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Long non-coding RNAs in nervous system function and disease

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Abstract

Central nervous system (CNS) development, homeostasis, stress responses, and plasticity are all mediated by epigenetic mechanisms that modulate gene expression and promote selective deployment of functional gene networks in response to complex profiles of interoceptive and environmental signals. Thus, not surprisingly, disruptions of these epigenetic processes are implicated in the pathogenesis of a spectrum of neurological and psychiatric diseases. Epigenetic mechanisms involve chromatin remodeling by relatively generic complexes that catalyze DNA methylation and various types of histone modifications. There is increasing evidence that these complexes are directed to their sites of action by long non-protein-coding RNAs (lncRNAs), of which there are tens if not hundreds of thousands specified in the genome. LncRNAs are transcribed in complex intergenic, overlapping and antisense patterns relative to adjacent protein-coding genes, suggesting that many lncRNAs regulate the expression of these genes. LncRNAs also participate in a wide array of subcellular processes, including the formation and function of cellular organelles. Most lncRNAs are transcribed in a developmentally regulated and cell-type specific manner, particularly in the CNS, wherein over half of all lncRNAs are expressed. While the numerous biological functions of lncRNAs are yet to be characterized fully, a number of recent studies suggest that lnRNAs are important for mediating cell identity. This function seems to be especially important for generating the enormous array of regional neuronal and glial cell subtypes that are present in the CNS. Further studies have also begun to elucidate additional roles played by lncRNAs in CNS processes, including homeostasis, stress responses and plasticity. Herein, we review emerging evidence that highlights the expression and function of lncRNAs in the CNS and suggests that lncRNA deregulation is an important factor in various CNS pathologies including

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neurodevelopmental, neurodegenerative and neuroimmunological disorders, primary brain tumors, and psychiatric diseases.

Keywords

CoREST; epigenetic; long non-coding RNA (lncRNA); neural stem cell (NSC); neuron; non-coding RNA (ncRNA); oligodendrocyte; repressor element-1 silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF)

Introduction

The human central nervous system (CNS) is the most highly evolved and sophisticated biological system. It is comprised of an enormous array of distinct regional neuronal and glial cell subtypes that are organized into dynamic neural networks, which are, in turn, responsible for mediating the functional repertoire of the CNS including its ability to perform higher order cognitive and behavioral functions (Graff and Mansuy, 2008). One of the central aims of modern neurobiology is to understand the molecular mechanisms that underpin the elaboration of these neural cells and neural networks, and recent advances in epigenetic sciences have uncovered novel insights into these processes (MacDonald and Roskams, 2009; Mehler and Mattick, 2007; Mehler, 2008). Developmental stage- and cell type-specific epigenetic mechanisms are now thought to be responsible for producing, maintaining, and refining neural cell identity and function, by regulating the selective deployment of gene networks throughout life in response to interoceptive and environmental stimuli. Therefore, epigenetic processes are also implicated in mediating CNS homeostasis, stress responses, plasticity and disease (MacDonald and Roskams, 2009; Robertson, 2005; Tsankova et al., 2007). These epigenetic regulatory mechanisms involve chromatin remodeling via DNA methylation and histone code modifications at a plethora of sites around the genome and are mediated by an extraordinary array of generic enzymes/complexes/molecular scaffolds that include Polycomb- and Trithorax-group proteins, which are essential for most if not all developmental processes and programs (Kouzarides, 2007; Ringrose and Paro, 2007; Schwartz and Pirrotta, 2007). What determines the locus-selectivity of these enzymes is uncertain, but recent evidence suggests that they are recruited to their sites of action by non-protein-coding RNAs (ncRNAs) (Dinger et al., 2008; Khalil et al., 2009; Mattick et al., 2009).

The precise temporal and spatial expression of ncRNAs appears to be exceptionally important for mediating CNS form and function. Genomic organization is extremely intricate and encompasses multiple layers of regulatory and functional elements, including many interleaved, overlapping and antisense protein-coding mRNA and ncRNA transcripts (Carninci et al., 2005; Cheng et al., 2005; Kapranov et al., 2007a; Kapranov et al., 2007b; Katayama et al., 2005; Mattick and Makunin, 2006). Indeed, the genome is transcribed into a spectrum of ncRNAs that are implicated in a wide range of structural, regulatory, and catalytic processes. Some of these classes of ncRNAs are well known, such as ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs), whose roles in mediating the pathogenesis of CNS disorders (e.g., mitochondrial enchephalopathies) have been characterized, at least in part (Sproule and Kaufmann, 2008). Additional classes of ncRNAs that have more recently been identified include a wide range of long ncRNAs (lncRNAs) and various types of short ncRNAs (microRNAs [miRNAs], piwiRNAs [piRNAs], small nucleolar RNAs [snoRNAs], promoter-associated small RNAs [PASRs] and transcription initiation RNAs [tiRNAs], among others) (Taft et al., 2010). This ncRNA circuitry appears to be selectively and dynamically deployed in each neural cell, and the developing and adult nervous systems exhibit specific regional, cellular and subcellular localization profiles of ncRNAs (Fineberg et al., 2009; Mehler and Mattick, 2007; Mehler, 2008; Mercer et al., 2008b; Mercer et al., 2010; Ponjavic et al., 2009;

