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Article

Mechanism of Autism Spectrum Disorder and The Involvement of microRNA

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Abstract—**Autism Spectrum Disorder or ASD refers to a broad range of neurodevelopmental disorder characterised by persistent deficits in social abilities, repetitive behavioural pattern and restricted interest propensity that usually developed throughout childhood. It is referred as spectrum disorder due to its wide variation of subsets that includes several conditions. Autism is referred as spectrum of disorders with wide range of subtypes due to its aetiologically diverse nature. Even each person with ASD within the same subsets may experience a distinct set of strengths and challenges in terms of learning, thoughts and problem-solving ranging from highly skilled to being severely affected. The genesis of it is incompletely comprehensible despite numerous studies have been done to elucidate the pathogenic mechanisms beneath this whole range of impaired neurodevelopmental condition. In this review, literature search was performed with primary focus was given to known mechanism of ASD and specific involvement of microRNA. Given the complexity of ASD with diversity of clinical manifestations, it can be considered as multifactorial aetiopathogenesis disorder that is associated with diverse genetic factors that may also be predisposed by environmental exposures and prenatal factors. Environmental risk factor that may modulate the genetic factors predisposing towards ASD includes advanced parental age, prenatal and perinatal factors, medications and toxic materials exposure. This is supported by epigenetic theory which in other words, the environmental risk factors may increase the tendency for the abnormal genes to be expressed at much earlier stage without changing the primary DNA sequence. Meanwhile, spontaneous de novo mutation and neurobiological factors have been proposed to be the factors contributing to ASD. Currently, there are a lot of studies pivoting on identifying the microRNA involved in dysregulation of gene expression in autistic individuals by microRNA expression profiling. These approaches were able to elucidate the specific microRNAs that involves in regulating gene expression at post-transcriptional level. Subsequent pathway analysis had enabled the understanding of potential mechanisms that lead to ASD. As ASD is a heterogenous disorder in nature, the quest to reveal its definite mechanism is challenging. Genetic, neurobiological and environmental factors were regarded as its main causes. A growing number of reports have supported the involvement of microRNA in the mechanism of ASD. Detection of microRNA in extracellular fluids such as serum, saliva and plasma are the key to identify pathways and processes involved in ASD pathophysiology. Further preclinical validation of these microRNAs target transcripts may be beneficial to support its clinical application. Validated microRNAs may potentially use as non-invasive biomarker in early detection and later on opening up opportunities for future potential therapies for ASD.**

Keywords— **Autism; Gene expression; Mechanism; MiRNA.**

I. INTRODUCTION

A person with ASD is indistinguishable from other people in terms of physical features, however, their distinctive communication, interaction, behavioural and learning capabilities set them apart from other people. It is referred as spectrum disorder due to its wide variation of subsets that include several conditions such as autistic disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), childhood disintegrative disorder and Asperger syndrome. Even each person with ASD within the same subsets may experience a distinct set of strengths and challenges in terms of learning, thoughts and problem-solving ranging from highly skilled to severely affected [1].

Based on Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria, a diagnosis of ASD requires characteristics which focus on persistent deficits in social-emotional reciprocity such as failure in generating mutually anticipated interactions, irrational nonverbal

communicative behavior in social interactions and lack of ability to show expected social behavior. The criteria also centered on restricted, repetitive patterns of behavior, interests or activities such as stereotypies, echolalia, perseverative interests and amplified or reduced sensory input especially towards sensory aspects of the environment. These symptoms or behavior must be apparent during early developmental period and must show significant impairments towards daily function and routine for it to be the indicator for ASD diagnosis [1].

