular Therapy - Nucleic Acids 21:251–263

Marler K, Suetterlin P, Dopplapudi A, Rubikaite A, Adnan J, Maiorano N, Lowe A, Thompson I, Pathania M, Bordey A, Fulga T, Van Vactor D, Hindges R, Drescher U (2014) BDNF promotes axon branching of retinal ganglion cells via miRNA-132 and p250GAP. J Neurosci 34(3):969–979

Marrale M, Albanese NN, Calì F, Romano V (2014) Assessing the impact of copy number variants on miRNA genes in autism by Monte Carlo simulation. PLoS ONE 9:e90947

McPhilemy C, Dillenburger K (2013) Parents' experiences of applied behaviour analysis (ABA)-based interventions for children diagnosed with autistic spectrum disorder. British Journal of Special Education 40(4):154–161

Miranda DM, Wigg K, Kabia EM, Feng Y, Sandor P, Barr CL (2009) Association of SLITRK1 to Gilles de la Tourette syndrome. Am J Med Genet B Neuropsychiatr Genet 150B:483–486

Mol Debes N, Hjalgrim H, Skov L (2008) Limited knowledge of Tourette syndrome causes delay in diagnosis. Neuropediatrics 39(02):101–105

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. https://doi.org/10.1186/s13229-015-0040-1

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. https://doi.org/10.1186/s13041-019-0508-6

Németh N, Kovács-Nagy R, Székely A, Sasvári-Székely M, Rónai Z (2013) Association of impulsivity and polymorphic microRNA-641 target sites in the SNAP-25 gene. PLoS ONE 8(12):e84207

Neo W, Yap K, Lee S, Looi L, Khandelia P, Neo S, Makeyev E, Su I (2014) MicroRNA miR-124 controls the choice between neuronal and astrocyte differentiation by fine-tuning Ezh2 expression. J Biol Chem 289(30):20788–20801

Novotny M, Valis M, Klimova B (2018) Tourette Syndrome: A Mini-Review. Front Neurol 9:139. https://doi.org/10.3389/fneur.2018.00139

Nuzziello N, Craig F, Simone M, Consiglio A, Licciulli F, Margari L, Grillo G, Liuni S, Liguori M (2019) Integrated analysis of microRNA and mRNA expression profiles: an attempt to disentangle the complex interaction network in attention deficit hyperactivity disorder. Brain sciences 9(10):288

O'Brien J, Hayder H, Zayed Y, Peng C (2018) Overview of microRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol 9:402

O'Neill S, Rajendran K, Halperin J (2012) More than child's play: the potential benefits of play-based interventions for young children with ADHD. Expert Rev Neurother 12(10):1165–1167

O'Roak B, Morgan T, Fishman D, Saus E, Alonso P, Gratacòs M, Estivill X, Teltsh O, Kohn Y, Kidd K, Cho J, Lifton R, State M (2010) Additional support for the association of SLITRK1 var321 and Tourette syndrome. Mol Psychiatry 15(5):447–450

Olusanya BO, de Vries PJ (2018) African Consortium of the Global Research on Developmental Disabilities Collaborators. Nurturing care for children with developmental disabilities: a moral imperative for sub-Saharan Africa. Lancet Child Adolesc Health 2:772–774

Ornoy A, Spivak A (2019) Cost effectiveness of optimal treatment of ADHD in Israel: a suggestion for national policy. Health Econ Rev 9:24. https://doi.org/10.1186/s13561-019-0240-z

Orom UA, Nielsen FC, Lund AH (2008) MicroRNA-10a binds the 5′ UTR of ribosomal protein mRNAs and enhances their translation. Mol Cell 30:460–471

Otaegi G, Pollock A, Hong J, Sun T (2011) MicroRNA miR-9 modifies motor neuron columns by a tuning regulation of FoxP1 levels in developing spinal cords. J Neurosci 31:809–818

Ozkul Y, Taheri S, Bayram K, Sener E, Mehmetbeyoglu E, Öztop D, Aybuga F, Tufan E, Bayram A, Dolu N, Zararsiz G, Kianmehr L, Beyaz F, Doganyigit Z, Cuzin F, Rassoulzadegan M (2020) A heritable profile of six miRNAs in autistic patients and mouse models. Sci Rep, 10(1)