Royo and Cavaille, 2008). These environmentally sensitive ncRNA networks are thought to efficiently couple bioenergetic properties with information storage and processing capacity and to be responsible for orchestrating a wide array of biological processes (Mattick, 2003; St Laurent and Wahlestedt, 2007). In the CNS, these factors are implicated in mediating critical functions including brain patterning, neural stem cell (NSC) maintenance, neurogenesis and gliogenesis, stress responses, homeostasis, and synaptic and neural network connectivity and plasticity (Mehler and Mattick, 2007; Mehler, 2008). Therefore, not surprisingly, perturbations in the expression and function of these ncRNAs are increasingly being linked to the molecular pathophysiology of CNS disorders (Mehler and Mattick, 2007; Mehler, 2008; Taft et al., 2010).

Although lncRNAs are one of the most abundant classes of ncRNAs encoded within the genome and are highly expressed in brain (Mercer et al., 2008b; Ponjavic et al., 2009; Ravasi et al., 2006); see below), they remain poorly characterized, and their roles in the CNS have not been studied in detail. This class of ncRNA generally encompasses transcripts longer than 200 nt, of which there are tens if not hundreds of thousands expressed from mammalian genomes (Birney et al., 2007; Carninci et al., 2005; Cheng et al., 2005; Kapranov et al., 2007a; Katayama et al., 2005). Many lncRNAs are transcribed from genomic loci exhibiting chromatin signatures that indicate their transcription is dynamically regulated in a cell type-specific manner (Guttman et al., 2009). In addition, many lncRNAs are 5′ capped, polyadenylated, and spliced, like mRNAs (Carninci et al., 2005; Kapranov et al., 2007a; Okazaki et al., 2002; Ponjavic et al., 2007), although others are not (Cheng et al., 2005). Biophysical analyses of lncRNAs suggest that they can form a myriad of functional secondary structures (Pedersen et al., 2006; Torarinsson et al., 2008; Washietl et al., 2005). Some lncRNAs also serve as precursors for shorter regulatory ncRNAs (e.g., snoRNAs and miRNAs) (Mattick and Makunin, 2005). The functional properties of lncRNAs seem to be associated, in part, with their genomic architecture. Some lncRNAs are found in intergenic regions while others are organized in antisense, bi-directional, or intronic configurations with key protein-coding genes. These pairs of lncRNAs and protein-coding mRNAs exhibit expression profiles that are often highly complex, including concordant and discordant patterns (Dinger et al., 2008; Guttman et al., 2009; Khalil et al., 2009; Mercer et al., 2008b; Mercer et al., 2009; Mercer et al., 2010; Pang et al., 2009; Ponjavic et al., 2009), suggesting that lncRNAs play diverse roles in regulating the expression of associated protein-coding genes.

A major function of lncRNAs appears to be to modulate the epigenetic status of proximal and distal protein-coding genes through *cis*- and *trans*-acting mechanisms that include the recruitment of chromatin remodeling complexes to specific genomic loci thereby regulating chromatin structure over a single gene promoter, a gene cluster, or an entire chromosome (Dinger et al., 2008; Khalil et al., 2009; Mattick et al., 2009; Ng et al., 2007; Redrup et al., 2009). For example, *HOTAIR* is a lncRNA transcribed from the *HOXC* locus that recruits the Polycomb group (PcG) chromatin remodeling complex, PRC2, to the *HOXD* locus where it creates a repressive chromatin environment across 40 kb of the locus (Rinn et al., 2007). Moreover, a recent study examining a subset of human intergenic lncRNAs showed that a significant proportion is bound by PRC2, either alone or in combination with other chromatin remodeling complexes, such as those formed by CoREST and SMCX (Khalil et al., 2009).

