ISSN 1927-5587

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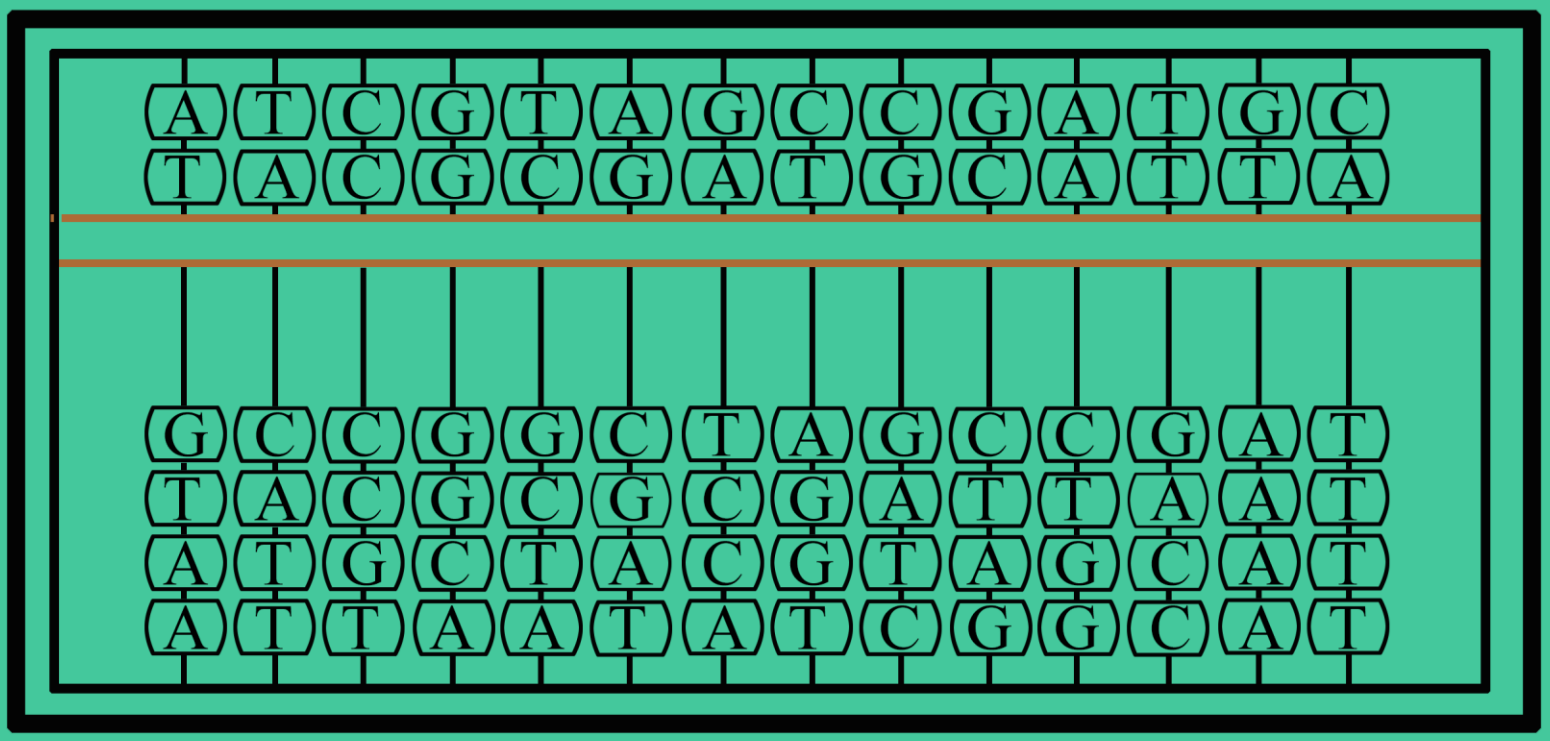

ISSN 1927-5587
14004
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2014
Vol.4

http://cmb.biopublisher.ca

Computational Molecular Biology (online), 2014, Vol. 4
ISSN 1927-5587
http://cmb.biopublisher.ca