Pagliaroli L, Vereczkei A, Padmanabhuni SS, Paschou P, Barta C (2017) T35 - Microrna regulation of candidate genes for Tourette syndrome. Eur Neuropsychopharmacol 27(3):S453–S454

Pagliaroli L, Vereczkei A, Padmanabhuni SS, Tarnok Z, Farkas L, Nagy P, Rizzo R, Wolanczyk T, Szymanska U, Kapisyzi M, Basha E, Koumoula A, Androutsos C, Tsironi V, Karagiannidis I, Paschou P, Barta C (2020) Association of genetic variation in the 3′UTR of LHX6, IMMP2L, and AADAC with Tourette syndrome. Front Neurol 11:803. https://doi.org/10.3389/fneur.2020.00803

Parisi P, Verrotti A, Paolino MC, Ferretti A, Raucci U, Moavero R, Curatolo P (2014) Headache and attention deficit and hyperactivity disorder in children: common condition with complex relation and disabling consequences. Epilepsy Behav 32:72–75

Park JH, Shin C (2014) MicroRNA-directed cleavage of targets: mechanism and experimental approaches. BMB Rep 47(8):417–423

Parkin GM, Udawela M, Gibbons A, Dean B (2018) Glutamate transporters, EAAT1 and EAAT2, are potentially important in the pathophysiology and treatment of schizophrenia and affective disorders. World J Psychiatry 8(2):51–63

Patel C, Cooper-Charles L, McMullan DJ, Walker JM, Davison V, Morton J (2011) Translocation breakpoint at 7q31 associated with tics: further evidence for IMMP2L as a candidate gene for Tourette syndrome. Eur J Hum Genet 19:634–639

Peng C, Li N, Ng YK, Zhang J, Meier F, Theis FJ, Merkenschlager M, Chen W, Wurst W, Prakash N (2012) A unilateral negative feedback loop between miR-200 microRNAs and Sox2/E2F3 controls neural progenitor cell-cycle exit and differentiation. The Journal of Neuroscience: the official journal of the Society for Neuroscience 32(38):13292–13308

Peng Y, Croce C (2016) The role of MicroRNAs in human cancer. Sig Transduct Target Ther 1:15004

Peprah E (2011) Fragile X syndrome: the FMR1 CGG repeat distribution among world populations. Ann Hum Genet 76(2):178–191

Pinto D, Delaby E, Merico D, Barbosa M, Merikangas A, Klei L, Thiruvahindrapuram B, Xu X, Ziman R, Wang Z, Vorstman JA, Thompson A, Regan R, Pilorge M, Pellecchia G, Pagnamenta AT, Oliveira B, Marshall CR, Magalhaes TR, Lowe JK, Scherer SW (2014) Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. Am J Hum Genet 94(5):677–694

Plessen KJ, Ravi B, Bradley SP (2009) Imaging evidence for anatomical disturbances and neuroplastic compensation in persons with Tourette syndrome. J Psychosomat Res 67:559–573

Popov N, Madjirova N, Minkov I, Vachev T (2012) Micro RNA HSA-486-3P gene expression profiling in the whole blood of patients with autism. Biotechnol Biotechnol Equip 26(6):3385–3388

Putkonen N, Laiho A, Ethell D, Pursiheimo J, Anttonen AK, Pitkonen J, Gentile AM, de Diego-Otero Y, Castrén ML (2020) Urine