LncRNAs also fulfill a range of other functions in cell and developmental biology, including interaction with promoter elements and transcription factors to modulate transcriptional activity. For example, the lincRNA *Evf2* is transcribed from an ultraconserved distal enhancer that recruits positive (i.e., DLX) and negative (i.e., MECP2) transcription factors to the enhancer to modulate the expression of adjacent protein-coding genes (Bond et al., 2009). Furthermore, through sequence specific interactions, lncRNAs can regulate mRNA post-transcriptional processing and translation (Beltran et al., 2008). LncRNAs can also participate

in forming structural compartments of the cell. For example, the lncRNA *Neat1* (also known as *MEN ε/β*) is an essential architectural and functional component of paraspeckles, a nuclear subdomain implicated in the regulation of mRNA nuclear export (Bond and Fox, 2009; Clemson et al., 2009; Sasaki et al., 2009; Sunwoo et al., 2009), which is specifically induced upon cell differentiation (Chen and Carmichael, 2009), including neuronal differentiation (M.B. Clark and J.S. Mattick, unpublished observations). Similarly, the lncRNA *Gomafu* is expressed in a subset of differentiating neural progenitor cells and post-mitotic neurons, and is localized in a novel nuclear microdomain (Sone et al., 2007).

Many lncRNAs are also dynamically expressed in the nervous system of other species, including insects (for review see (Amaral and Mattick, 2008). Some lncRNAs are relatively conserved across different species implying that they play important biological roles common to those species (Marques and Ponting, 2009; Ponting et al., 2009). On the other hand, some lncRNAs are not well conserved but are known to be functional, suggesting that they may have been subject to lineage-specific selection pressures and evolutionary innovations associated with phenotypic divergence (Pang et al., 2006; Pheasant and Mattick, 2007). It is also possible that many transcripts may have diverged in primary sequence but still retained elements of conserved secondary structure (Torarinsson et al., 2008; Washietl et al., 2005). The potential adaptive roles played by lncRNAs in the human CNS are highlighted by a recent study that reported non-coding sequences comprise 47 of 49 regions of the human genome that are highly conserved among mammalian species but show accelerated changes in the human lineage since divergence from our common primate ancestor (Pollard et al., 2006). These observations suggest that recent adaptive selection of these regions may have given rise to innovations in human brain form and function. In fact, the lncRNA *HAR1F* is transcribed from one of these regions and specifically co-expressed in Cajal-Retzius cells of the human neocortex with the critical neural factor RELN (Pollard et al., 2006), which mediates seminal neural developmental processes and is implicated in the pathophysiology of a broad range of neurological and psychiatric disorders (Botella-Lopez et al., 2009; D'Arcangelo, 2006; Muller et al., 2009; Pisante et al., 2009; Serajee et al., 2006; Shifman et al., 2008; Tamura et al., 2007; Won et al., 2006).

lncRNAs in the central nervous system

Highly environmentally sensitive epigenetic processes are responsible for integrating complex cell-intrinsic and local- and long-distance environmental signals that include specific temporal and spatial profiles of gradient morphogens, growth factors, additional cell signaling cues, combinatorial transcription factor codes and neuronal activity, which together orchestrate the selective deployment of genes and functional gene networks that establish, maintain, and refine neural cell identity and connectivity throughout life (Mehler, 2008). LncRNAs are often located proximal to genes encoding regulatory proteins suggesting that they play a key role in these processes. Indeed, a number of transcriptomic studies have begun to reveal dynamic profiles of lncRNA expression and function in developing and adult tissues, including embryonic stem (ES) cells (Dinger et al., 2008; Sheik Mohamed et al., 2009), the immune system (Pang et al., 2009), muscle (Sunwoo et al., 2009), the vascular system (Li et al., 2009), the retina (Blackshaw et al., 2004; Rapicavoli and Blackshaw, 2009; Young et al., 2005), neural cell subtypes (Mercer et al., 2010), and the brain (Mercer et al., 2008b; Ponjavic et al., 2009).

lncRNA expression in brain and neural differentiation

A study utilizing data from the Allen Brain Atlas found that, of 1,328 lncRNAs examined, 849 are expressed within the adult mouse brain, with almost half (623) exhibiting selective profiles for specific regions, cell types, and subcellular compartments (Mercer et al., 2008b). It should be noted that the majority are easily detectable by in situ hybridization in particular cells in, for example, the olfactory bulb, hippocampus, cortex or cerebellum (Fig. 1), which might be

expected if these RNAs are involved in regulating specific processes, and which also explains their low abundance in whole brain transcriptomic profiling analyses. Similarly the *Caenorhabditis elegans* miRNA *lsy-6*, which was discovered by genetic studies to control left-right asymmetry in taste-receptor neurons, is expressed in a very limited subset of neurons and was initially difficult to verify biochemically (Johnston and Hobert, 2003). Thus, it will be important to undertake deeper and more focused transcriptomic studies on specific regions and specific cells in order to reveal the full repertoire of lncRNAs in the brain.