Publisher

Sophia Publishing Group

Editor–in–Chief

Dr. Henry Smith

Edited by

Editorial Team of Computational Molecular Biology
Email: edit@cmb.biopublisher.ca
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Computational Molecular Biology (online), 2014, Vol. 4
ISSN 1927-5587
http://cmb.biopublisher.ca

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Computational Molecular Biology 2014, Vol. 4, No. 5
http://cmb.biopublisher.ca

A Review **Open Access**

Long Non-coding RNAs: key players in brain and central nervous system development

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Computational Molecular Biology, 2014, Vol.4, No.5 doi: 10.5376/cmb.2014.04.0005
Received: 09 Mar., 2014
Accepted: 26 Apr., 2014
Published: 04 Jul., 2014

Preferred citation for this article:
Lv et al., 2014, Long Non-coding RNAs: key players in brain and central nervous system development, Computational Molecular Biology, Vol.4, No.5, 1-13 (doi: 10.5376/cmb.2014.04.0005)

Abstract Regulatory long non-coding RNAs have been emerged as a major contribution of cognitive evolution in mammalian central nervous system and brain tissues. Though proteins have relatively conserved during evolution, the lncRNAs have evolved rapidly to cope with essential and widespread cellular regulation, partly by directing generic protein function. Long non-coding RNAs, highly yet specifically expressed in mammalian brain, provide tissue- and neuronal activity-specific epigenetic and transcriptional regulation. lncRNAs have been documented to be essential for brain development and be involved in brain related diseases. We suggest that lncRNAs are important to modulate diverse central nervous system processes and are the major factor that is important to the brain development, which may be employed to develop novel diagnostic and therapeutic strategies to treat brain related diseases. Moreover, animal models with altered lncRNA expressions and high-throughput approaches would help to understand the mechanisms of lncRNAs in brain development and the etiology of lncRNA-driven human neurological diseases.

Keywords Long Non-coding RNAs; Central nervous system; Neurogenesis; Brain development; RNA-Seq

Background

The central nervous system (CNS) has been under high evolution and brain is an advanced animal organs. CNS includes distinct categories of neuronal and glial cell types. The amazing cognitive and behavioral functions in brain may involve in neural networks comprised by billions of neurons (Graff and Mansuy, 2008). It is still unknown of the molecular mechanisms about the cooperation among these neurons, though advances in epigenetic areas have been increasing (MacDonald and Roskams, 2009). Based on current view of points and accumulating evidences, epigenetic factors are considered to affect mammalian development and cell differentiation. Furthermore, aberrant epigenetic modification changes by DNA methylation and histone modifications have key roles in human diseases (Kaut et al., 2014; Coppieters et al., 2013; Besingi and Johansson, 2014; Zykovich et al., 2013; Bryant et al., 2014; Sanchez-Mut et al., 2013; Robertson, 2005; MacDonald and Roskams, 2009; Liu et al., 2014; Lv et al., 2010; Lv et al., 2012; Liu et al., 2011; Zhang et al., 2010). For example, the enzymes and complexes such as Polycomb proteins and Trithorax-group proteins, are basal for developmental processes (Kouzarides, 2007; Ringrose and Paro, 2007). However, the mechanisms of loci specificity have only started to be discovered. Recent evidences suggested that the chromatin associated proteins are guided by non-coding RNAs (ncRNAs) (Khalil et al., 2009; Dinger et al., 2008; Mattick, 2009).

The spatio-temporal expression patterns of ncRNAs seem important for CNS function. ncRNAs are implicated in a variety of biological processes including structural (for example, ribosomal RNAs), regulatory (for example, long and micro non-coding RNAs) and catalytic processes. In mammalian brain, ncRNAs are implicated in brain patterning, neuro-genesis, synaptic and neuron connectivity (Mehler and Mattick, 2007) and CNS disease (Taft et al., 2010).