Currently, the ASD prevalence in Malaysia has not been quantified through epidemiological study, however, the usage of MCHAT as screening tool for ASD among 18 to 36 months infant during check-ups in health clinics by Ministry of Health Malaysia has found that the prevalence of ASD in Malaysia was approximately 1.6 in 1000 in 2006 [2] The global prevalence of ASD was 7.7 per 1000 (1 in 132) has been reported in a 2010 systematic review of epidemiologic studies [3]. The United States of America (USA) on the other hand has recorded overall prevalence of ASD of 18.5 per 1000 8 years old (1 in 54) in 2016 [4], [5]. These estimations from the ADDM Network are based on collected data from health and special education records of 8 years old children living in 11 communities across the USA. Systematic reviews of epidemiologic studies propose that the increased awareness and amendment in case definition account for the increasing prevalence of ASD over time ever since the late 1990s [3], [6-9]. Other than that, studies also have shown that early detection of ASD, availability of specialized services and diagnostic substitution have also contributed in the surge of prevalence of ASD [6], [9-16]. In a systematic review of 54 studies concentrating the male-to-female ratio of prevalence of ASD, the overall ratio reported was 4.2 whereby a ratio closer to 3 was reported in much higher quality studies suggesting that there is possibility whereby ASD could be under diagnosed in female [17-19]. In terms of genomic association between siblings, the estimated prevalence of ASD in a sibling of a child with ASD is approximately 10%, ranging from 4% to as high as 20% based on associated medical condition or syndrome in index ASD child [20-24]. Besides that, as reported in certain studies, the prevalence of ASD in sibling of affected child may varies commensurate with the gender of the siblings whereby younger male siblings of a child with ASD tends to be more affected but the risk of recurrence is higher in affected female child's sibling [25] which is corresponding to the risk for ASD in siblings of affected children as stated in practice guideline provided by the 2013 American College of Medical Genetics and Genomics. The guideline has also lined out that the risk may increase up to more than 30% with increased incidence of ASD in the siblings (two or more affected children) [23], [26], [27].

Autism is referred as spectrum of disorders with wide range of subtypes due to its aetiologically diverse nature. The genesis of it is incompletely comprehensible despite numerous studies have been done to elucidate the pathogenic mechanisms beneath this whole range of impaired neurodevelopmental condition. However, most studies mainly concur that this intriguing condition may be influenced by both genetic and environmental factors where genetic factors were stated to be the predominant one [28-33]. In support of this notion, an epidemiological study has identified up to 25% ASD cases are of genetic aberration while the cause of majority of the cases is unknown [31]. Other than that, higher concordance rates in autism for monozygotic twins compared to dizygotic twins showed a strong genetic components underlying ASD [34-36]. Concomitantly, the environment contribution on the other hand was outlined in a few analogous twin studies that had obtained variable concordance rate according to diagnosis. It was proposed that environmental factors are implicated in ASD [34], [37].

II. RESULTS AND DISCUSSION

Recently, by using whole-exome sequencing, geneticist has found higher rate of rare, *de novo*, single nucleotide variants and mutated gene in children with ASD if compared to their unaffected siblings [38]. Chromosomal rearrangements as well as rare *de novo* copy-number variants are said to be present in approximately 10-20% of individuals with ASD while only 1-2% of the unaffected general populations [31]. These genes are classified into two groups. The first group are genes that encode for proteins which involve in brain function and the second group are genes that encode for proteins that regulate other gene expression. As we shall discuss, while multiple hypotheses have been proposed responsible for the genetic origin of ASD, some has received more empirical support and some remains unclear with less supportive evidence albeit it is likely that the pathogenesis of this disorder involves polygenic mechanisms reflecting the wide phenotypic variabilities of autism. These, gene disorders are routinely identified in over the last two decades by chromosome microarray analysis (CMA) [30], [32]. Thus far, over 200 autism susceptibility genes have been identified, contributing to ASD aetiological pathogenesis studies [32]. Given the complexity of ASD with diversity of clinical manifestations, it can be considered as multifactorial aetiopathogenesis disorder that is associated with diverse genetic factors that may also be predisposed by environmental exposures and prenatal factors [32], [38], [39].

A. Environmental Risk Factors

The twin concordance rate as mentioned earlier, suggest that both genetical and environmental are prominently associated with ASD. On the other hand, the nongenetic basis that may affect the neonate brain development during pregnancy comprises of advanced parental age, prenatal and perinatal factors, medications and toxic materials exposure. Advanced maternal and paternal age being the most highly supported nongenetic risk factor ratified with utmost evidences, appear to be independent risk factor with increment of ASD risk by 18% and 21% respectively for every 10 years ageing [40]. Advanced maternal age being a well-known risk for chromosomal abnormalities while older paternal age is currently associated with independent deleterious *de novo* gene mutation in their children [41-43]. Prenatal and perinatal factors on the other hand focus on the endogenous and exogenous risk factor during pregnancy. The endogenous risk factors revolve around what's originating from within maternal or fetal unit such as short interval pregnancies (fewer than 12 months apart) and maternal health conditions include gestational diabetes mellitus, hypertension disease in pregnancy, obesity and intrapartum bleeding [32], [39].