The first round of three-dimensional studies in the adult mouse brain (Mercer et al., 2008b) provides clear evidence that the majority of all lncRNAs, of which there are at least 30,000 (Carninci et al., 2005) and possibly an order of magnitude more, are expressed in the nervous system. Many of these lncRNAs are derived from complex genomic loci including those that are imprinted and those that encompass key neural protein-coding genes, in *cis*-antisense, intronic, or bidirectional configurations. Further, many of these pairs exhibited conservation of their genomic organization in other species, implying that the relationships are meaningful. A complementary study examining a more restricted subset of intergenic lncRNAs enriched for evolutionarily constrained sequences showed that over 200 of these lncRNAs are expressed in the developing and adult mouse brain (Ponjavic et al., 2009). Intriguingly, these lncRNAs are largely derived from genomic loci located proximal to protein-coding genes with similar expression profiles in the brain. Moreover, the majority of these protein-coding genes are transcriptional regulators and other factors implicated nervous system development. Intriguingly, a significant proportion of lncRNAs expressed in the mouse brain are transcribed from genomic loci adjacent to protein-coding genes expressed in the vomeronasal organ and olfactory bulb supporting the emerging view that the expression of the odorant receptor repertoire is coordinated by epigenetic processes and specifically implicating lncRNAs as a key part of this regulatory mechanism (Kambere and Lane, 2007).

An additional study identified more than 1,000 evolutionarily conserved intergenic lncRNAs in mouse by analyzing chromatin signatures from four mouse cell types, including neural precursor cells (NPCs) (Guttman et al., 2009). A functional analysis of the expression of these lncRNAs revealed the presence of a “brain cluster” of lncRNAs that is associated with biological processes including hippocampal development, oligodendrocyte (OL) myelination, brain aging, CREB and PGC1-alpha transcriptional regulation, and GABAergic neuronal (GABAN), G protein coupled receptor and calcineurin signaling pathways. Another recent study demonstrated that 169 lncRNAs are differentially expressed during the sequential processes of mouse ventral forebrain-derived NSC mediated lineage restriction, GABAN and OL lineage specification, progressive OL lineage maturation, and terminal differentiation including myelination (Mercer et al., 2010). These dynamically regulated lncRNAs are also associated with protein-coding genes that play roles in diverse neural developmental processes including, for example, *AK053922*, a lncRNA transcribed from the *Gli3* locus, and *Sox8OT*, a lncRNA transcribed from the *Sox8* locus. The dynamic and context-selective Gli transcriptional response code mediates gradient morphogen signaling by Sonic hedgehog (SHH), a master regulator of brain development (Yu et al., 2009). Similarly, Sox8 is a SRY-box transcription factor that mediates progressive stages of OL maturation (Stolt and Wegner, 2009). In addition, this study found that lncRNAs not associated with neural genes are also differentially expressed during developmental transitions. For example, the *BIC* (*B-cell integration cluster*) lncRNA was upregulated during neurogenesis but downregulated during oligodendrogliogenesis suggesting that it may play a role in neuronal-glial fate transitions.

lncRNA regulation of cell fate decisions, cellular differentiation, synaptic plasticity and behavior

Detailed analyses of specific lncRNAs that are dynamically expressed in the CNS reveal potential roles in mediating neural cell fate decisions. For example, Sox2 is a key transcription factor that is required for neural induction and maintenance of neural stem and progenitor cells, and a recent study demonstrated that the *Sox2OT* lncRNA, which contains the *Sox2* gene within one of its introns and is transcribed in the same direction (Fantes et al., 2003), is expressed in regions of constitutive adult neurogenesis (Mercer et al., 2008b). Another recent study demonstrated that *Sox2OT* is dynamically regulated in CNS structures during development, where it may be responsible for modulating Sox2 expression (Amaral et al., 2009). Similarly, Nkx2.2, a transcription factor that is critical for OL lineage specification, is also subject to regulation by a lncRNA, *Nkx2.2AS*, which is transcribed antisense to the *Nkx2.2* gene. A recent study reported that forced expression of *Nkx2.2AS* in NSCs *in vitro* enhances their differentiation along the OL lineage, in part, by inducing an increase in *Nkx2.2* mRNA levels (Tochitani and Hayashizaki, 2008). This observation implies not only that *Nkx2.2AS* has a regulatory effect on the transcription of *Nkx2.2 in cis* but also influences other factors responsible for OL lineage specification *in trans*. Together, these observations suggest that, in concert with cell–intrinsic and environmental signals, a range of lncRNA-mediated epigenetic mechanisms participate in orchestrating neural cell identity.

