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# Functions of noncoding RNAs in neural development and neurological diseases

**Shan Bian**[1] and **Tao Sun**[1,*]

[1]Department of Cell and Developmental Biology, Weill Medical College of Cornell University, 1300 York Avenue, Box 60, New York, NY 10065

## Abstract

The development of the central nervous system (CNS) relies on precisely orchestrated gene expression regulation. Dysregualtion of both genetic and environmental factors can affect proper CNS development and results in neurological diseases. Recent studies have shown that similar to protein coding genes, noncoding RNA molecules have a significant impact on normal CNS development and on causes and progression of human neurological disorders. In this review, we have highlighted discoveries of functions of noncoding RNAs, in particular microRNAs and long noncoding RNAs, in neural development and neurological diseases. Emerging evidence has shown that microRNAs play an essential role in many aspects of neural development, such as proliferation of neural stem cells and progenitors, neuronal differentiation, maturation and synaptogenesis. Misregulation of microRNAs is associated with some mental disorders and neurodegeneration diseases. In addition, long noncoding RNAs are found to play a role in neural development by regulating expression of protein coding genes. Therefore, examining noncoding RNA-mediated gene regulations has revealed novel mechanisms of neural development and provided new insights into the etiology of human neurological diseases.

### Keywords

neural development; mental disorders; neurodegeneration diseases; noncoding RNAs; microRNAs (miRNAs); long noncoding RNAs (lncRNAs); neural stem cells

## Introduction

Noncoding RNAs (ncRNAs) are functional RNA molecules that do not show protein translation capability. ncRNAs consist of ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), piwi-interacting RNAs (piRNAs), microRNAs (miRNAs), and long noncoding RNAs (lncRNAs) and so on. These ncRNAs have shown to play distinct but also conserved roles in normal development and pathological processes in invertebrates and vertebrates. Studies have reported that many miRNAs as well as lncRNAs are specifically expressed in the central nervous system (CNS) [1–5]. In this review, we will focus on revealing the functions of miRNAs and lncRNAs in the CNS development and neurological disorders.

miRNAs are ~22 nucleotides (nt) highly conserved small noncoding RNAs found in almost all eukaryotic cells [6]. Like coding genes, miRNAs are mainly transcribed by the RNA Polymerase II (Pol II) into long primary miRNA transcripts (pri-miRNAs), while a subset of miRNAs has been shown to be transcribed by RNA Pol III [7]. Pri-miRNAs are cleaved by Drosha, a class 2 RNase III enzyme, to produce short hairpin stem-loop structures, known as

*Corresponding author: tas2009@med.cornell.edu, Tel. 212-746-6671; Fax: 212-746-8175.

precursor miRNAs (pre-miRNAs) [8]. Pre-miRNAs are then processed into about 20–25 nucleotides double-stranded mature miRNAs by RNase III enzyme Dicer [9]. The duplex undergoes unwinding and the strand with the weakest base pairing at its 5′ terminus, together with Dicer and many associated proteins including Argonaute proteins, form an active RNA-induced silencing complex (RISC) [10, 11]. A miRNA recognizes and binds to the non-coding portion of target messenger RNAs (mRNAs), typically in the 3'-untranslated region (3'-UTR), by imperfect complementary sequence recognition, particularly the seed sequence of the mature miRNA [11, 12]. Once bound, the RISC can negatively regulate miRNA targets by degrading the mRNA or repressing its translation [6, 13]. miRNAs are able to target numerous mRNAs and so their regulatory potential is large. Moreover, several evidences indicate regulatory feedback loop between miRNA and their targets [14].

miRNAs are classified into intergenic and intragenic miRNAs, depending on their genomic location [15–17]. Intergenic miRNAs are located at intergenic regions (between genes). These miRNAs are usually transcribed using their own promoters. Intragenic miRNAs normally lie in intronic regions of coding genes with the same orientation. They are often transcribed together with the host genes. Additionally, some miRNAs can be co-transcribed as clusters [18].

Emerging evidence has demonstrated potential functions of lncRNAs in many biological events. The majority of the human genome has previously been considered as “junk” DNA, since only about 1.5% of the human genome, which occupies over 3 billion DNA base pairs, consists of protein coding genes [19]. A recent study of a large-scale complementary DNA (cDNA) sequencing project has shown that only one fifth of transcripts of the human genome are protein-coding genes, while the rest four fifths are RNA transcripts that don’t encode proteins [20]. These RNA transcripts are normally longer than 200 nucleotides, thus they are called lncRNAs. Except no open reading frame (ORF) found within lncRNAs, they share many features with coding mRNAs such as 5’ capping, and usually contain exons and introns [21]. However, some studies point out that lncRNAs may or may not be polyadenylated, and are often transcribed from either strand within a protein-coding gene [22]. Because of the huge number and different features of genomic location and orientation of lncRNAs, the potential functions of lncRNAs haven’t yet been well characterized. However, it is unlikely that lncRNAs are “junk” transcripts. lncRNAs have been shown to modulate gene transcription via different mechanisms. For example, some *cis*-antisense lncRNAs complementary to protein coding transcripts regulate expression of the coding genes [23–27]; some lncRNAs modulate the function of transcription factors by acting as co-regulators [26, 28–32]. Moreover, some studies have shown that lncRNAs are involved in epigenetic regulation such as chromatin and histone modification and X-chromosome inactivation [33–39].

Therefore, noncoding RNAs such as miRNAs and lncRNAs participate in regulating gene expression in many ways. The underlying mechanisms of noncoding RNA functions in normal development and under disease conditions are beginning to be uncovered.

## miRNA functions in the CNS development, a Dicer ablation approach

Since Dicer is the key enzyme in miRNA processing, several studies have reported the global effects of miRNAs in the CNS development by ablating Dicer and in turn blocking biogenesis of all miRNAs in specific regions and at different developing stages in the CNS using tissue specific Cre lines.

Conditional deletion of *Dicer* from the mouse cerebral cortex using the *Emx1*-Cre line results in a significant reduction in cortical size, which is caused by reduced neural stem cell and neural progenitor pool, increased apoptosis and impaired neuronal differentiation [40–

43]. *Dicer* ablation from the mouse CNS using the *Nestin*-Cre line has confirmed the cortical defects and revealed abnormal expansion and differentiation of oligodendrocytes in the spinal cord [43]. *Dicer* deletion from postmitotic neurons in the cortex and the hippocampus using *calmoduln kinase II* (*CaMKII*) promoter-driven *Cre* transgenic mice results in smaller cortex, enhanced cortical cell death, impaired axonal path finding and dendritic branching in the hippocampal CA1 region [44]. Ablation of *Dicer* in the hippocampus at different time points using *Emx1-Cre*, *Nestin-Cre* and *Nex-Cre* lines has revealed miRNA functions in hippocampal progenitor proliferation and differentiation [45]. Conditional deletion of *Dicer* in the dopaminoceptive neurons in the basal ganglia using a *dopamine receptor-1* (*DR-1*) *Cre* line causes a reduced brain size and mass, and smaller striatal medium spiny neurons [46].