For short interval pregnancies, the mechanism could be due to the preterm brain is vulnerable towards certain forms of grey and white matter injury that may damage the subcortical and cortical connectivity. However, the elevated risk of ASD is likely aggravated by complication in regard to prematurity. While exogenous factors, are related to baby's medication exposure prior or after birth. For example, the prenatal usage of anti-convulsant Valproate and asthma medication specifically β2-adrenergic receptor agonists have also been linked to ASD risk [44].

A Neurodevelopmental alteration in ASD is supported by the epigenetic hypothesis which is referring to a relevant modification to the genome that influence gene expression without alteration of nucleotide sequence. The environmental risk factors may increase the tendency for the abnormal genes to be expressed at much earlier stage without changing the primary DNA sequence [45], [46]. Epigenetic modifications involve DNA methylation of histone protein that are complexed with DNA to form the chromatin. Methylation is an appropriate illustration that elucidates the effect of environmental factors on gene expression, concurrently explaining the mechanism of ASD upon involvement of neural development regulation during early life [32], [39]. According to studies, methylation modifications have stable DNA structure and are able to be transmitted and passed down across generation [47].

B. De Novo Mutation

Previously, the cause of ASD was associated to syndromes such as fragile X syndrome and Rett syndrome (3, 95) and hereditary chromosomal abnormalities (123) [31]. Subsequently, the ASD genetic studies witness a possibility of penetrant new mutation (*de novo* mutation) such that only identical twins would be able to inherit such genetic predisposition and it is definitely not passed down by familial aggregation. This phenomenon is explained in recent studies, where it revealed that there is human mutation rate of approximately 1.1 x 10-8 (0.76 x 10-8 to 2.2 x 10-8) mutation per base per generation in any single conceptus [48-50]. Having said that, about sixty new mutations acquired by every newborn and among these, approximately 0.86 novel destructive mutation is thought to lead to amino acid alteration which is corresponding to average of roughly one new coding mutation per newborn as conjured in certain studies [51-53]. *De novo* mutation or spontaneous germline mutation of critical genes has been well established to be account for multiple development of number of disorders and consequential clinical problems such as Rett syndrome and certain type of cancers respectively and is widely linked with advanced paternal age [30]. In spite of that, the failure of conventional linkage and genome-wide association studies in identifying the underlying Autism gene prove that this mechanism is still poorly explored in ASD due to its rather heterogenous nature in terms of both genetic and phenotypic albeit the accelerated identification of certain deleterious mutation in ASD candidate gene, such as those encoding neuroligins, neurexins, and SHANKs which play pivotal role in synaptic dysfunction which is a key player in ASD susceptibility [30]. Defects in these vital synaptic proteins which are enriched in pre- and post-synaptic membrane may lead to dysfunctional synaptic transmission which is a key mechanism resulting in social reciprocal deficits and restricted, repetitive behavioral patterns among ASD individuals [30], [33].

C. Neurobiological Abnormalities

According to neuroanatomical studies, macrocephaly or brain overgrowth is frequently observed in approximately 20% autistic children through three-dimensional magnetic resonance imaging (MRI) [33]. This approach is attempted to enhance our understanding regarding the mechanism of ASD in terms of neurobiological. This macrocephaly is considered abnormal as it occurs in accelerating manner corresponding to a brain structural abnormalities study in ASD children that shows an overall of 9.8% increase of cerebral volume in comparison with unaffected children [54]. These findings prove that there is early atypical brain development that consequently leads to widespread alteration in neural connectivity. Besides increment in volume, cytoarchitectural aberrations of the brain regions including the frontal lobe, parieto-temporal lobe, cerebellum and subcortical limbic structures has been observed in autistic brains during early brain development [6], [55], [56].