LncRNAs are also implicated in processes responsible for modulating synaptic plasticity and promoting long-term changes in synaptic strength. For example, the rodent-specific *BC1* and primate-specific *BC200* lncRNAs, which are derived from transposable elements and transcribed by RNA polymerase III, are selectively targeted to postsynaptic dendritic compartments, where they modulate local protein synthesis by repressing the initiation of translation through an eIF4A-dependent mechanism (Brosius, 1999; Kondrashov et al., 2005; Lin et al., 2008; Martignetti and Brosius, 1993). Knockout of *BC1* in mice produces no overt phenotype in the cage, but behavioral phenotypes including reduced exploration and increased anxiety in less constrained environments, leading to reduction in survival rates (Lewejohann et al., 2004); see also below). Similarly, *NTAB* is a lncRNA that is expressed in developing and adult rat brain, where it is also found in neuronal processes (French et al., 2001).

LncRNAs are also involved in retinal development. In mouse, the lncRNA *TUG1* was identified as being up-regulated by taurine, a cysteine derivative required for proper neural development. TUG1 is expressed during retinal development and its inactivation causes loss or malformation of the outer segments of photoreceptors and affects the expression of other genes involved in eye development (Young et al., 2005). TUG1 is also upregulated in T-cell differentiation (Pang et al., 2009), adding to the list of intriguing similarities and functional parallels between the brain and the immune system (Habibi et al., 2009; Mattick and Mehler, 2008). TUG1 is highly conserved in mammals but not found in other vertebrates, as is also the case for the lncRNA *Gomafu* discussed earlier.

Regulation of lncRNA expression in the nervous system

The factors influencing the expression of lncRNAs, in general, and within the CNS in particular, are not well characterized. However, the expression of lncRNAs and protein-coding genes is mediated by some common regulatory mechanisms, including morphogens and transcription factors (Cawley et al., 2004; Dinger et al., 2008; Guttman et al., 2009; Mercer et al., 2010; Zhang et al., 2009). For example, the transcription factor, Pax2, plays a role in patterning of the mouse embryonic midbrain and hindbrain, and *Ncrms*, a lncRNA, is specifically regulated by Pax2 in this region (Bouchard et al., 2005). Intriguingly, *Ncrms* serves as a host gene for *miR-135a* (Rodriguez et al., 2004), an oncogenic miRNA that is dysregulated

in medulloblastoma (Ferretti et al., 2009). These observations illustrate the complex bidirectional relationships that exist between the genetic and epigenetic networks mediating oncogenesis.

In addition, recent evidence suggests not only that lncRNAs regulate epigenetic processes (Mattick et al., 2009) but also that perturbations of these processes can alter the expression of lncRNAs. For example, a study performed utilizing an *in vitro* OL developmental paradigm showed dynamic changes in long ncRNA expression profiles in response to treatment with trichostatin A (TSA), a histone deacetylase inhibitor that prevents maturation of OL progenitors by suppressing OL-specific gene expression (Mercer et al., 2010). These findings indicate that lncRNAs are regulated by the same transcriptional and epigenetic mechanisms as protein-coding genes.

Furthermore, a recent study found that the master epigenetic regulator, repressor element-1 silencing transcription factor/neuron-restrictive silencing factor (REST/NRSF), plays a role in modulating the expression of lncRNAs (Johnson et al., 2009). This study determined that a significant proportion of repressor element 1/neuron restrictive silencer element (RE1/NRSE) REST binding motifs are within 10 kb of lncRNAs and subsequently verified that a number of these lncRNAs are targets of REST regulation, in both mouse and human (Johnson et al., 2009). This study raises a number of interesting possibilities because the roles of REST in the CNS have been the focus of intense examination: Firstly, RE1-associated genes can be modulated by the independent or combinatorial actions of REST and CoREST, which both serve as dynamic modular platforms for the recruitment of a diverse array of factors that participate in genomic locus-specific and more widespread epigenetic remodeling (Qureshi and Mehler, 2009). Thus, CoREST is also likely to have a role in regulating the expression of a subset of lncRNAs. Secondly, distinct but overlapping cell type- and developmental stage-specific REST and CoREST transcriptional networks are implicated in modulating seminal neural developmental and homeostatic processes (Qureshi and Mehler, 2009). Therefore, lncRNAs that are regulated by REST and CoREST may play context-specific roles in NSC maintenance, neuronal and glial cell specification, progressive maturation, terminal differentiation, and activity dependent plasticity. Thirdly, many lncRNAs are bound to chromatin remodeling complexes containing CoREST or other factors, implying that chromatin remodeling complexes containing REST are similarly associated, directly or indirectly, with the function of lncRNAs (Khalil et al., 2009). In addition, deregulation of REST and CoREST functions is linked to a range of CNS pathologies that include cancer (i.e., glioblastoma, medulloblastoma, and neuroblastoma), neurodegenerative disease (i.e., Huntington's disease), neurodevelopmental disorders (i.e., Down syndrome and X-linked mental retardation [XLMR]), epilepsy, and ischemia (Qureshi and Mehler, 2009).