Since *Wnt1*-Cre is active in neural crest cells, apoptosis of neural crest -derived cells, and subsequently a loss of the enteric, sensory and sympathetic neurons are reported in *Wnt1-Cre Dicer* conditional knockout mice [47]. Another investigation of *Wnt1*-Cre mediated *Dicer* ablation has found malformation of the midbrain and cerebellum, reduced dopminergic neuron differentiation and malformation of the dorsal root ganglia [48]. Ablation of *Dicer* using the *Olig1-Cre* line does not affect motor neuron development, but reduces the number of astrocytes and oligodendrocyte progenitor cells (OPCs) in the spinal cord, and results in a great reduction of mature oligodendrocytes in the brain and an impaired myelination [49, 50]. Similarly, *Dicer* ablation using the *2',3'-cyclic nucleotide 3' phosphodiesterase* (*Cnp*)-Cre line, which is active in the oligodendrocyte lineage, causes a great reduction of OPCs and mature oligodendrocytes [51].

Conditional ablation of *Dicer* in specific regions in the CNS and in distinct cell lineages has demonstrated the importance of the miRNA-mediated pathway in the CNS development and in differentiation of different cell types. However, because Dicer is also involved in maintaining the heterochromatin assembly, likely by the short interfering RNA (siRNA) pathway, the CNS defects in *Dicer* knockout mice need to be carefully interpreted [52, 53]. Examining functions of individual miRNAs will help reveal precise roles of miRNAs in the CNS development.

## miRNA functions in the development of neural stem cells and progenitors

Neural stem cells (NSCs) and neural progenitors (NPs) are identified in both embryonic and adult CNS in mammals [54]. NSCs can self-renew and differentiate into multiple lineages such as neurons, astrocytes and oligodendrocytes [54, 55]. Both intrinsic factors, for instance transcription factors, epigenetic and post-transcriptional regulators, and extrinsic signals from the stem cell microenvironment play important roles in regulating self-renewal and differentiation of NSCs [55–57]. Several reports have shown that miRNAs are also essential for the development of NSCs and NPs in the CNS *in vivo* and in cultures (Fig. 1).

let-7, the first identified miRNA [58], has been shown to regulate NSC proliferation and differentiation by targeting the nuclear receptor TLX and the cell cycle regulator cyclin D1 [59]. Over-expression of *let-7b* inhibits NSC proliferation and enhances differentiation, while knockdown of *let-7b* promotes NSC proliferation [59]. It appears that the expression levels of let-7 in NSCs are controlled by a feedback regulation of Lin-28, a pluripotency factor that controls miRNA processing in NSCs [60]. Lin-28 binds to the *let-7* precursor and inhibits its processing by Dicer. On the other hand, the expression of Lin-28 is repressed by let-7 and miR-125, allowing the maturation of let-7. This feedback loop reveals an autoregulation between miRNA let-7 and miR-125, and the transcription factor Lin-28 during NSC development [60] (Fig. 2A).

miR-124 is identified as a brain-enriched miRNA and its expression is upregulated during neuronal differentiation [61]. Over-expressing *miR-124* in cultured NSCs and in embryonic cortical NPs using lenti-virus and *in utero* electroporation, respectively, promotes neurogenesis and stimulates cortical progenitor migration [62]. In the adult brain, NSCs are identified in the subventricular zone (SVZ). In cultured adult NSCs derived from the SVZ and in the SVZ *in vivo*, knocking down *miR-124* causes an increase of dividing cells and a decrease of postmitotic neurons, while over-expressing *miR-124* enhances neuronal differentiation [63]. Moreover, miR-124 regulates neuronal differentiation by suppressing Sox9 expression in adult NSCs [63]. A recent study has shown that miR-124 regulates neuronal differentiation through a mutual inhibition mechanism of Ephrin-B1 [64]. In addition, miR-124 promotes differentiation of NPs by modulating a network of nervous system-specific alternative splicing through suppressing expression of PTBP1, which encodes a global repressor of alternative pre-mRNA splicing [65]. Together, miR-124 plays a general role in promoting differentiation of embryonic and adult NSCs and NPs. It appears that miR-124 executes its function through repressing various targets (Fig. 3A).

miR-9 is another CNS-enriched miRNA. miR-9 is shown to inhibit NSC proliferation but promote differentiation through a feedback regulation of a nuclear receptor TLX [66] (Fig. 2B). In human embryonic stem cell (ESC) derived NPs, miR-9 is shown to have a positive effect on proliferation and to promote migration by directly targeting Stmn1, which increases microtubule instability [67]. The opposite effect of miR-9 on proliferation is perhaps caused by differential physical contacts of miR-9 with target genes and the different culture systems.

In the CNS of *Xenopus*, miR-9 function is required for the development of the forebrain and hindbrain through different mechanisms: progenitors lacking *miR-9* in the forebrain undergo apoptosis, but *miR-9* deficient progenitors in the hindbrain fail to exit the cell cycle [68]. In zebrafish, miR-9 promotes differentiation of NPs that give rise to neurons at the midbrain-hindbrain domain and controls the organization of the midbrain-hindbrain boundary by targeting several genes in the Fgf signaling, such as fgf8-1 and fgfr1 [69]. In the chick spinal cord, miR-9 defines a subtype of motor neurons that project axons to the axial muscles by specifically targeting FoxP1 [70]. In the mouse brain, miR-9 function is demonstrated by the generation of *miR-9-2* and *miR-9-3* double knockout mice. *miR-9* double mutants show reduced cortical layers, disordered migration of interneurons, and misrouted thalamocortical axons and corticofugal axon projections, suggesting an important role of miR-9 in NP proliferation, differentiation and migration during brain development [71]. Moreover, it appears that miR-9 regulates multiple target genes, including Foxg1, Pax6 and Gsh2, which have shown to be essential in cortical development [71]. Therefore, miR-9 plays an important role in many aspects of the CNS development, such as neuronal differentiation and migration, and cell type specification (Fig. 3B).