microRNA profiling displays miR-125a dysregulation in children with fragile X syndrome. Cells 9(2):289
Radhakrishnan B, Anand AP, A. (2016) Role of miRNA-9 in brain development. J Exp Neurosci 10:101–120
Ragusa M, Majorana A, Banelli B, Barbagallo D, Statello L, Casciano I, Guglielmino MR, Duro LR, Scalia M, Magro G, Di Pietro C, Romani M, Purrello M (2010) MIR152, MIR200B, and MIR338, human positional and functional neuroblastoma candidates, are involved in neuroblast differentiation and apoptosis. J Mol Med (Berl) 88(10):1041–1053
Ramaiah M, Tan K, Plank TM, Song HW, Dumdie JN, Jones S, Shum EY, Sheridan SD, Peterson KJ, Gromoll J, Haggarty SJ, Cook-Andersen H, Wilkinson MF (2019) A microRNA cluster in the Fragile-X region expressed during spermatogenesis targets FMR1. EMBO Rep 20(2):e46566
Randall M, Egberts K, Samtani A, Scholten R, Hooft L, Livingstone N, Sterling-Levis K, Woolfenden S, Williams K (2018) Diagnostic tests for autism spectrum disorder (ASD) in preschool children. Cochrane Database of Systematic Reviews, 7(7), CD009044
Rathje M, Waxman H, Benoit M, Tammineni P, Leu C, Loebrich S, Nedivi E (2019) Genetic variants in the bipolar disorder risk locus SYNE1 that affect CPG2 expression and protein function. Mol Psychiatry. https://doi.org/10.1038/s41380-018-0314-z
Reilly C, Atkinson P, Das KB, Chin RF, Aylett SE, Burch V, Neville BG (2014) Neurobehavioral comorbidities in children with active epilepsy: a population-based study. Pediatrics 133(6):e1586–e1593
Rizzo R, Ragusa M, Barbagallo C, Sammito M, Gulisano M, Calì PV, Pappalardo C, Barchitta M, Granata M, Condorelli AG, Barbagallo D, Scalia M, Agodi A, Di Pietro C, Purrello M (2015) Circulating miRNAs profiles in Tourette syndrome: molecular data and clinical implications. Mol Brain 8:44
Ronzoni L, Tagliaferri F, Tucci A, Baccarin M, Esposito S, Milani D (2016) Interstitial 6q25 microdeletion syndrome: ARID1B is the key gene. Am J Med Genet A, 170a, pp. 1257–1261
Ryan B, Joilin G, Williams JM (2015) Plasticity-related microRNA and their potential contribution to the maintenance of long-term potentiation. Front Mol Neurosci 8:4
Sainz J, Serrano R, Borrero C, Turmo E (2012) First trimester contingent test as a screening method for Down's syndrome. A prospective study in the general population. The Journal of Maternal-Fetal & Neonatal Medicine 25(11), pp. 2221–2224
Sánchez-Mora C, Ramos-Quiroga JA, Garcia-Martínez I, Fernàndez-Castillo N, Bosch R, Richarte V, Palomar G, Nogueira M, Corrales M, Daigre C, Martínez-Luna N, Grau-Lopez L, Toma C, Cormand B, Roncero C, Casas M, Ribasés M (2013) Evaluation of single nucleotide polymorphisms in the miR-183-96-182 cluster in adulthood attention-deficit and hyperactivity disorder (ADHD) and substance use disorders (SUDs). Eur Neuropsychopharmacol 23(11):1463–1473
Santorum M, Wright D, Syngelaki A, Karagioti N, Nicolaides K (2017) Accuracy of first-trimester combined test in screening for trisomies 21, 18 and 13. Ultrasound Obstet Gynecol 49(6):714–720
Santra M, Zhang Z, Yang J, Santra S, Santra S, Chopp M, Morris D (2014) Thymosin β4 uUp-regulation of microRNA-146a promotes oligodendrocyte differentiation and suppression of the toll-like proinflammatory pathway. J Biol Chem 289(28):19508–19518
Sarachana T, Zhou R, Chen G, Manji H, Hu V (2010) Investigation of post-transcriptional gene regulatory networks associated with autism spectrum disorders by microRNA expression profiling of lymphoblastoid cell lines. Genome Medicine 2(4):23