lncRNAs in diseases of the central nervous system

Neurodevelopmental disorders

LncRNAs are implicated in the pathophysiology of neurodevelopmental disorders associated with genomic imprinting, such as Prader-Willi syndrome (PWS) and Angelman syndrome (AS) (Koerner et al., 2009). In fact, a number of paternally expressed lncRNAs are derived from this imprinted cluster, although their specific roles are not well characterized. Some of these lncRNAs are responsible for epigenetic gene regulation within the imprinted cluster indirectly by serving as hosts for snoRNAs. Other lncRNAs may be directly involved in modulating gene expression within the imprinted cluster. For example, *Ube3a-as* is a lncRNA transcribed antisense to the maternally expressed *Ube3a* gene, a candidate gene for AS, suggesting that *Ube3a-as* may be responsible for repressing paternal *Ube3a* expression. Indeed, some studies have shown that repression of *Ube3a* is dependent on *Ube3a-as* (Chamberlain and Brannan, 2001; Johnstone et al., 2006). However, other data has demonstrated that silencing of paternal

Ube3a can occur in the absence of *Ube3a-as* and implies a more complex regulatory relationship underlying the imprinting of *Ube3a* (Le Meur et al., 2005). Intriguingly, a recent finding suggests that lncRNAs derived from the PWS-AS domain are nuclear-retained mediating the spatial organization of gene expression through dynamic modulation of nuclear architecture (Vitali et al., 2010).

LncRNAs may influence the pathogenesis of fragile X syndrome (FXS) and fragile X-associated tremor and ataxia syndrome (FXTAS), which are, respectively, caused by mutation and pre-mutation in the protein-coding *FMR1* gene. *FMR4* is a primate-specific lncRNA that appears to share a bidirectional promoter with the *FMR1* gene (Khalil et al., 2008). A recent study showed that, like *FMR1*, *FMR4* is also silenced in FXS patients because of a CGG expansion repeat in the 5′ untranslated region (UTR) of the *FMR1* gene and up regulated in pre-mutation carriers (Khalil et al., 2008). Further, short interfering RNA (siRNA) mediated knockdown of *FMR4* did not affect *FMR1* expression, suggesting that *FMR4* does not simply regulate *FMR1* and also that its expression might independently contribute to the clinical presentation of FXS. In fact, siRNA knockdown of *FMR4* resulted in alterations in cell cycle regulation and increased apoptotic cell death, whereas over-expression of *FMR4* caused an increase in cell proliferation. Similarly, another lncRNA, *ASFMR1*, which is derived from the *FMR1* locus, may also be important in mediating the complex clinical phenotypes associated with mutations at this genomic site. A recent study showed that *ASFMR1* is a spliced and polyadenylated antisense transcript, which overlaps the 5′ UTR CGG repeat region of *FMR1* (Ladd et al., 2007). Intriguingly, alternative splicing of *ASFMR1* seems to exhibit premutation-specific profiles. Further, like *FMR1* and *FMR4*, *ASFMR1* is also silenced in FXS patients and up regulated in pre-mutation carriers suggesting that a common process is responsible for regulating the expression these transcripts. In fact, binding sites for the CTCF chromatin insulator protein flank the CGG repeat suggesting that CTCF establishes the local chromatin structure at the repeats. Indeed, this mechanism plays a role in regulation of ncRNA transcription and establishing local chromatin structure at other expansion repeat disease loci (e.g., *DM1*) (Cho et al., 2005; Filippova et al., 2001).