Long non-coding RNAs (lncRNAs) are ncRNAs that are longer than 200 nt and are abundant in brain cell types (Mercer et al., 2008). The classical lncRNAs are transcribed through the same transcriptional machinery as other mRNAs, that is, RNA polymerase II (PolII) occupancy in lncRNA promoter and active histone modifications that are associated with lncRNA promoter and gene body (Ilott and Ponting, 2013). The number of all lncRNAs in mouse is estimated as at least 40,000, which is more than the number of protein-coding genes (Managadze et al., 2013). Most lncRNAs are poorly annotated, and their functions including the roles in CNS functions have not been widely studied. The functions of lncRNAs appear to associate with the genomic localization. For example, lncRNAs can be in close with development associated key genes. Neighboring protein-coding genes can exhibit concordant or discordant expression patterns with lncRNAs (Dinger et al., 2008; Ponjavic et al., 2009), implying the potentially regulatory roles of lncRNAs. Given most of lncRNAs are specifically expressed in brain, the tissue specificity and brain region specificity of lncRNAs seems to be exceptionally vital for regulating CNS functions (Mercer et al., 2008).

Some lncRNAs can regulate the epigenetic modifications of protein-coding genes by cis- or trans-acting fashions that need recruiting chromatin remodeling factors to particular genomic loci (Khalil et al., 2009; Redrup et al., 2009). One classical example of this kind is the HOXC loci where a lncRNA HOTAIR is transcribed and HOTAIR recruits Polycomb protein complex PRC2 to HOXD loci and represses HOXD in trans (Rinn et al., 2007).

1 lncRNAs in the central nervous system

The proximity of lncRNAs to genes related to regulatory development proteins implies that lncRNAs can play important roles in mammalian organ development. Actually, many transcriptomic studies have revealed the dynamic lncRNA expression profiles and their functions among developing, fetal and adult tissues, in additional to embryonic stem (ES) cells (Dinger et al., 2008; Sheik Mohamed et al., 2010), neural cell subtypes (Mercer et al., 2010; Aprea et al., 2013; Lin et al., 2011), and brain (Mercer et al., 2008; Ponjavic et al., 2009; Lv et al., 2013a; Lv et al., 2013b).

1.1 lncRNA expression in brain and neural differentiation

To quickly explore the brain developmental stage specificity and brain specificity, the Allen Brain Atlas (http://www.brain-map.org/) is an option. The Allen Brain Atlas covers in situ hybridization (ISH) data and is a constantly updating website, from which we are able to examine the expression of hundreds of lncRNAs in various tissues in adult and developing mouse brains (Ng et al., 2012a). ~ 64% of 1328 lncRNAs investigated by Allen Brain Atlas are detectable in adult mouse brain and are expressed selectively for specific brain regions especially in hippocampus and cerebellum (Mercer et al., 2008). The brain region specificity is expected as the expression is low in whole brain transcriptome profiling. Therefore, it is necessary to perform transcriptome studies on specific brain regions to improve the lncRNA detection power. In addition, in situ hybridization maps in Allen Brain Atlas revealed that the most lncRNA are expressed in CNS (Mercer et al., 2008). The lncRNAs expressed in CNS are complex, including imprinted transcripts, cis-antisense, intronic and bidirectional transcripts (Carninci et al., 2005). Furthermore, many lncRNAs expressed in CNS exhibited cross-species conservation, which is meaningful as conservation may indicate functionality. Ponjavic et al. have found over 200 lncRNAs that are detectable in developing and adult brain (Ponjavic et al., 2009), which are mainly located near transcriptional regulators with similar expression patterns and a large more conserved lncRNAs may await to be discovered in near future.

Particular lncRNAs which are differentially expressed during CNS differentiation are potential regulators in mediating neural functions. *Sox2*, an important transcription factor in ES cells, is necessary for neural development. One study has demonstrated that *Sox2OT*, a lncRNA containing Sox2 in its introns, is expressed in adult neurogenesis (Mercer et al., 2008). Another report indicated that *Sox2OT* might be responsible for modulating *Sox2* expression (Amaral et al., 2009). Taken together, current evidences may

suggest that lncRNAs can mediate the expression of other factors to orchestrate neural cell identity.

RNA sequencing (RNA-seq) followed by computational analysis has been widely used to identify tissue restricted expressed lncRNAs. Kaushik et al. had used this approach to identify lncRNA transcripts from five different tissues of adult zebrafish (Kaushik et al., 2013). They identified 442 predicted lncRNA transcripts and 77 differentially expressed lncRNAs. Within the differentially expressed lncRNAs, 61% are brain restricted expressed.