Schendel DE, Overgaard M, Christensen J, Hjort L, Jørgensen M, Vestergaard M, Parner ET (2016) Association of psychiatric and neurologic comorbidity with mortality among persons with autism spectrum disorder in a Danish population. JAMA Pediatr 170(3):243–250
Schröder J, Ansaloni S, Schilling M, Liu T, Radke J, Jaedicke M, Schjeide B-MM, Mashychev A, Tegeler C, Radbruch H (2014) MicroRNA-138 is a potential regulator of memory performance in humans. Front Hum Neurosci 8:501
Sehovic E, Spahic L, Smajlovic-Skenderagic L, Pistoljevic N, Dzanko E, Hajdarpasic A (2020) Identification of developmental disorders including autism spectrum disorder using salivary miRNAs in children from Bosnia and Herzegovina. PLoS ONE 15(4):e0232351
Shaham L, Vendramini E, Ge Y, Goren Y, Birger Y, Tijssen MR, McNulty M, Geron I, Schwartzman O, Goldberg L, Chou ST, Pitman H, Weiss MJ, Michaeli S, Sredni B, Göttgens B, Crispino JD, Taub JW, Izraeli S (2015) MicroRNA-486-5p is an erythroid oncomiR of the myeloid leukemias of Down syndrome. Blood 125(8):1292–1301
Shenoy A, Danial M, Blelloch RH (2015) Let-7 and miR-125 cooperate to prime progenitors for astrogliogenesis. EMBO J 34:1180–1194
Shi WL, Liu ZZ, Wang HD, Wu D, Zhang H, Xiao H, Chu Y, Hou QF, Liao SX (2016) Integrated miRNA and mRNA expression profiling in fetal hippocampus with Down syndrome. J Biomed Sci 23:48
Shilon Y, Pollak Y, Benarroch F, Gross-Tsur V (2008) Factors influencing diagnosis delay in children with Tourette syndrome. Eur J Paediatr Neurol 12(5):398–400
Siegel G, Obernosterer G, Fiore R, Oehmen M, Bicker S, Christensen M, Khudayberdiev S, Leuschner PF, Busch CJ, Kane C (2009) A functional screen implicates microRNA-138-dependent regulation of the depalmitoylation enzyme APT1 in dendritic spine morphogenesis. Nat Cell Biol 11:705
Siew WH, Tan KL, Babaei MA, Cheah PS, Ling KH (2013) MicroRNAs and intellectual disability (ID) in Down syndrome, X-linked ID, and fragile X syndrome. Front Cell Neurosci 7:41
Simionescu A, Stanescu A (2020) Missed Down syndrome cases after first trimester false-negative screening—lessons to be learned. Medicina 56(4):199
Simonsen T, Sørensen S, Ekelund C, Jørgensen F (2013) Prenatal characteristics of false negative cases from first-trimester screening of Down syndrome (trisomy 21). Prenat Diagn 33(4):400–402
Sinkus ML, Graw S, Freedman R, Ross RG, Lester HA, Leonard S (2015) The human CHRNA7 and CHRFAM7A genes: a review of the genetics, regulation, and function. Neuropharmacology 96(Pt B):274–288
Smith A, Kenny PJ (2018) MicroRNAs regulate synaptic plasticity underlying drug addiction. Genes Brain Behav 17(3):e12424
Smith E, Hokstad S, Næss K (2020) Children with Down syndrome can benefit from language interventions: results from a systematic review and meta-analysis. J Commun Disord 85:105992
Smith M (2017) Hyperactive around the world? The History of ADHD in Global Perspective. Soc Hist Med, p.hkw127
Snyder M, Simmons L, Kitzman J, Coe B, Henson J, Daza R, Eichler E, Shendure J, Gammill H (2015) Copy-number variation and false positive prenatal aneuploidy screening results. N Engl J Med 372(17):1639–1645
Solomon L, Peltz L (2008) Separation, autism, and residential treatment. Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie canadienne de psychiatrie de l'enfant et de l'adolescent, 17(1), pp. 26–28
Spratt P, Ben-Shalom R, Keeshen C, Burke K, Clarkson R, Sanders S, Bender K (2019) The autism-associated gene Scn2a contributes to dendritic excitability and synaptic function in the prefrontal cortex. Neuron 103(4):673-685.e5
Srivastav S, Walitza S, Grünblatt E (2018) Emerging role of miRNA in attention deficit hyperactivity disorder: a systematic review. Atten Defic Hyperact Disord 10(1):49–63