In addition, lncRNAs may play a role in the development of brain malformations. Genetic defects of *Sox2* cause various syndromes of micropthalmia and of optic nerve hypoplasia associated with a number of CNS developmental abnormalities. The *Sox2OT* gene encompasses the entire Sox2 gene, is dynamically regulated in the CNS during development, and is implicated in modulating *Sox2* expression (Amaral et al., 2009). Therefore, a direct role for *Sox2OT* or an indirect role through effects on *Sox2* in mediating the clinical features of these and related syndromes cannot be excluded. Similarly, velocardiofacial syndrome (VCFS) or DiGeorge Syndrome is a clinically heterogeneous disorder characterized by developmental brain malformations, cognitive and behavioral abnormalities, and an increased risk of psychiatric disorders (i.e., schizophrenia and bipolar disorder). Intriguingly, VCFS is caused by deletions of the 2q11.2 chromosomal region that includes *DGCR5*, a REST regulated lncRNA, which suggests a potential role for this lncRNA in mediating neural developmental processes and the phenotype of this disorder (Johnson et al., 2009).

Further, lncRNAs may be involved in the pathobiology of Down's syndrome (DS). *NRON* is a lncRNA that mediates the cytoplasmic to nuclear shuttling of the NFAT transcription factor (Willingham et al., 2005). In animal models, deregulation of the *DSCR1* and *DYRK1A* genes act synergistically to prevent nuclear occupancy of NFATc transcription factors leading to reduced NFATc activity and to many features of DS, suggesting a potential link between *NRON* activity and DS pathophysiology (Arron et al., 2006).

Neurodegenerative disorders

A lncRNA may influence the pathogenesis of Alzheimer's disease (AD). BACE1 (β-site amyloid precursor protein-cleaving enzyme 1) is an enzyme that cleaves amyloid precursor protein (APP) and generates amyloid β (Aβ) peptides, which form amyloid plaques in the brains of patients with AD. The mechanisms that regulate the expression and function of BACE1 in AD are complex and not completely understood, but they include a conserved antisense transcript, *BACE1-AS*, which modulates *BACE1* gene expression. *BACE1-AS* levels are increased in tissues from AD patients and in an APP transgenic mouse model of AD (Faghihi et al., 2008). In addition, neuronal cells exposed to diverse cell stressors (e.g., reactive oxygen species, chronic hypoxia, and $A\beta_{1-42}$) exhibited increased expression and nuclear to cytoplasmic translocation of *BACE1-AS* transcripts, where *BACE1-AS* promotes the stabilization of *BACE1* mRNA and up-regulation of BACE1 protein, which, in turn, leads to production of Aβ peptide. These findings imply that *BACE1-AS* is deregulated in AD, which induces feed-forward regulation of BACE1, increases Aβ levels, and thus may promote the pathogenesis of AD. These observations are particularly interesting because modulating amyloidogenic APP metabolism represents an important candidate strategy for treating AD, and targeting *BACE1-AS* may circumvent some of the challenges posed by current approaches aimed at inhibiting β-secretase activity. In fact, identification of potent and selective β-secretase inhibitors has been difficult, with only a single β-secretase inhibitor drug candidate, CTS-21166, having advanced into Phase I clinical trials because of medicinal chemistry issues, such as the properties of the β-secretase active site (Frisardi et al., 2009).

Another study utilized human AD brain tissue to link alterations in levels of a lncRNA, *BC200*, with AD pathogenesis (Mus et al., 2007). Increased levels of *BC200* were found in brain regions that are preferentially affected in AD, such as Brodmann's area 9 and the hippocampus, which correlated with disease severity measured by Clinical Dementia Rating scores. Further, in advanced stages of AD, *BC200* was mis-localized and clustered in the perikaryon. These observations suggest that deregulation of these synaptic lncRNAs is involved in the synaptic and neural network dysfunction that is found in both early and later stages of AD.