The above studies have demonstrated that the major role of let7, miR-124 and miR-9 is to induce differentiation of NSCs and NPs into specific cell types. miRNAs that promote proliferation of NSCs and NPs have also been identified (Fig. 1). miR-134 plays a role in enhancing proliferation of cortical NPs by targeting doublecortin (Dcx) and/or Chordin-like 1 (Chrdl-1) [72] (Fig. 3C). miR-25 is shown to be a major player in the miR-106-25 cluster in neural development. Overexpression of *miR-25* but not *miR-106b* and *miR-93* promotes adult NP proliferation [73]. Interestingly, the expression of the miR-106-25 cluster is regulated by FoxO3, a transcription factor maintaining the NSC population [74].

miRNAs regulate target gene expression at a post-transcriptional level. Recent work has shown that miRNAs themselves are also controlled by epigenetic regulators in the NSC development. miR-137, whose expression is co-regulated by DNA methyl-CpG-binding

protein (MeCP2) and transcriptional factor Sox2, is shown to modulate adult NSC proliferation and cell fate determination by targeting Ezh2, a histone methyltransferase and Polycomb group protein [75] (Fig. 3D). Ectopic expression of *miR-137* in adult NSCs enhances the proliferation, while knockdown of *miR-137* promotes the differentiation of adult NSCs [75]. miR-184 expression is suppressed by methyl-CpG binding protein 1 (MBD1), and miR-184 promotes adult NSC proliferation by repressing the expression of Numb-like (Numbl) [76].

Taken together, self-renewal, proliferation and differentiation of NSCs and NPs are controlled by complex gene regulation networks that consist of both protein coding genes and noncoding miRNAs. During proliferation and differentiation of NSCs and NPs, one miRNA can have multiple target genes (Figs. 1 and 3). The availability of physical contacts and the binding affinity of a miRNA and its targets perhaps determine interactions of the miRNA with the specific targets. The interactions of miRNAs and their target genes eventually produce proper protein output of key factors that control precise specification of distinct cell types in different regions of the CNS, and ensure accurate CNS functions.

## miRNA regulation of neuronal maturation and synapse formation

Neuronal maturation, neurite outgrowth and synaptogenesis allow the assembly of a functional CNS to control complex behaviors. miRNAs have been shown to play a critical role in these progresses.

miR-124 functions not only in neuronal differentiation but also in neurite outgrowth and synaptogenesis (Fig. 3A). In primary cortical neurons, ectopic miR-124 expression enhances neurite outgrowth [77]. Cdc42 and Rac1 belong to the Rho family and have been shown to regulate actin filaments and microtubules [78]. miR-124 regulates neurite outgrowth by inhibiting Cdc42 expression and altering the localization of Rac1 in mouse P19 embryonic carcinoma cells [77]. In the nervous system of *Aplysia californica*, miR-124 is highly expressed in the sensory-motor synapse [79]. Over-expression of miR-124 results in a remarkable reduction of long-term facilitation (LTF) of the synapses, while inhibition of miR-124 shows the opposite phenotype. The regulation of miR-124 on long-term plasticity is through targeting cAMP response element-binding (CREB), a cellular transcriptional factor [79]. Furthermore, miR-124a is shown to be required for hippocampal axogenesis through suppression of LIM homeobox 2 (Lhx2) [80].

miR-137 has been reported to promote NSC proliferation and inhibit neuronal differentiation [75]. A recent study has shown that miR-137 negatively regulates neuronal maturation (Fig. 3D). Ectopic expression of *miR-137* inhibits neuronal maturation, dendritic morphogenesis and spine development both in cultured hippocampal neurons and in mouse brains. Conversely, lack of *miR-137* promotes neuronal maturation [81]. miR-137 regulates neuronal maturation by targeting Mind bomb 1 (Mib1), an ubiquitin ligase, since ectopic expression of Mib1 enhances dendritic elongation and rescues the defects in neuronal maturation caused by miR-137 [81].

miR-133b is specifically expressed in dopaminergic neurons (DNs) in midbrains and is deficient in the midbrain of Parkinson's disease patients [82]. miR-133b is shown to inhibit the maturation and function of DNs by targeting paired-like homeodomain transcription factor Pitx3. In *Pitx3* deficient mouse model, miR-133b expression is significantly reduced; suggesting that miR-133b expression is under the regulation of Pitx3 [82, 83]. These reports indicate a negative feedback regulation between Pitx3 and miR133b in balancing the development of DNs [82] (Fig. 2C).

Several studies have shown the importance of miRNAs in synaptogenesis. The *miR-132*/*miR-212* cluster is reported to mediate the dendritic growth and spine formation [84]. Conditional deletion of the *miR-132*/*miR-212* cluster results in a great reduction in the dendrite length and spine density. Additionally, *miR-132* over-expression transgenic mice show decreased dendritic spine density and impaired novel object recognition memory [85]. As a predicted target of miR-132, MeCP2 is down-regulated in *miR-132* transgenic mice [85]. Furthermore, miR-132 is identified as a fragile X mental retardation protein (FMRP)-associated miRNA, and affects neuronal morphology and modifies synaptic strength in a FMRP-dependent manner [86].

miR-134 is a brain-specific miRNA and is localized to the synapto-dendritic compartment of rat hippocampal neurons. miR-134 is found to negatively regulate the size of dendritic spines, which are the postsynaptic sites of excitatory synaptic transmission, by targeting and repressing Limk1 [87] (Fig. 3C). Based on a large-scale screening in the synapto-dendritic compartment in primary hippocampal neurons, miR-138 is found to be highly expressed in synaptosomes, a biochemical fraction that is important for synaptic protein synthesis and storage [88]. In a single cell fluorescent sensor assay, inhibition of miR-138 leads to a significant increase of spinal volume without changing the synaptic puncta number [89]. These functional regulations of miR-138 on synaptic development and synaptic transmission are related to its target acyl-protein thioesterase 1 (APT1), whose activity is required for spine enlargement [89].

Functions of miRNAs in neurite outgrowth and synaptogenesis suggest that miRNAs may directly regulate local translation of target proteins that are essential for these biological events [90]. The transportation of miRNAs to a subcellular location in neurons, and the turnover of miRNAs on the binding sites of target genes during neuronal maturation and synaptogenesis still remain interesting research topics.

## miRNAs in neurological disorders

Misregulation of miRNAs is associated with the pathogenesis of different human neurological diseases such as neurodevelopmental disorders, neurodegeneration diseases and affective mental disorders (Table 1).

miRNAs have been proven to play a critical role in the etiology of human neuropsychiatric disorders. Variations of the *SLITRK1* gene in the 3’-UTR binding site for human miR-189 is detected in DNA samples of patients with Tourette's syndrome (TS), a developmental neuropsychiatric disorder [91]. The Fragile X syndrome, a common human mental retardation, is caused by a loss of RNA-binding protein FMRP. FMRP is found to be associated with the miRNA processing pathway [92]. miR-19b, miR-302b* and miR-323-3p have been reported to repress the expression of FMRP, suggesting a role of miRNAs in the pathogenesis of Fragile X syndrome [93]. A double-stranded RNA-binding protein DGCR8 is involved in miRNA processing, and functions as an essential Drosha co-factor [94]. *DGCR8* is commonly deleted in patients with DiGeorge syndrome, characterized by a variety of defects, including schizophrenia and microcephaly [95]. Abnormal miRNA biogenesis may contribute to the etiology of DiGeorge syndrome [96].