Stamova B, Ander B, Barger N, Sharp F, Schumann C (2015) Specific regional and age-related small noncoding RNA expression patterns within superior temporal gyrus of typical human brains are less distinct in autism brains. J Child Neurol 30(14):1930–1946

Steeves TD, Fox SH (2008) Neurobiological basis of serotonin-dopamine antagonists in the treatment of Gilles de la Tourette syndrome. Prog Brain Res 172:495–513

Sullivan JC, Miller LJ, Nielsen DM, Schoen SA (2014a) The presence of migraines and its association with sensory hyperreactivity and anxiety symptomatology in children with autism spectrum disorder. Autism 18(6):743–747

Sullivan K, Stone W, Dawson G (2014b) Potential neural mechanisms underlying the effectiveness of early intervention for children with autism spectrum disorder. Res Dev Disabil 35(11):2921–2932

Tang F, Kaneda M, O'Carroll D, Hajkova P, Barton SC, Sun YA, Lee C, Tarakhovsky A, Lao K, Surani MA (2007) Maternal microRNAs are essential for mouse zygotic development. Genes Dev 21(6):644–648

Tang G, Gudsnuk K, Kuo S, Cotrina M, Rosoklija G, Sosunov A, Sonders M, Kanter E, Castagna C, Yamamoto A, Yue Z, Arancio O, Peterson B, Champagne F, Dwork A, Goldman J, Sulzer D (2014) Loss of mTOR-Dependent macroautophagy causes autistic-like synaptic pruning deficits. Neuron 83(5):1131–1143

Tepper JM, Abercrombie ED, Bolam JP (2007) Basal ganglia macrocircuits. *Progr*. Brain Res 160:3–7

Thapar A, Cooper M, Eyre O, Langley K (2013) What have we learnt about the causes of ADHD? J Child Psychol Psychiatry 54(1):3–16

Tian T, Zhang Y, Wu T, Yang L, Chen C, Li N, Li Y, Xu S, Fu Z, Cui X, Ji C, Chi X, Tong M, Chen R, Hong Q, Hu Y (2019) miRNA profiling in the hippocampus of attention-deficit/hyperactivity disorder rats. J Cell Biochem 120(3):3621–3629

Tollånes MC, Wilcox AJ, Stoltenberg C, Lie RT, Moster D (2016) Neurodevelopmental disorders or early death in siblings of children with cerebral palsy. Pediatrics 138(2):e20160269

Toma C, Torrico B, Hervas A, Salgado M, Rueda I, Valdes-Mas R, Buitelaar JK, Rommelse N, Franke B, Freitag C (2015) Common and rare variants of microRNA genes in autism spectrum disorders. The World Journal of Biological Psychiatry 16:376–386

Tossell K, Andreae LC, Cudmore C, Lang E, Muthukrishnan U, Lumsden A, Gilthorpe JD, Irving C (2011) Lrrn1 is required for formation of the midbrain-hindbrain boundary and organiser through regulation of affinity differences between midbrain and hindbrain cells in chick. Dev Biol 352:341–352

Trompeter H-I, Abbad H, Iwaniuk KM, Hafner M, Renwick N, Tuschl T, Schira J, Muller HW, Wernet P (2011) MicroRNAs MiR-17, MiR-20a, and MiR-106b act in concert to modulate E2F activity on cell cycle arrest during neuronal lineage differentiation of USSC. PLoS ONE 6:e16138

Truesdell S, Mortensen RD, Seo M, Schroeder JC, Lee J, Letonqueze O, Vasudevan S (2012) MicroRNA-mediated mRNA translation activation in quiescent cells and oocytes involves recruitment of a nuclear microRNP. Scientific Reports 2:842

Turic D, Langley K, Williams H, Norton N, Williams NM, Moskvina V, Van den Bree MB, Owen MJ, Thapar A, O'Donovan MC (2005) A family based study implicates solute carrier family 1-member 3 (SLC1A3) gene in attention-deficit/hyperactivity disorder. Biol Psychiatry 57(11):1461–1466

Vaccaro T, Sorrentino J, Salvador S, Veit T, Souza D, de Almeida R (2018) Alterations in the microRNA of the blood of autism spectrum disorder patients: effects on epigenetic regulation and potential biomarkers. Behav Sci 8(8):75

Vaishnavi V, Manikandan M, Tiwary BK, Munirajan AK (2013) Insights on the functional impact of microRNAs present in autism-associated copy number variants. PLoS ONE 8:e56781

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. Molecular Autism 5(1):40

Vasudevan S, Steitz JA (2007) AU-rich-element-mediated upregulation of translation by FXR1 and Argonaute 2. Cell 128:1105–1118

Wallace TL, Bertrand D (2013) Importance of the nicotinic acetylcholine receptor system in the prefrontal cortex. Biochem Pharmacol 85:1713–1720

Wallace TL, Porter RHP (2011) Targeting the nicotinic alpha7 acetylcholine receptor to enhance cognition in disease. Biochem Pharmacol 82:891–903

Wang JZ, Gao X, Wang ZH (2014) The physiology and pathology of microtubule-associated protein tau. Essays Biochem 56:111–123

Wang T, Bray SM, Warren ST (2012) New perspectives on the biology of fragile X syndrome. Curr Opin Genet Dev 22:256–263

Wang X, Tan L, Lu Y, Peng J, Zhu Y, Zhang Y, Sun Z (2015) MicroRNA-138 promotes tau phosphorylation by targeting retinoic acid receptor alpha. FEBS Lett 589:726–729