1.2 High-throughput approaches to study the lncRNAs in CNS development.

A study systematically found more than 1600 conserved lincRNAs in four mouse cell types based on chromatin signatures (Guttman et al., 2009). The cell types they investigated include neural precursor cells (NPCs). Their analysis found that those lncRNAs that are associated with "brain cluster" are related to some brain related biological processes, such as hippocampal development and oligodendrocyte (OL) myelination.

The results together with others (Lv et al., 2013a; Lv et al., 2013b; Ng et al., 2012b; Qureshi and Mehler, 2012) have highlighted the importance of lncRNAs in regulation of cellular fate in neural cells and brain. Increasing evidences suggested that lncRNAs can control epigenetic targeting via their ability to bind RNA, DNA and protein (Guttman and Rinn, 2012; Mercer and Mattick, 2013; Tsai et al., 2010). lncRNAs contain functional three-dimensional structures that can form scaffolds or molecular 'sponges' and in turn allow activity-dependent regulation (Tripathi et al., 2010; Mercer and Mattick, 2013; Tsai et al., 2010; Barry et al., 2013). *Malat1*, as an example, has been shown to relate with synapse formation by acting as splicing factor 'sponge', suggested that lncRNAs have alternative splicing functions in neural cells (Anko and Neugebauer, 2010). As an earlier mechanistic study, a lncRNA related to alternative splicing in neuronal cells was reported for Gomafu (Barry et al., 2013). The expression of *Malat1* was generally stable during induction of stimulating neurons, implying that *Malat1* plays a different role in human neuronal functions, or perhaps has regulatory functions in distinct subtypes of neural cells. In addition, lncRNAs are also associated with mRNA transcription, translation and decay (Tripathi et al., 2013; Mercer and Mattick, 2013). Altogether, the enormous regulatory potentials of investigated lncRNAs and even more candidates would call for more detailed studies about the distinct group of non-coding RNAs.

The differential lncRNA expression patterns should be interpreted by experimental or computational functional analysis. As a first step, Mercer et al. (Mercer et al., 2010) systematically analyzed lncRNAs that had significant changes in expression and found that several of these lncRNAs were part of or close to protein-coding gene loci with a known function in brain and CNS development. In addition, a software Scripture was used to reconstruct the transcriptome of mouse ES cells, neuronal precursor (NP) cells and lung fibroblast cells. The full-length transcript structures for most annotated genes and a large number of lncRNAs were construct (Guttman et al., 2010). Another study found that there were ~170 lncRNAs that are differentially expressed during lineage commitment of neuron and oligodendrocyte (OL), neuronal-glial transitions, and developmental stages of OL (Mercer et al., 2010). Recently, a study used RNA-seq to identify lncRNAs that may be important in neurogenic commitment process (Aprea et al., 2013). Some selected lncRNAs have been validated. Recently, Ramos et al. utilized high-throughput approaches including RNA-seq and ChIP-seq to identify lncRNAs related to distinct neural cell types and lncRNAs having important roles in embryonic and adult neurogenesis (Ramos et al., 2013).

In addition, more and more lncRNAs were associated with conserved enhancer elements that regulate the brain development. p300 and H3K4me1 marks have been employed in one work to identify enhancers in mouse that are mediated by neuronal activity (Kim et al., 2010). These predicted enhancers are rich in putative lncRNAs, expanding in either direction from the CBP binding positions and within 2000 bp from

enhancer. The enhancer lncRNAs were also found in the intergenic region that are between the *Dlx-5* and *Dlx-6* loci within the *Dlx* loci. The region covers with a piece of conserved intergenic enhancer (Zerucha et al., 2000). *Dlx-6* is a homeobox element and itself a transcription factor and is vital in embryonic brain developmnet (Wang et al., 2010).