Schizophrenia is a syndrome of reality distortion along with alterations in thought, emotional processing, volition and cognition. Several miRNAs are found more highly expressed in the prefrontal cortex of schizophrenic patients than normal subjects [97]. A report has shown that miR-181b is upregulated, while its target genes calcium sensor gene visinin-like 1 (VSNL1) and ionotropic AMPA glutamate receptor subunit (GRIA2), which are associated with schizophrenia, are downregulated in the superior temporal gyrus of schizophrenic patient brain samples [98]. The *N*-methyl-D-aspartate (NMDA) glutamate

receptor signaling regulates neurotransmission and synaptic plasticity, and executes many brain functions. Dysfunction of the NMDA receptor signaling pathway results in cognitive disorders, which show symptoms of schizophrenia and autism. miR-219 is shown to specifically target calcium/calmodulin-dependent protein kinase II γ subunit (CaMKIIγ), a component of the NMDA receptor signaling [99]. Knockdown of *miR-219* in the mouse brain alters the behavioral responses associated with disrupted NMDA receptor signaling [99]. Furthermore, autism spectrum disorder (ASD) is a neural developmental disorder featured in an impaired communication ability and social interaction, as well as repetitive or restricted behavior. miRNA expression profiles of ASD patients have been performed to explore a potential role of miRNAs in the pathogenesis of Autism [100–102].

Alzheimer's disease (AD) is a neurodegenerative disease that is the most common form of dementia. It includes changes in memory and functions of the hippocampus. Comparisons in the hippocampus of fetal, adult and AD brains have identified miRNAs that are highly expressed in the fetal hippocampus but differentially regulated in AD patients, for instance an upregulation of miR-9 and miR-128 in AD patients [103]. Another expression profiling analysis of miRNAs in short post-mortem interval (PMI) human brains has revealed an upregulation of miR-9, miR-125b and miR-146a in the temporal lobe in the AD patient brains [104].

Several miRNAs are found downregulated in AD brain tissues, such as miR-15a and the miR-107 and miR-29a/b-1 cluster [105–107]. The expression of miR-107 is greatly decreased even in early stages of the AD patients [105]. β-site amyloid precursor protein-cleaving enzyme (BACE1), which contributes to the accumulation of amyloid-β peptides (Aβ), the key molecule in the pathogenesis of AD, has been identified as the target of miR-107 [105]. During the AD progression, the expression of BACE1 is upregulated but miR-107 expression is decreased [105]. Moreover, the miR-29a/b-1 cluster is significantly decreased in AD patients accompanied by an abnormally high expression of BACE1. In a cell culture system, the miR-29a/b-1 cluster is shown to negatively regulate the expression of BACE1 and the accumulation of Aβ peptide [106]. In addition, miR-298 and miR-328 are reported to repress the expression of BACE1 [108]. Furthermore, the expression of amyloid precursor protein (APP) and accumulation of Aβ is negatively regulated by miR-101 in cultured hippocampal neurons, suggesting a potential role of miR-101 in AD progression [109]. miR-146a, which is regulated by the NF-κB signaling, is upregulated in AD brains, and miR-146a targets complement factor H (CFH), a repressor of the inflammatory response of the brain [110].

Huntington's disease (HD) is a genetic disorder with programmed degeneration of brain neurons. Patients have behavioral and motor symptoms and cognitive decline leading to dementia. The expression profile of miRNAs in two transgenic mouse models of HD has shown that miRNAs such as miR-22, miR-29c and miR-128 are downregulated [111]. In human samples, the expression of miR-9/9$^{*}$, miR-29b and miR-124a are downregulated, while miR-132 is upregulated with increasing HD grade compared to controls [112]. Previous studies indicate that aberrant cellular distribution of RE1-silencing transcription factor (REST) is one of the molecular mechanisms underlying HD etiology. The REST repressor complex, including mSin3, REST co-repressor 1 (CoREST) and MeCP2, regulate expression levels of miR-9/9*, miR-124a and miR-132 [113]. Interestingly, miR-9 and miR-9$^{*}$ have targeting effects on REST and CoREST, respectively, suggesting REST silencing complex and miR-9/9$^{*}$ form a negative feedback loop during HD development [114] (Fig. 2D). Furthermore, miR-34b is elevated in plasma from HD patients even before the symptom onsets, suggesting miR-34b a potential biomarker for HD diagnosis [115].

Parkinson's disease (PD) results from a loss of dopaminergic neurons in the substantia nigra. It involves abnormalities in movement variably accompanied by sensory, mood and cognitive changes. Alpha-synuclein accumulation is related to the pathogenesis of PD. A study has shown that miR-7 and miR-153 negatively regulate α-synuclein in primary neurons [116]. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxin PD mouse model, miR-7 is downregulated, suggesting that miR-7 may protect cells from oxidative stress [117]. Moreover, a recent study has demonstrated that a single nucleotide polymorphism (SNP) in the 3'-UTR of fibroblast growth factor 20 (FGF20) destroys a target site for miR-433. Thus, miR-433 is linked to an increased risk of AD by indirectly causing overexpression of α-synuclein [118].

miRNAs are also associated with prion-induced neurodegeneration [119, 120]. In the mouse brains infected with mouse-adapted scrapie, miRNAs such as miR-342-3p, miR-320 and let-7b are greatly upregulated, while miR-337-3p and miR-338-3p are downregulated during the disease process [119]. Among potential targets of these miRNAs predicted by the computational algorithms, 119 genes are also de-regulated during the prion-induced neurodegeneration [119].

Down's syndrome (DS), also called trisomy 21, is a genetic disease caused by an extra copy of entire or part of the human chromosome 21. DS patients usually have physical growth abnormality, heart defects, leukemia, low-cognitive ability and Alzheimer's disease [121]. Since DS is caused by an extra copy of the chromosome 21, which leads to over-expression of many genes located on it, it is possible that miRNAs located on the chromosome 21 play a role during the DS pathological process by negatively regulating expression of target genes and subsequently contribute to the symptoms of DS. Indeed miRNAs that are located on the chromosome 21, including let-7c, miR-99a, miR-125b-2, miR-155 and miR-802, are found upregulated in the fetal hippocampus and heart samples from DS patients, while their target genes are found decreased [122, 123]. Gain and loss of function of *miR-155* and *miR-802* have shown that they target MeCP2, which is downregulated in the DS brain [124]. In addition, an upregulation of miR-125b and downregulation of its target CDKN2A are found in advanced AD and DS brains [125].