Weaver L, Rostain AL, Mace W, Akhtar U, Moss E, O'Reardon JP (2012) Transcranial magnetic stimulation (TMS) in the treatment of attention-deficit/hyperactivity disorder in adolescents and young adults: a pilot study. J ECT 28(2):98–103

Wiechec M, Nocun A, Knafel A, Wiercinska E, Sonek J, Rozmus-Warcholinska W, Orzechowski M, Stettner D, Plevak P (2017) Combined screening test for trisomy 21—is it as efficient as we believe? J Perinat Med, 45(2)

Wilens T, Spencer T (2010) Understanding attention-deficit/hyperactivity disorder from childhood to adulthood. Postgrad Med 122(5):97–109

Wong SS, Ritner C, Ramachandran S, Aurigui J, Pitt C, Chandra P, Ling VB, Yabut O, Bernstein HS (2012) miR-125b promotes early germ layer specification through Lin28/let-7d and preferential differentiation of mesoderm in human embryonic stem cells. PLoS ONE 7(4):e36121

Wu J, Morris J (2013) Trends in maternal age distribution and the live birth prevalence of Down's syndrome in England and Wales: 1938–2010. Eur J Hum Genet 21:943–947

Wu L, Zhao Q, Zhu X, Peng M, Jia C, Wu W, Zheng J, Wu XZ (2010) A novel function of microRNA let-7d in regulation of galectin-3 expression in attention deficit hyperactivity disorder rat brain. Brain Pathol 20(6):1042–1054

Wu LH, Cheng W, Yu M, He BM, Sun H, Chen Q, Dong YW, Shao XT, Cai QQ, Peng M, Wu XZ (2017) Nr3C1-Bhlhb2 axis dysregulation is involved in the development of attention deficit hyperactivity. Mol Neurobiol 54(2):1196–1212

Wu LH, Peng M, Yu M, Zhao QL, Li C, Jin YT, Jiang Y, Chen ZY, Deng NH, Sun H, Wu XZ (2015b) Circulating microRNA Let-7d in attention-deficit/hyperactivity disorder. Neuromolecular Med 17(2):137–146

Wu Y, Parikshak N, Belgard T, Geschwind D (2016) Genome-wide, integrative analysis implicates microRNA dysregulation in autism spectrum disorder. Nat Neurosci 19(11):1463–1476

Xu W, San Lucas A, Wang Z, Liu Y (2014) Identifying microRNA targets in different gene regions. BMC Bioinformatics 15(Suppl. 7):S4

Xu X, Yan Q, Wang Y, Dong X (2017) NTN4 is associated with breast cancer metastasis via regulation of EMT-related biomarkers. Oncol Rep 37:449–457

Xu Y, Li W, Liu X, Chen H, Tan K, Chen Y, Tu Z, Dai Y (2013a) Identification of dysregulated microRNAs in lymphocytes from children with Down syndrome. Gene 533(2):278–286

Xu Y, Li W, Liu X, Ma H, Tu Z, Dai Y (2013b) Analysis of microRNA expression profile by small RNA sequencing in Down syndrome fetuses. Int J Mol Med 32(5):1115–1125

Yang Y, Xu S, Xia L, Wang J, Wen S, Jin P, Chen D (2009) The Bantam microRNA is associated with drosophila fragile X mental retardation protein and regulates the fate of germline stem cells. PLoS Genet 5(4):e1000444

Yasmeen S, Melchior L, Bertelsen B, Skov L, Debes N, Tümer Z (2013) Sequence analysis of SLITRK1 for var321 in Danish patients with Tourette syndrome and review of the literature. Psychiatr Genet 23(3):130–133

Yasui DH, Scoles HA, Horike S, Meguro-Horike M, Dunaway KW, Schroeder DI, LaSalle JM (2011) 15q11.2-13.3 chromatin analysis reveals epigenetic regulation of CHRNA7 with deficiencies in Rett and autism brain. Hum Mol Gen 20:4311–4323

Ye C, Hu Z, Wu E, Yang X, Buford UJ, Guo Z, Saveanu RV (2016) Two SNAP-25 genetic variants in the binding site of multiple microRNAs and susceptibility of ADHD: A meta-analysis. J Psychiatr Res 81:56–62