1.3 Regulation of lncRNA expression in the nervous system

How lncRNAs are regulated in CNS and what factors can influence lncRNA expression are not well understood. The main ideas are that lncRNAs are under similar regulatory mechanisms with that of protein-coding genes (Dinger et al., 2008; Guttman et al., 2009; Cawley et al., 2004; Mercer et al., 2010; Zhang et al., 2009). For instance, Pax2, a transcription factor, functions in formation of the mouse brain; while *Ncrms* is a lncRNA that is exactly mediated via Pax2 (Bouchard et al., 2005). Interestingly, *Ncrms* is the host gene for miR-135a (Rodriguez et al., 2004), a miRNA, which has reversed expression pattern in medulloblastoma, compared with normal brain (Ferretti et al., 2009). The evidences suggest that genetic and epigenetic factors can both mediate tumorigenesis. In another example, *Sox2*, which is a pluripotency related transcription factor, plays an important role in the preservation of the Neural Stem Cells (NSCs) in embryonic and adult brain (Pevny and Placzek, 2005). In *Sox2* gene loci, a lncRNA exists, which is named by *Sox2* overlapping transcript (*Sox2OT*). Genomic studies showed that it shares same transcriptional direction with the *Sox2* gene. *Sox2* and *Sox2OT* transcribe stably in mouse embryonic stem cells and are down regulated during stem cell differentiation. Amaral et al. detected that in the neurogenic region of the adult mouse brain *Sox2OT* is expressed and is under dynamic regulation during CNS development, suggesting that it can regulate the self-renewal and neurogenesis of stem cells (Amaral et al., 2009).

Nkx2.2as, which is a lncRNA antisense to the *Nkx2.2* gene, is transcribed in the embryonic brain and is necessary to oligodendrocyte development (Price et al., 1992). Aberrant transcription of *Nkx2.2as* in Neural Stem Cell (NSC) can induce the oligodendrocyte differentiation by *Nkx2.2* upregulation, indicating that *Nkx2.2as* regulates NSC differentiation by increasing the expression of *Nkx2.2* (Tochitani and Hayashizaki, 2008).

In addition, recent evidences imply that the perturbed epigenetic processes can alter the lncRNA expression patterns (Mattick, 2009). When treated with trichostatin A (TSA), OL development process is changed. OL maturation is inhibited by TSA which is a histone deacetylase inhibitor by suppressing OL-specific gene expression (Mercer et al., 2010). We summarized the examples of loss of gene function studies in brain and CNS in Table 1, which can be achieved by locally administered RNA interference (RNAi) reagents. Taken together, it is indicated that lncRNAs are regulated by similar transcriptional and epigenetic factors with protein-coding genes.

Though lncRNAs are expressed across various tissues, the functions in brain development can be explored if using a traditional knockout approach. For instance, mice with knockouts of lncRNAs *Hotair* (Li et al., 2013) and *Xist* (Marahrens et al., 1997) resulted in severe phenotypes, but mice with a knockout of the ubiquitously and highly expressed lncRNA *Malat1* displayed no obvious phenotype (Eissmann et al., 2012). Regulation of synaptogenesis (Bernard et al., 2010), alternative splicing (Tripathi et al., 2010), control of cell cycles (Tripathi et al., 2013) and diseases (Gutschner et al., 2013) have been reported for *Malat1*, but it is still unknown what the precise role is for this abundant and broadly expressed lncRNA. The results indicated that further functional analyses are needed, which is helpful to uncover the functional roles within neural cells.

2 lncRNAs in diseases of the CNS and brain

Disruptions to genome-wide lncRNA-mediated functions could have negative consequences, which is particularly important in the mammalian brain and nervous system where most tissue-specific lncRNAs are expressed. Indeed, it is emerging that lncRNAs are involved in the pathology of neurological diseases related to imprinting, for instance, Prader–Willi syndrome (PWS) and Angelman syndrome (AS) (Koerner et al., 2009). Additionally, lncRNAs that are