Cerebral infarction (Stroke) is related to a disturbance in the blood supply to the brain. miRNA expression profiling in young stroke patients has shown 138 upregulated miRNAs and 19 downregulated miRNAs [126]. miR-21 is found to be upregulated in neurons in the ischemic boundary zone after stroke in rat brains. miR-21 protects ischemic neurons, after oxygen and glucose deprivation, from cell death by targeting tumor necrosis factor α family member FAS ligand gene (FASLG), a cell death inducer [127]. Recent study has shown that miR-124a is downregulated in neural progenitor cells of the SVZ after stroke [128]. By targeting Notch signaling ligand Jagged-1 (JAG1), miR-124a impairs precursor proliferation and promotes neuronal differentiation after stroke [128].

In the temporal lobe epilepsy (TLE) rat model as well as in human TLE, the expression of miR-146a is found upregulated and is expressed in reactive astrocytes in the hippocampus, mainly in the regions where neuronal cell loss and reactive gliosis occur [129]. This observation implies the possible involvement of miR-146a in the modulation of the astroglial inflammatory response during the TLE processes and provides a potential target for clinical treatment of TLE.

Depression is an affective mental disorder with a low mood, a loss of interests in activities, and sometimes, a cognitive impairment. A study has shown an association of the T allele of the rs76481776 polymorphism of pre-miR-182 with the late insomnia in major depression (MD) patients [130]. Overexpression of *miR-182* causes reduction of miR-182 targeting

genes Adenylate cyclase type 6 (ADCY6), Circadian Locomotor Output Cycles Kaput (CLOCK) and Delta sleep-inducing peptide (DSIP), which are involved in molecular clock regulation, suggesting that miR-182 might contribute to the dysregulation of circadian rhythms in the MD patients with insomnia [130]. The polymorphism in the ss178077483 of pre-miR-30e is also found to be associated with a higher risk of the MD disorder [131].

A miRNA expression profiling analysis in the prefrontal cortex of patients with bipolar disorder (BD), also known as manic-depressive disorder, has identified differentially expressed miRNAs [132]. miR-134 is suggested as a biomarker of mania episodes in BD, based on an analysis of expression levels of miRNAs in the circulating blood before and after the treatment of bipolar mania patients [133]. In addition, chronic treatment with selective serotonin reuptake inhibitor (SSRI) fluoxetine in mice results in an upregulation of miR-16 and downregulation of SERT, which is a target of miR-16, suggesting that miRNAs participate in the therapeutic action of SSRI [134]. Several miRNAs are found to be dysregulated after the chronic treatment with mood stabilizers Lithium and Valproate [135]. Among these miRNAs, miR-34a expression is reduced after the treatment, while its target metabotropic glutamate receptor 7 (GRM7) is upregulated [135]. These studies suggest a role of miRNAs in the clinical therapy of antidepression medications.

In summary, these studies indicate that similar to coding genes, misregulation of miRNAs also contributes to the pathogenesis of neurodegeneration diseases and mental disorders (Table 1). miRNA expression profiles using patient samples have shown that expression levels of many miRNAs are altered. Thus, it is a daunting task to figure out major miRNAs that are directly associated with the causes and progression of neurological diseases. Moreover, it is likely that neurological disorders are the result of altered networks of gene expression regulations of coding genes and noncoding RNAs.

## lncRNAs in the CNS development

Based on *in situ* hybridization data from the Allen Brain Atlas (http://www.brain-map.org/), 849 lncRNAs from diverse locations in the genome have shown distinct expression patterns in different regions, cell types and subcellular localization in adult mouse brains [4]. Similar to miRNAs, lncRNAs are also classified into intergenic and intragenic populations. Even though functions of lncRNAs in the CNS development are largely unclear, studies of intragenic lncRNAs that are associated with protein-coding genes in the genome are emerging. Bioinformatic investigation of genomic locations and comparisons of expression patterns of lncRNAs and their adjacent protein coding transcripts have implied a potential *cis*-regulation mechanism of lncRNAs in modulating the transcription of coding genes in the developing and adult mouse brains [136].

*Nkx2.2 antisense* (*Nkx2.2as*) is an antisense lncRNA to *Nkx2.2* gene, which is expressed in the developing mammalian forebrain and is required for oligodendrocyte development [137] (Fig. 4A). Ectopic expression of *Nkx2.2as* in NSCs in cultures induces oligodendrocyte differentiation through an upregulation of the *Nkx2.2* mRNA level, suggesting that *Nkx2.2as* regulates NSC differentiation, at least partially, by promoting *Nkx2.2* expression [25].

*Embryonic ventral forebrain-1 (Evf1)* is a 2.7 kb lncRNA transcribed upstream of the mouse *Dlx-6* gene [138]. As an alternatively spliced form of *Evf1*, *Evf2* is transcribed from the intergenic region between the *Dlx-5* and *Dlx-6* loci, and is overlapped with the conserved *Dlx-5/6* intergenic enhancer [26, 139] (Fig. 4B). Dlx-6 is a homeobox containing transcription factor and plays an important role in forebrain neurogenesis [140]. Induced by the Sonic hedgehog (Shh) signaling pathway, *Evf2* has been proven to function as a transcriptional co-activator of Dlx-2 and activates the *Dlx5/6* enhancer during forebrain

development [26]. Deletion of *Evf2* results in a reduction of GABAergic interneurons and impaired synaptic inhibition in the developing hippocampus [141].

Sox2 is a transcription factor and plays a key role in the maintenance of the undifferentiating state of embryonic and adult NSCs [142]. *Sox2 overlapping transcript Sox2OT* is a lncRNA containing *Sox2* gene and shares the same transcriptional orientation with *Sox2* (Fig. 4C). Similar to *Sox2*, *Sox2OT* is stably expressed in mouse embryonic stem cells and down-regulated during differentiation. *Sox2OT* is expressed in the neurogenic region of the adult mouse brain, and is dynamically regulated during vertebrate CNS development, implying its role in regulating NSC self-renewal and neurogenesis [4, 143].

*Retinal noncoding RNA 2* (*RNCR2*), an intergenic lncRNA also known as *Gomafu* and *Miat*, is an abundant polyadenylated RNA in the developing retina [144]. *RNCR2* is highly expressed in both mitotic and postmitotic retinal progenitors. Knockdown of *RNCR2* leads to an increase of amacrine cells and Müller glial cells in postnatal retina. Mis-localization of *RNCR2* from nuclear to cytoplasm photocopies the effects caused by *RNCR2* knockdown, suggesting that *RNCR2* is required for retinal precursor cell specification [145].