Yi YH, Sun XS, Qin JM, Zhao QH, Liao WP, Long YS (2010) Experimental identification of microRNA targets on the 3′ untranslated region of human FMR1 gene. J Neurosci Methods 190:34–38

Young H, Oreve M, Speranza M (2018) Clinical characteristics and problems diagnosing autism spectrum disorder in girls. Arch Pediatr 25(6):399–403

Yu D, Jiao X, Cao T, Huang F (2018) Serum miRNA expression profiling reveals miR-486-3p may play a significant role in the development of autism by targeting ARID1B. NeuroReport 29(17):1431–1436

Yin S, Yu Y, Reed R (2015) Primary microRNA processing is functionally coupled to RNAP II transcription in vitro. Sci Rep 5:11992

Yu Q, Li E, Li L, Liang W (2020) Efficacy of interventions based on applied behavior analysis for autism spectrum disorder: a meta-analysis. Psychiatry Investigation 17(5):432–443

Yuan S, Schuster A, Tang C, Yu T, Ortogero N, Bao J, Zheng H, Yan W (2016) Sperm-borne miRNAs and endo-siRNAs are important for fertilization and preimplantation embryonic development. Development 143(4):635–647

Zadehbagheri F, Hosseini E, Bagheri-Hosseinabadi Z, Rekabdarkolaee HM, Sadeghi I (2019) Profiling of miRNAs in serum of children with attention-deficit hyperactivity disorder shows significant alterations. J Psychiatr Res 109:185–192

Zbucka-Kretowska M, Niemira M, Paczkowska-Abdulsalam M, Bielska A, Szalkowska A, Parfieniuk E, Ciborowski M, Wolczynski S, Kretowski A (2019) Prenatal circulating microRNA signatures of foetal Down syndrome. Sci Rep 9:2394

Zerbo O, Leong A, Barcellos L, Bernal P, Fireman B, Croen LA (2015) Immune mediated conditions in autism spectrum disorders. Brain Behav Immun 46:232–236

Zhang J, Weinrich JAP, Russ JB, Comer JD, Bommareddy PK, DiCasoli RJ, Wright CVE, Li Y, van Roessel PJ, Kaltschmidt JA (2017) A role for dystonia-associated genes in spinal GABAergic interneuron circuitry. Cell Rep 21(3):666–678

Zhang J, Zhou W, Liu Y, Liu T, Li C, Wang L (2018) Oncogenic role of microRNA- 532–5p in human colorectal cancer via targeting of the 5' UTR of RUNX3. Oncol Lett 15:7215–7220

Zhang Y, Chen M, Qiu Z, Hu K, McGee W, Chen X, Liu J, Zhu L, Wu JY (2016a) MiR-130a regulates neurite outgrowth and dendritic spine density by targeting MeCP2. Protein Cell 7:489–500

Zhang Y, Ueno Y, Liu XS, Buller B, Wang X, Chopp M, Zhang ZG (2013) The MicroRNA-17-92 cluster enhances axonal outgrowth in embryonic cortical neurons. J Neurosci 33:6885–6894

Zhang Z, Zheng F, You Y, Ma Y, Lu T, Yue W, Zhang D (2016) Growth arrest specific gene 7 is associated with schizophrenia and regulates neuronal migration and morphogenesis. Mol Brain, 9(1)

Zhao Y, Flandin P, Long JE, Cuesta MD, Westphal H, Rubenstein JL (2008) Distinct molecular pathways for development of telencephalic interneuron subtypes revealed through analysis of Lhx6 mutants. J Comp Neurol 510:79–99

Zhou F, Zhang C, Guan Y, Chen Y, Lu Q, Jie L, Gao H, Du H, Zhang H, Liu Y, Wang X (2017) Screening the expression characteristics of several miRNAs in G93A-SOD1 transgenic mouse: altered expression of miRNA-124 is associated with astrocyte differentiation by targeting Sox2 and Sox9. J Neurochem 145(1):51–67

Zimprich A, Hatala K, Riederer F, Stogmann E, Aschauer H, Stamenkovic M (2008) Sequence analysis of the complete SLITRK1 gene in Austrian patients with Tourette's disorder. Psychiatr Genet 18(6):308–309

Zong W, Liu S, Wang X, Zhang J, Zhang T, Liu Z, Wang D, Zhang A, Zhu M, Gao J (2015) Trio gene is required for mouse learning ability. Brain Res 1608:82–90