Table 1 lncRNAs involved in brain and CNS development and the resulting phenotypes in model animal systems

lncRNA	Process	Phenotype	Reference(s)
Dlx1os	Homeodomain transcription factor regulation in developing brain	Morphologically normal together with mild skull and neurological defects by gene inactivation	(Kraus et al., 2013)
Dlx6os1	Homeodomain transcription factor regulation in developing brain	Morphologically normal together with altered GABAergic interneuron development by gene inactivation	(Feng et al., 2006)
Malat1	Tumorigenesis	Normal animal development by gene inactivation	(Zhang et al., 2012)
Miat	Retina development	Defects in specification of retina cell types by knockdown and overexpression in neonatal retina	(Rapicavoli et al., 2010)
Six3os1	Retina development	Defects in specification of retina cell types by knockdown and overexpression in neonatal retina	(Rapicavoli et al., 2011)
Tug1	Retina development	Defects in differentiation of photoreceptor progenitor cells after knockdown in neonatal retina	(Young et al., 2005)
RNCR2	Retina development	Knockdown leads to the increase of amacrine cells and Müller glial cells in post-natal retina	(Rapicavoli et al., 2010)
Vax2os	Retina development	Defects in differentiation of photoreceptor progenitor cells after overexpression in neonatal retina	(Meola et al., 2012)

Note: Long non-coding RNAs: new players in cell differentiation and development

Table 2 lncRNAs involved in diseases of the CNS

lncRNA	Genomics	Evidence	Disease	Reference(s)
Ube3a-as	Antisense to *Ube3a*	responsible for repressing paternal *Ube3a* expression; silencing of paternal *Ube3a* can occur in the absence of *Ube3a-as*	PWS-AS	(Vitali et al., 2010)
FMR4	share a bidirectional promoter with the *FMR1* gene	is silenced in FXS; *FMR4* does not simply regulate *FMR1*	FXS	(Khalil et al., 2008)
ASFMR1	antisense to the 5′ UTR region of *FMR1*	is silenced in FXS	FXS	(Ladd et al., 2007)
Sox2OT	encompasses the entire *Sox2* gene	implicated in modulating *Sox2* expression	CNS developmental abnormalities	(Amaral et al., 2009)
A region in 2q11.2	2q11.2 chromosomal region that includes DGCR5, a REST regulated lncRNA	VCFS is caused by deletions of the region	velocardiofacial syndrome (VCFS)	(Johnson et al., 2009)
NRON	mediates the cytoplasmic to nuclear shuttling of the *NFAT*	*NRON* is potentially associated with DS through *NFAT*	Down's syndrome (DS)	(Arron et al., 2006)

Table 2 Continue

BACE1-AS	Antisense to *BACE1*	modulates *BACE1* gene expression; *BACE1-AS* levels are increased in tissues from AD patients	Alzheimer's disease (AD)	(Faghihi et al., 2008)
BC200	Chromosome 11, p11.2, an ~600,000 bp region	Increased levels of *BC200* were found in brain that are preferentially affected in AD	Alzheimer's disease (AD)	(Mus et al., 2007)
ATXN8OS	Antisense to *ATXN8*	implicated in the molecular pathophysiology of SCA8	spinocerebellar ataxia type 8 (SCA8)	(Daughters et al., 2009; Koob et al., 1999; Moseley et al., 2006)
An unnamed lncRNA	associated with the cyclin D1 gene promoter	Recruit FUS/TLS to repress cyclin D1	amyotrophic lateral sclerosis (ALS)	(Wang et al., 2008)
An unnamed lncRNA	lncRNA transcripts derived from the mouse T early α (TEA) promoter	Responsible in part for MS	Multiple sclerosis (MS)	(Huseby et al., 2012; Friese and Fugger, 2009)
M21981	nested within individual introns of the *IL2RA* gene	is upregulated with T-cell activation and is identified by genome-wide association studies (GWAS) to be susceptible to MS	Multiple sclerosis (MS)	(International Multiple Sclerosis Genetics et al., 2007)
Tmevpg1	is transcribed from a cluster of cytokine genes, neighboring *Ifng*	Is associated with a MS mouse model	Multiple sclerosis (MS)	(Vigneau et al., 2003)
H19	With *IGF2* in the same cluster	Deregulated *H19* is associated with various diseases	medulloblastomas, meningiomas and gliomas	(Albrecht et al., 1996; Yoon et al., 2002; Muller et al., 2000; Berteaux et al., 2005)
anti-NOS2A	Antisense to *NOS2A*	is evolved by duplication of the *NOS2A* gene followed by internal DNA inversion	negatively regulated *NOS2A*, which is induced in human glioblastoma	(Broholm et al., 2003)
AK042766	5kb from *Meis1*	are correlated with *Meis1*, which is lowered in expression in RLS	Restless Legs Syndrome (RLS)	(Ponjavic et al., 2009)
DISC2	Antisense to protein-coding gene DISC1	Disruption of *DISC* genomic loci is linked to many psychiatric diseases	schizophrenia, schizoaffective disorder, bipolar disorder, major depression, and autistic spectrum disorders	(Chubb et al., 2008; Millar et al., 2000; Williams et al., 2009)