## lncRNAs in neurological disorders

Scattered studies have shown that lncRNAs are also involved in neurobiological disorders. *Sox2OT* has been identified as one of a potential biomarkers of AD for both early and late stages [146]. *BC200 RNA* is a 200 nt noncoding RNA that is expressed in the nervous system [147]. In human nervous system, *BC200 RNA* is expressed by a subpopulation of neurons analogous to *BC1* RNA, a 152 nt noncoding RNA localized in the dendrite-rich neuropil areas [147]. *BC200 RNA* and *BC1* are likely regulators of local protein expression in the postsynaptic dendritic microdomains [148]. A study has shown that *BC200 RNA* is upregulated in the frontal cortex of the AD brains compared to the age-matched controls. The expression level of *BC200 RNA* is increased in parallel with the AD progression [149]. However, in another independent work in a rigorously controlled study of short post-mortem AD brains, *BC200 RNA* is found to be significantly decreased [150].

*Human accelerated region 1* (*HAR1*) belongs to HAR family, which contains a set of 49 segments of the human genome that are conserved through vertebrate evolution but strikingly different in humans [151]. *HAR1* is located on the long arm of the chromosome 20 and overlaps with lncRNA *HAR1F*, which is expressed in Cajal-Retzius cells in the human fetal cortex [151]. The expression of *HAR1* is inhibited by transcription repressor REST in brain samples of HD patients, suggesting a potential role of HAR1 in neurodegeneration disorders [152].

## Perspectives

It has been well accepted that noncoding RNAs, in particular miRNAs, play a critical role in neural development and functions. Identification of region and cell type specific miRNAs in the CNS will help determine actions of individual miRNAs in the CNS development. Moreover, investigation of how specific expression of miRNAs is regulated during development by identifying miRNA promoters and binding transcription factors will reveal the transcriptional logic of miRNA expression and functions. Because one miRNA has multiple targets, it remains a challenge to dissect the networks of miRNA-targets in the CNS development.

The association of miRNAs and human neurological diseases still requires comprehensive investigation. Because of the fast development of miRNA synthesis and delivery techniques, it is promising to use miRNAs as diagnostic biomarkers and as new therapeutic tools for

neurological disorders. Moreover, to better understand the etiology of miRNA-mediated human neurological diseases, one needs to develop proper genetic tools to generate animal models with altered miRNA expressions.

There is no doubt that examining lncRNAs functions in neural development and under disease conditions will remain an exciting research focus. Genome wide RNA sequencing and bioinformatic analysis will help identify region and cell type specific lncRNAs in the CNS and their association with protein coding genes in the genome. Examining how lncRNAs manipulate the gene expression will continue to reveal novel gene regulation mechanisms in neural development.

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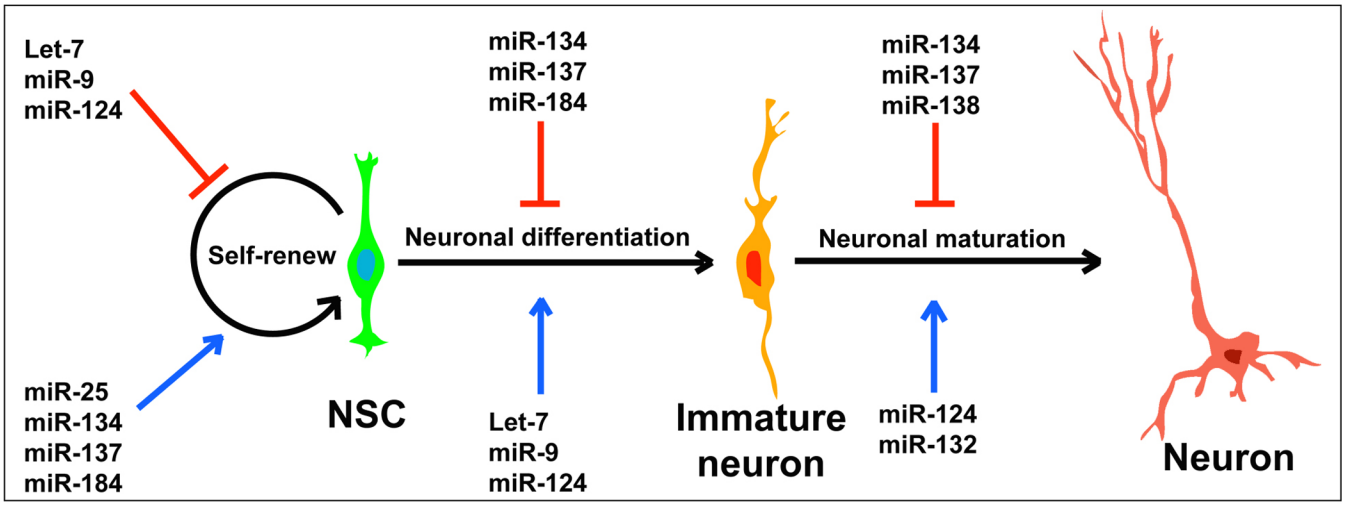


**Figure 1.**
A list of representative miRNAs that function on neural stem cell (NSC) self-renewal, neuronal differentiation and neuronal maturation.