The hypertrophic cerebellum with hypoplasia of cerebellar vermis and hemispheres have significantly reduce the cerebellar function alluding to its putative role as sensory and motor coordination [57]. Other than that, neuroimaging studies that uses diffusion tensor imaging (DTI and functional MRI have propounded that ASD involves abrogation of white matter tracts in brain regions that in turn lead to aberrant connectivity across diverse brain regions [58-60]. This further elucidate the neuroanatomy dysfunction is related with the core symptoms of autism.

D. MicroRNA and gene expression

Gene expression is defined as phenotypic manifestation of a gene into protein or functional RNA structures, such as tRNAs & ribosomal RNAs by the process of genetic translation and genetic transcription respectively. Gene expression in complex organism such as humans, animals and plant are heavily dependent on different factors such as development, environment, diseases or drugs. Therefore, the involved regulatory mechanisms in gene expression are currently widely studied as one of the key issues in genomic medicine [57].

MicroRNAs (miRNAs) are a class of small, endogenous RNAs with an average of 22 nucleotides in length that play critical regulatory role in animals and plants gene expression [60]. They target specific mRNAs at post-transcriptional level for degradation or regulation by interacting with the 3′ UTR of target mRNAs to suppress expression. However, other studies also reported interactions of miRNAs with other region including 5′ UTR, coding sequence, and gene promoters [61]. Other than mRNAs suppression, miRNAs has been found responsible in activating gene expression and it may shuttle intracellularly and extracellularly to control the rate of gene expression as recent studies suggested [59]. These abnormal gene expressions in turn will lead to translational degradation or repression which play key roles in neurogenesis, neuronal maturation and functions.

Numerous studies have suggested microRNA abnormal expression is observed in several neurological and

neuropsychiatric disorders including Huntington's disease, schizophrenia and bipolar disorder [58], [62]. Studies by Abu-Elneel et al. [63] and Talebizadeh et al. [64] that discovered dysregulation of microRNA in the cerebellar cortex of individuals with autism and lymphoblastoid cell lines respectively have steered the focus towards neurodevelopmental disorders such as ASD.

While microRNAs are present abundantly in the brain for crucial functions, specifically neuronal development and plasticity, they also are able to transfer intracellularly and extracellularly to serve its function for gene expression. Therefore, microRNA can be found in plasma, serum, urine and saliva of humans [65-68] which make it easier to obtain samples to perform microRNA expression profiling. Furthermore, serum microRNAs in particular are known to be distinctively stable, reproducible and resistant to RNase actions suggesting its potential efficacy as noninvasive biomarkers for ASD [69]. Detail list of microRNAs expressed in different samples from different studies that were discussed in this article is presented in Table I (appendix).

In a study by Vasu *et al* [69], a total of 14 altered expression of microRNAs were observed in the ASD samples compared to those of controls in a preliminary microarray screening. They were further validated by qualitative polymerase chain reaction (qPCR) which showed significant diagnostic value for 13 differentially expressed miRNAs for ASD. These findings were compared to previous reports that have shown distinctive microRNA expression in postmortem brain [63] of individuals with ASD and in the lymphoblastoid cell lines [64]. The same pattern of upregulation and downregulation are observed in hsa-miR-181b-5p and hsa-miR-328 as in the brain while hsa-miR-181b-5p, hsa-miR-195-5p and hsa-miR-320a as in the lymphoblastoid cell lines. The former with same direction of regulation as in the brain suggest that both microRNAs in serum may become peripheral biomarkers for miRNA expression profile of autistic individuals. On the other hand, there are 5 microRNAs: miR-181b-5p, miR-320a, miR-572, miR-130a-3p and miR-19b-3p, which were observed with high values for sensitivity, specificity and the area under the curve that likely may reflect microRNA-based prediction of ASD. Altogether, these 5 microRNAs predicted several relevant neurological pathways for the target genes which have been implicated serving for ASD pathogenesis [63], [64], [70].