differentially expressed between ESCs and differentiated neurons are related to schizophrenia (SZ), bipolar disorder (BD) and even autism spectrum disorders (ASD) (Lin et al., 2011). We have summarized several lncRNAs involved in diseases of the CNS and brain in Table 2.

The induced pluripotent stem cell technology, together with next generation sequencing (Stadtfeld and Hochedlinger, 2010) and even newer single-cell sequencing (Eberwine et al., 2014) is viable to generate tissue- and developmental stage-specific neural cells. These technologies, focusing on cell types, will be helpful to reveal more lncRNAs which act as critical regulators of normal human brain activity and associated disorders.

3 Perspectives

What we already know it that non-coding RNAs, particularly lncRNAs, have an important role in CNS development and brain functions. Large-scale predictions and compilation of brain subregion and CNS cell specific lncRNAs would aid determination of the actions of specific lncRNAs in brain and CNS development. In addition, comprehensive exploration of how expression specificity of lncRNAs is mediated during CNS and brain development can present the transcriptional patterns of lncRNA transcription and biological functions.

For miRNAs may have a large number of targets for lncRNAs, it is still a problem to work out the miRNA-lncRNA networks in brain and CNS development, though related researches have been reported (Liu et al., 2013). The relationships of lncRNAs and human brain related diseases would require systematic exploration. It is meaningful to use lncRNAs as diagnostic and treating targets for neurological diseases. Furthermore, developing tools based on disease-related lncRNAs to produce animal models with permutated lncRNA expression patterns would help to comprehend the disease-causing reasons of lncRNA-driven human brain-related disorders.

Our understandings towards genomic architecture have been dramatically updated, as the lncRNAs are found to be equally important in biological systems and in regulation of CNS with protein-coding genes. It is certain that exploring lncRNAs functions in neural development and disease conditions would be a research focus. lncRNAs are important for regulating CNS development and pathophysiology of CNS and brain. The regulatory functions involving regulatory, structural and catalytic functions for lncRNAs. By regulating genome-wide transcriptions, lncRNAs can dynamically mediate spatiotemporally the global gene networks. As the aforementioned brain region specific expression property for lncRNAs, transcriptomic and functional studies should be performed in different kinds of CNS cells and different subregions of brain, which would help explain whether lncRNAs have epigenetic and other functional roles. Considering GWAS has been performed for many CNS disorders, it is necessary and easy to investigate if the mined disorder related SNPs are related to lncRNAs, though it is difficult to predict the causality of variations in these lncRNA sequences (Mattick et al., 2009).

In addition, therapeutic strategies including RNA interference (RNAi) technology and customized high-throughput methods are needed for targeting lncRNAs with aberrant expression in brain and CNS diseases. Taken together, we indicate that lncRNAs are important to modulate various brain related processes and are a major factor that is important to the brain development, which may be employed to develop meaningful diagnostic and treating approaches to treat brain and CNS related diseases. High-throughput RNA sequencing together with computational analysis would be useful to identify brain subregion and CNS-specific lncRNAs, together with their association with nearby protein-coding genes. Exploring how lncRNAs regulate gene transcription in *cis* or in *trans* is helpful to uncover novel non-coding RNA regulatory mechanisms in brain development and CNS differentiation.

Authors' contributions

JL drafted the manuscript. HBL and HL collected materials. QW and YZ conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

Acknowledgments

The authors thank National Natural Science Foundation of China for funding. This work is supported by the National Natural Science Foundation of China [31171383, 31271558, 31371478].

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