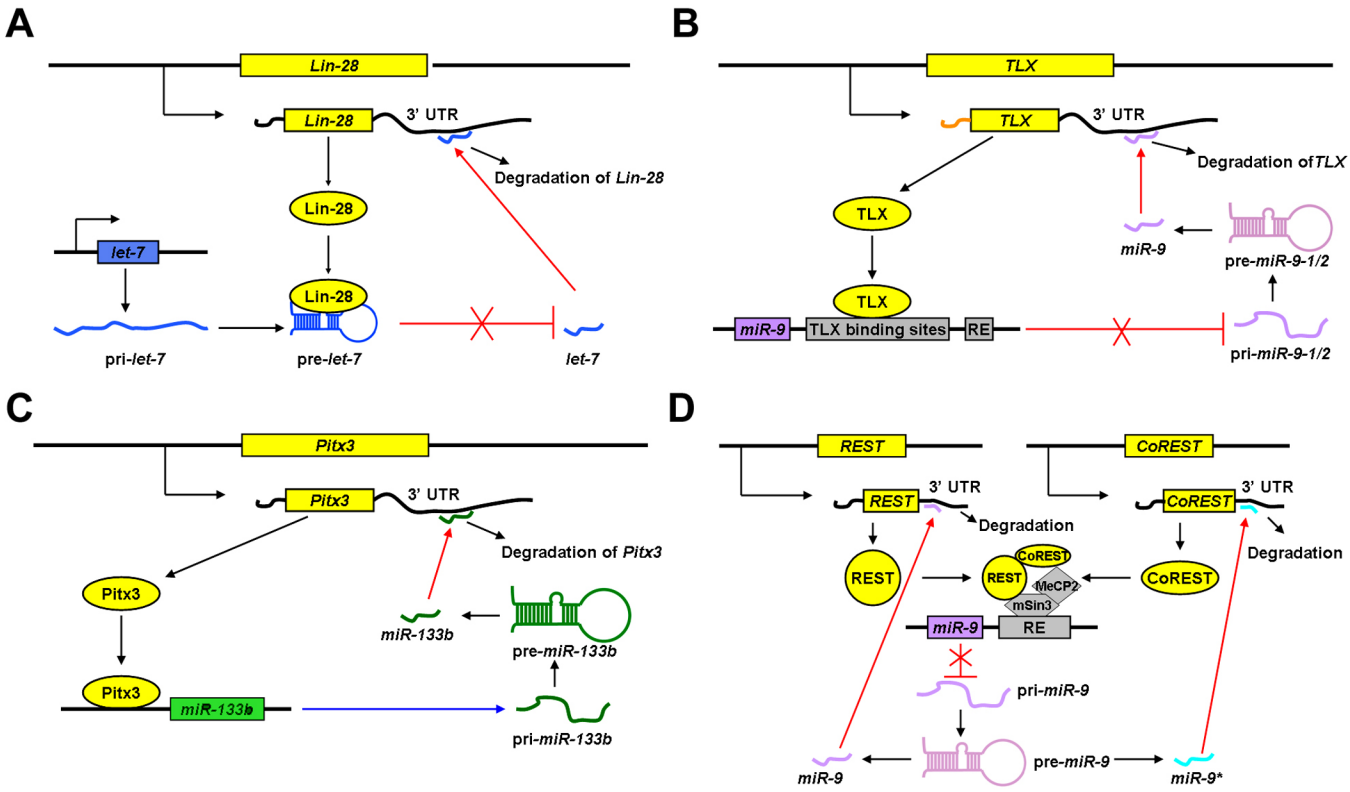


**Figure 2.**

A feedback regulation of miRNAs and their target genes. Protein coding genes inhibit (**A, B, D**) or promote (**C**) biogenesis of miRNAs, while miRNAs post-transcriptionally silence output of these proteins.

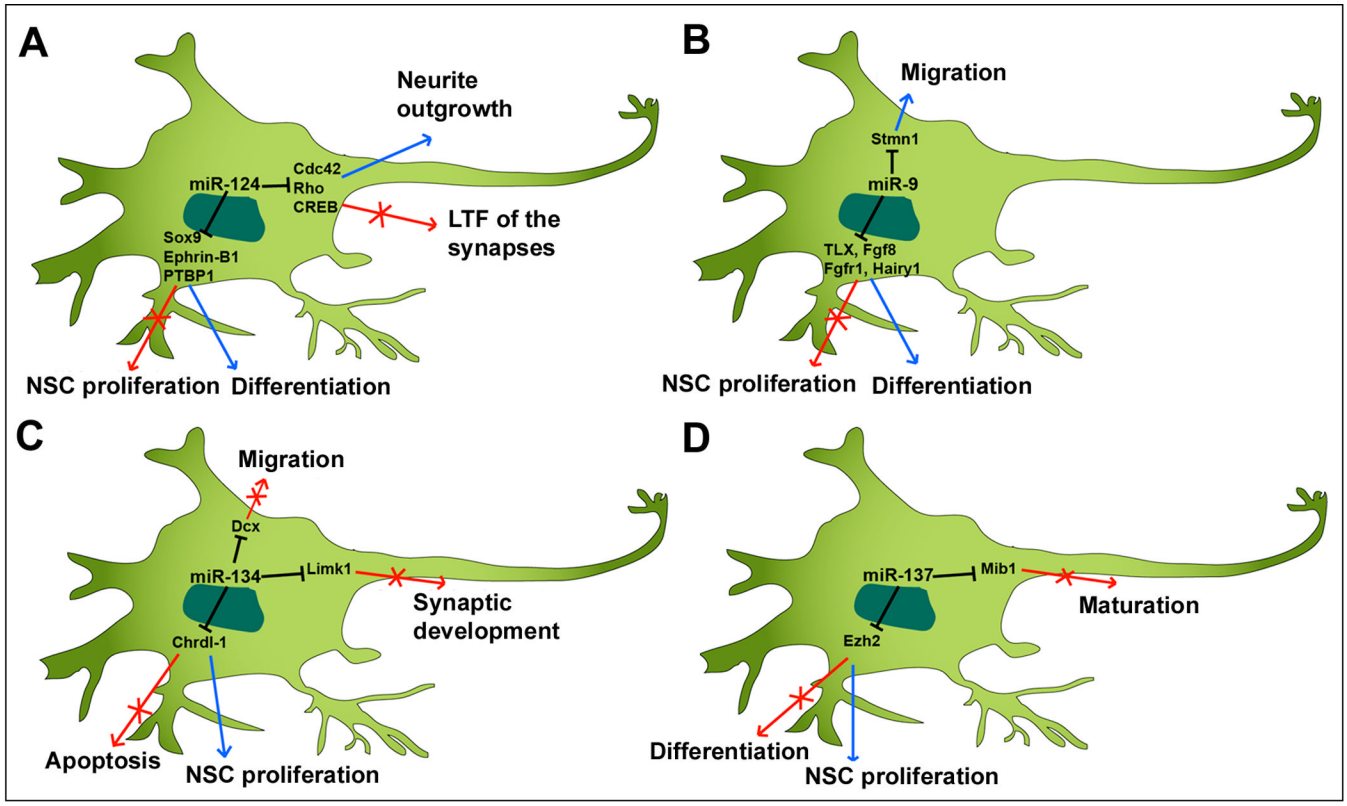


**Figure 3.**

miRNAs, such as miR-124 (**A**), miR-9 (**B**), miR-134 (**C**) and miR-137 (**D**), control proliferation and apoptosis of neural stem cells and progenitors, neuronal differentiation, migration, and maturation and synaptogenesis by targeting various genes.