In a primary investigation of gene regulatory network related to microRNA expression among ASD individuals in China [70], 5 microRNAs (miR-103a, miR-34b, miR-let-7a, miR-let-7d, and miR-1228) were confirmed to be abnormally expressed in the peripheral blood of autistic individuals and the pathways of their target genes were identified from Kyoto encyclopedia of genes and genomes (KEGG) biological pathway. Corresponding with previous study, elevation of miR-34b in spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD) supports the current results elucidating both neurodevelopmental and neurodegenerative diseases association with miR-34b involvement. Furthermore, miR-34b target genes are highly associated with the CNS neuronal development, long-term memory and tight junction pathways breakdowns that may lead to diseases such as systemic inflammatory response syndrome (SIRS), inflammatory bowel disease and autism [70]. The altered expression of this microRNA and its target genes (LAMP1, AP3D1, GNS, M6PR, SCARB2, AZI2, DDX3X, CYLD, MRAS, MLLT4, CTNNA1, CASK) illustrate the roles miR-34b serves in the pathophysiology of ASD. Besides that, this study has also outlined evidences of the role of miR-103a-3p in mechanism of ASD with its candidate target genes (BTRC, FBXW7, UBE4A, HERC2, UBE2J1, CUL4A, WWP1, CDC23, UBE2Q1, NPAS2, PRKAB2, BTRC, CLOCK, KIF5A, PPP2R3C, KIF5C, ITPR1, SCN1A, PPP2R5C, PLCB1) being closely related with CNS development, neuron projection morphogenesis and various pathways that include ubiquitin-mediated proteolysis (UPS), circadian rhythm-mammal and dopaminergic synapse. They also propose that abnormal ubiquitin-mediated proteolysis in ASD is contributed by aberrant expression of miR-103a-3p [70].

A recent study of microRNA expression profiling in 2018 also in China has observed 77 microRNAs expression discrepancy in serum from autistic individuals in contrast with the control. Among these 77 microRNAs, a significant overexpression of microRNA miR-486-3p was confirmed through qRT-PCR which distinctively reduced its target gene ARID1B mRNA expression. Meanwhile, western blot analysis showed translation repression of ARID1B protein expression in SH-SY5Y cells due to overexpression of miR-486-3p by binding directly to the 3′-UTR of ARID1B mRNA [71]. As per suggested by previous studies, ARID1B played a key role in CNS maturation and neuronal differentiation in brains of mammals [72], [73] and *de novo* deletion mutations of this gene have been observed in autism [74]. Therefore, they found it relevant to hypothesize that upregulation of miR-486-3p which in turn markedly suppressed its target gene ARID1B could be a post-transcriptional regulation mechanism of ARID1B in ASD [71]. Other than that, they also observed the upregulation of few similar microRNAs (miR-608a, miR-4728-5p, and miR-4788) as observed in previous study using lymphoblastoid cell lines samples of autistic individuals. From the findings, it is proposed that microRNA dysregulation in serum may partially reflect that of systemic changes in ASD while speculating the credibility of serum samples as an alternative tissue to study microRNA expression profiling in autistic individuals.

A study on identifying microRNAs by profiling olfactory mucosal stem cells (OMSCs) as an alternative to brain tissues in postmortem and lymphoblastoid cells has also been done in the past with purposes to overcome the limitations and to highlight the great potential of OMSCs as a relevant model for transcriptomic studies in identifying genes and pathways for neurodevelopmental disorders [75]. The analysis of microRNA expression profiling from this study has identified 4 dysregulated microRNAs: miR-146a, miR-221, miR-654-5p, and miR-656 in autistic patient relative to the control. They have proposed few findings regarding targeted genes and pathways that are associated with the aberrant expressed microRNAs. From the target prediction analysis, they proposed that the mRNA regulated by these microRNAs code for protein translational in immune response and inflammation as well as for neurodevelopmental processes which both have been reported to be involved in ASD mechanism. miR-146a which was observed to be upregulated two-fold has been remarkedly noted to be first identified in immune system regulation which might have played pivotal role in neuroinflammation. Therefore, strengthening their hypothesis that the neuroinflammatory processes reported in autistic brain is

contributed by aberrant miR-146 expression [75]. Using target prediction tools this study was able to identify additional neuronal transcripts regulated by miR-146a and miR-221 which targets GRIA3, which contributes in encoding a core subunit of AMPA receptor. Besides that, MAP1B, a validated target of miR-146a is also involved in AMPA receptor endocytosis regulation [76]. With these redundant involvements of miR-146a, its aberrant expression may alter AMPA receptor biology and implicate ionotropic GluR dysfunction in ASD [77]. On another note, both miR-146a and miR-221 has direct target towards KCNK2 3′UTR. KCNK2 is a crucial determinant of cortex neuronal excitability being a family of potassium leak channel family [78]. Upregulation of these microRNAs may suppress KCNK2 protein which in turn lead to failure or delay in neuronal migration as has been observed in ASD and intellectual disabilities (ID) [75].

Lastly, another microRNA expression profiling on prefrontal cortex of autistic individuals has determined overexpression of miR-142-5p, miR-142-3p, miR-451a, miR-144-3p, and miR-21-5p in the brain samples. As evidenced by hypomethylation at the promoter region of the miR-142 gene in the brain samples, this study has also suggested the role of epigenetic as one of the key mechanisms of dysregulation in ASD. DNA hypomethylation upregulate miR-142 expression resulting in the downregulation of monoamine oxidase A (MAOA) which in turn suppress D1 dopamine receptors translation [79]. This will highly affect the neurotransmitters pathway in the brain which lead to abnormal neural synapse in autistic individuals. With further bioinformatic analysis, this study has also identified miR-451a and miR-21-5p that targeted the 3′UTR of oxytocin receptor (OXTR) gene which is one of the main molecular pathways that regulate social behavior in mammals. The inhibition of translation of OXTR by miR-21-5p and strong downregulation of OXTR by miR 451a will decrease oxytocin that is highly implicated in several social behaviors. Therefore, this explains the reduction of plasma oxytocin levels that have been reported in individuals with ASD.

III. CONCLUSION

Up to this day, there is still no definite and clear pathophysiology of autism spectrum disorder as too many factors may contribute to it. However, with recent emergence of multidirectional studies on describing the roots of ASD, the mechanism and pathways that lead to ASD are now more comprehensible. Being a neurodevelopmental disorder, the genetic and neurobiological factors are often associated with its pathogenesis. Not to mention, the importance of environmental factors that may modulate existing genetic factors predisposing to this disorder. However, the much recent findings on role of microRNA on gene expression of ASD individuals at post transcriptional level have steered the focus towards identifying the abnormal microRNA that in turn dysregulate its targeted gene which contributed into further downstream pathways. This approach on observing alterations in gene expression may enclose the pathophysiological conditions underlying ASD. Bioinformatic predictions of miRNA-gene interactions could be further validated via *in vitro* or *in vivo* model utilising either primary cells, immortalized cell lines, induced-pluripotent stem (IPS) cells or commercially available collection of animal model. Furthermore, detection of microRNA in extracellular fluids such as serum, saliva and plasma may become a potentially useful non-invasive biomarker in early detection and later on opening up opportunities for diagnostic tests. Last but not least, these findings may largely contribute to the development of future potential therapies for ASD especially by the means of restoring microRNA levels or blocking its functions as how anti-miRNAs are being used as current strategies for microRNAs inhibitory targeting.