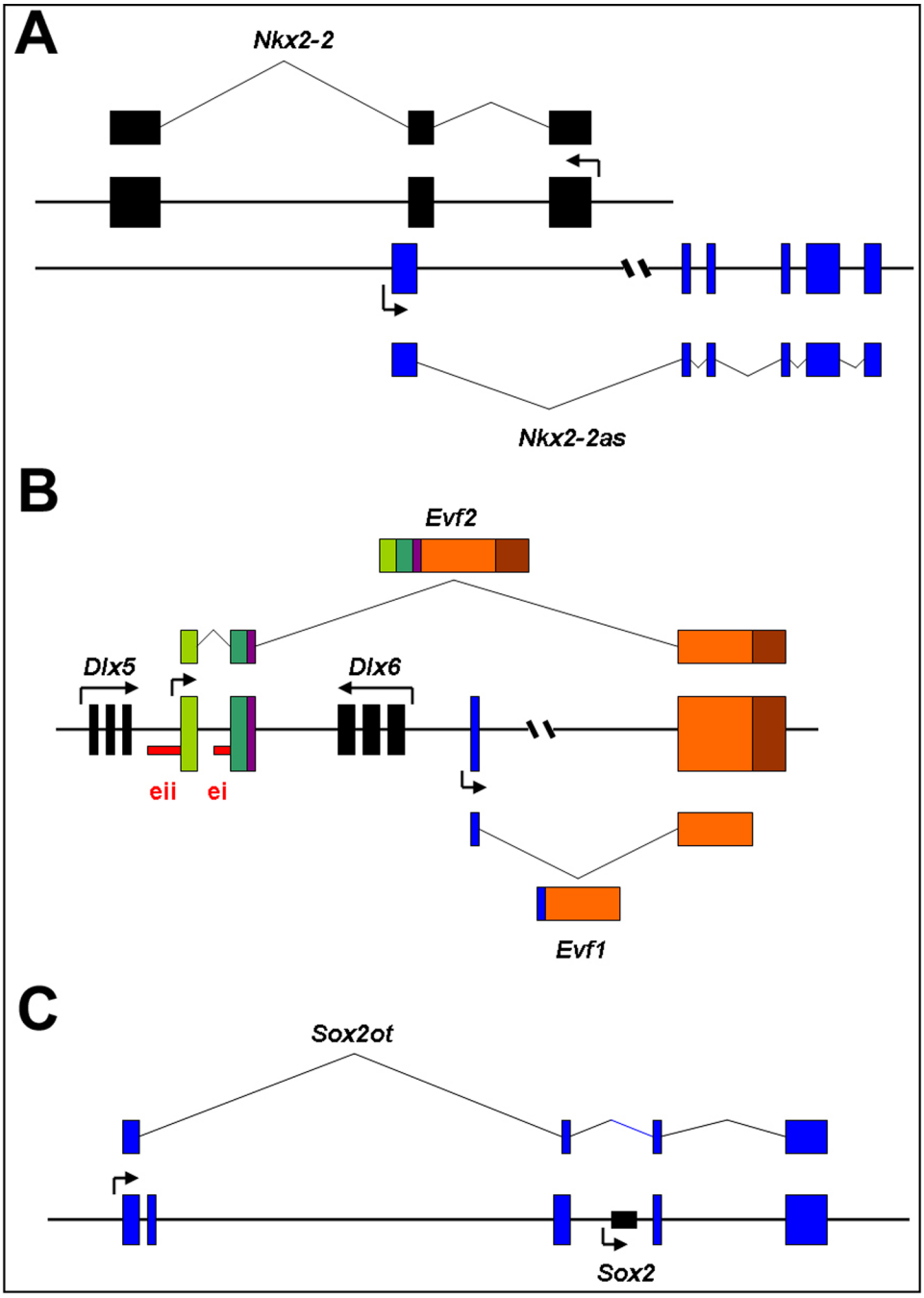


**Figure 4.**

Regulatory functions of representative long noncoding RNAs (lncRNAs) on expression of protein coding genes. **A**. *Nkx2.2 antisense* (*Nkx2.2as*) is an antisense lncRNA to *Nkx2.2* gene and promotes *Nkx2*-2 expression. **B**. *Evf2* is transcribed from the intergenic region between the *Dlx-5* and *Dlx-6* loci, and is overlapped with *Dlx-5/6* enhancer i (ei) and enhancer ii (eii) sequences. *Evf2* acts as a transcriptional co-activator of Dlx-2 and activates the *Dlx5/6* enhancer. **C**. *Sox2 overlapping transcript Sox2OT* is a lncRNA containing *Sox2* gene and shares the same transcriptional orientation with *Sox2*. *Sox2OT* is expressed in the neurogenic region of the adult mouse brain

**Table 1**

miRNAs involved in neurological disorders.

| Neurological disorders | miRNAs | Proven targets | Potential mechanisms | References |
|---|---|---|---|---|
| Tourette's syndrome | miR-189 | SLITRK1 | Mutation at the binding site for miR-189 in the target 3'UTR | [91] |
| Fragile X syndrome | miR-19b, miR-302b*, miR-323-3p | FMRP | Repression of FMR1 expression level | [93] |
| Schizophrenia | miR-181b,<br>miR-219 | VSNL1, GRIA2#CaMKIIγ | Upregulation of miR-181b in Schizophrenia<br>NMDA signaling and miR-219 forming a feedback loop in Schizophrenia | [98]<br>[99] |
| Alzheimer's disease (AD) | miR-107<br>miR-29a/b<br>miR-298, miR-328<br>miR-101<br>miR-146a | BACE1<br>BACE1<br>BACE1<br>APP<br>CFH | Downregulation of miR-107 and increase of its target BACE1 in AD<br>Downregulation of miR-29a/b and increase of its target BACE1 in AD<br>Repression of BACE1 expression and accumulation of Aβ<br>Repression of APP expression and accumulation of Aβ<br>Downregulation of miR-146a in AD | [105]<br>[106]<br>[108]<br>[109]<br>[110] |
| Huntington's disease (HD) | miR-9<br>miR-9*<br>miR-34b | REST<br>CoREST<br>? | Upregulation of miR-9/9* in HD<br>A potential biomarker for HD | [114]<br>[115] |
| Parkinson's disease (PD) | miR-7<br>miR-153<br>miR-433 | α-synuclein<br>FGF20 | Repression of α-synuclein accumulation<br>A SNP in the miR-433 binding site of FGF20 3'UTR in AD | [116]<br>[118] |
| Prion disease | miR-191<br>miR-342-3p, miR-320, let-7b, miR-328, miR-128, miR-139-5p, miR-146a, miR-337-3p, miR-338-3p | EGR1<br>? | De-regulation after infection with mouse-adapted scrapie | [119] |
| Down's syndrome (DS) | miR-155, miR-802<br>miR-125b | MeCP2<br>CDKN2A | Upregulation of miR-155 and miR-802 in DS and suppression of MeCP2<br>Upregulation of miR-125b in DS and suppression of CDKN2A | [124]<br>[125] |
| Stroke | miR-21<br>miR-124a | FASLG<br>JAG1 | Upregulation of miR-125b in Stroke and suppression of FASLG<br>Downregulation of miR-124a after Stroke | [127]<br>[128] |
| Epilepsy | miR-146a | ? | Upregulation after TLE | [129] |
| Depression and bipolar disorder (BD) | miR-182<br>miR-30e<br>miR-134<br>miR-16<br>miR-34a | ADCY6, CLOCK, DSIP<br>?<br>?<br>SERT<br>GRM7 | Polymorphism in the rs76481776 of the pre-miR-182<br>Polymorphism in the ss178077483 of the pre-miR-30e<br>A potential biomarker for bipolar disorders | [130]<br>[131]<br>[133]<br>[134]<br>[135] |

| Neurological disorders | miRNAs | Proven targets | Potential mechanisms | References |
|---|---|---|---|---|
| | | | Upregulation of miR-16 after SSRI treatment Downregulation of miR-34a after treatment using mood stabilizers | |