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APPENDIX

TABLE I
LIST OF UP- AND DOWN-REGULATED MICRORNAS IN DIFFERENT SAMPLES OF ASD PATIENTS

Data source	Upregulated microRNA	Downregulated microRNA	Type of sample
Abu-Elneel et al. 2008 [63]	hsa-miR-484, hsa-miR-21, hsa-miR-212, hsa-miR-23a, hsa-miR-598, hsa-miR-95, hsa-miR-129, hsa-miR-431, hsa-miR-7, hsa-miR-15a, hsa-miR-27a, hsa-miR-15b, hsa-miR-148b, hsa-miR-132, hsa-miR-128, hsa-miR-93,	hsa-miR-106a, hsa-miR-539, hsa-miR-652, hsa-miR-550, hsa-miR-432, hsa-miR-193b, hsa-miR-181d, hsa-miR-146b, hsa-miR-140, hsa-miR-381, hsa-miR-320a, hsa-miR-106b	Cerebellum cortex
Talebizadeh et al. 2008 [64]	miR-23a, miR-23b, miR-132, miR-146a, miR-146b, miR-663	miR-92 (a1-a2), miR-320, miR-363	Lymphoblastoid cell lines
Vasu et al. 2014 [69]	miR-101-3p, miR-106b-5p, miR-130a-3p, miR-195-5p, and miR-19b-3p	miR-151a-3p, miR-181b-5p, miR-320a, miR-328, miR-433, miR-489, miR-572, and miR-663a	Serum
Mor *et al.* 2015 [79]	hsa-miR-338-5p, hsa-miR-3168, hsa-miR-451a, hsa-miR-21-5p, hsa-miR-7-5p, hsa-miR-21-3p, hsa-miR-142-5p, hsa-miR-142-3p, hsa-miR-19a-3p, hsa-miR-211-5p, hsa-miR-19b-3p, hsa-miR-219-5p, hsa-miR-144-3p, hsa-miR-137, hsa-miR-34a-5p, hsa-miR-146a-5p, hsa-let-376c-3p, hsa-let-7a-5p, hsa-miR-379-5p, hsa-miR-92b-3p, hsa-miR-3960, hsa-miR-494, hsa-miR-155-5p	Not mentioned	Brain
Huang et al. 2015 [70]	hsa-miR-1273c, hsa-miR-4299, hsa-miR-5739, hsa-miR-6086, hsa-miR-494, hsa-miR-4270, hsa-miR-642a-3p, hsa-miR-4516, hsa-miR-4436a hsa-miR-1246, hsa-miR-575 hsa-miR-4721, hsa-miR-483-5p hsa-miR-1249, hsa-miR-4443 hsa-miR-921, hsa-miR-34b-3p hsa-miR-6125, hsa-miR-4669 hsa-miR-34c-3p, hsa-miR-4728-5p, hsa-miR-564, hsa-miR-574-5p, hsa-miR-4788	hsa-miR-451a, hsa-miR-16-5p, hsa-miR-940, hsa-miR-574-3, hsa-let-7d-5p, hsa-let-7a-5p, hsa-let-7f-5p, hsa-miR-92a-3p, hsa-miR-3613-3p, hsa-miR-20a-5p, hsa-miR-1228-3p, hsa-miR-3935, hsa-miR-4700-3p, hsa-miR-15b-5p, hsa-miR-15a-5p, hsa-miR-4436b-5p, hsa-miR-4665-5p, hsa-miR-19b-3p, hsa-miR-103a-3p, hsa-miR-195-5p	Peripheral blood
Ngunyen *et al.* 2016 [75]	miRNAs, miR-146a	miR-221, miR-654-5p, and miR-656	Olfactory mucosal stem cells
Yu et al. 2018 [71]	hsa-miR-106b-5p, hsa-miR-1185-1-3p, hsa-miR-1249-5p, hsa-miR-140-3p, hsa-miR-1471, hsa-miR-188-5p, hsa-miR-19a-3p, hsa-miR-24-3p, hsa-miR-296-5p, hsa-miR-30d-5p, hsa-miR-3141, hsa-miR-3196, hsa-miR-342-3p, hsa-miR-3648, hsa-miR-3667-5p, hsa-miR-3945, hsa-miR-4429, hsa-miR-4472, hsa-miR-4532, hsa-miR-4655-3p, hsa-miR-4728-5p, hsa-miR-4745-5p, hsa-miR-4778-5p, hsa-miR-4800-5p, hsa-miR-5006-5p, hsa-miR-5195-3p, hsa-miR-5585-3p, hsa-miR-6090, hsa-miR-642b-3p, hsa-miR-6752-3p, hsa-miR-6768-5p 3.772, hsa-miR-6785-5p, hsa-miR-6802-5p, hsa-miR-6808-5p, hsa-miR-6829-5p, hsa-miR-6865-5p, hsa-miR-486-3p, hsa-miR-5100, hsa-miR-557, hsa-miR-6086, hsa-miR-197-3p	hsa-miR-6785-3p, hsa-miR-6819-3p	Serum