In addition, a lncRNA also plays a key role in the pathogenesis of spinocerebellar ataxia type 8 (SCA8), an autosomal dominant disorder caused by an expansion repeat. SCA8 is characterized by bidirectional transcription of this expansion repeat from opposite strands forming both a protein-coding transcript encoding a polyglutamine expansion, ATXN8, and a lncRNA transcript containing a CUG expansion, *ATXN8OS* (Moseley et al., 2006). Both of these are implicated in the molecular pathophysiology of the disease implying that SCA8 may be caused by toxic protein and RNA functions (Daughters et al., 2009; Koob et al., 1999; Moseley et al., 2006). Indeed, a recent study found that the expanded *ATXN8OS* transcript accumulates in ribonuclear inclusions in the cerebellar cortex (i.e., Purkinje cells, Bergmann glia, and molecular layer interneurons) of SCA8 patients and in the cerebellar cortex and the deep cerebellar nuclei of transgenic mice expressing the SCA8 expansion (Daughters et al., 2009). These inclusions co-localized with splicing factor, MBNL1. In addition, evaluation of the GABA-A transporter 4 (GAT4) revealed dysregulation of CUGBP1-MBNL1-mediated alternative splicing and loss of GABAN-mediated inhibition within the granular cell layer, which is a hallmark of the disease. Together, these observations suggest that the mutant *ATXN8OS* transcript contributes to SCA8 pathogenesis by altering the activity of MBNL/CELF alternative splicing proteins. This mechanism is similar to the pathogenic role played by the mutant *DMPK* transcript that causes myotonic dystrophy type 1 (DM1), which is encoded by a protein-coding gene containing a CUG expansion repeat in its 3′-untranslated region (Lee and Cooper, 2009). Intriguingly, these examples suggest a common pathogenic mechanism for both lncRNAs and protein-coding RNAs.

Furthermore, a lncRNA may be implicated in amyotrophic lateral sclerosis (ALS). Mutations in the *FUS/TLS* gene cause a subset of ALS cases and, intriguingly, FUS/TLS acts as an RNA-binding protein (RBP) that can be recruited by a lncRNA to the genomic locus encoding cyclin D1, where it represses *cyclin D1* transcription (Wang et al., 2008). Because members of the cyclin-dependent kinase (Cdk) family are implicated in mediating apoptotic death of neurons, these observations may link aberrant FUS/TLS to neurodegeneration in ALS through abnormal lncRNA-mediated cyclin D1 transcriptional regulation. This mechanism may also influence the pathogenesis of other neurodegenerative diseases because FUS/TLS is also implicated in the neuropathology of spinal cerebellar ataxia types 1–3, dentatorubral-pallidoluysian atrophy, and Huntington's disease (HD) (Doi et al., 2008; Doi et al., 2009).

HD is particularly interesting because it is caused by an expansion repeat mutation in the *Htt* gene, which encodes a mutant protein with a polyglutamine stretch that seems to be at the nexus of PRC2-, REST-, and ncRNA-associated transcriptional dysregulation, one of the hallmarks of HD (Benn et al., 2008; Johnson et al., 2008; Marullo et al., 2008; Packer et al., 2008; Qureshi and Mehler, 2009; Seong et al., 2010; Zuccato et al., 2007). Indeed, mutant Htt promotes aberrant nuclear-cytoplasmic trafficking of REST and leads to the deregulation of REST target gene expression in tissues from animal models of HD and human HD. These genes include both protein-coding genes as well as ncRNAs, such as miRNAs. Because REST also regulates the expression of lncRNAs, it is therefore likely that HD tissues are also characterized by dysregulation of lncRNA expression. Furthermore, if a subset of lncRNAs binds to REST chromatin-remodeling complexes as it does to CoREST macromolecular complexes, then the potential disruption of REST-regulated lncRNA expression in HD may lead to additional disturbances in lncRNA-mediated chromatin and transcriptional regulatory processes through a feed-forward mechanism. In fact, a recent study demonstrated that Htt acts as a molecular facilitator of the PRC2 complex, which is bound by a subset of lncRNAs, providing further evidence for a lncRNA-mediated final common pathway for transcriptional dysregulation and, thus, neurodegeneration in HD (Seong et al., 2010).

Neuroimmunological disorders

Multiple sclerosis (MS) is a complex autoimmune disease, and recent immunopathological studies implicate abnormal $CD8^+$ T cell activity in the pathophysiology of MS (Friese and Fugger, 2009). Because lncRNAs are involved in $CD8^+$ T cell differentiation and activation, lncRNAs may also be important in the development and progression of MS. In fact, lncRNA transcripts derived from the mouse T early α (TEA) promoter are responsible, in part, for regulating downstream promoter usage and, thus, for generating the diversity of the T cell receptor repertoire (Abarrategui and Krangel, 2007). Further, a recent study utilizing mouse $CD8^+$ T cells identified hundreds of lncRNAs that are dynamically expressed during T cell differentiation and activation, including many transcribed from genomic loci encompassing protein-coding genes important for immune system functions and potentially for MS pathogenesis (Pang et al., 2009). For example, the mouse *IL2RA* locus encodes a number of lncRNAs that are nested within individual introns of the *IL2RA* gene, and the expression of one of these lncRNAs, *M21981*, is strongly up regulated with T cell activation. Homologous lncRNAs are present within the human *IL2RA* gene locus, and intriguingly, the human *IL2RA* locus has been identified by genome-wide association studies (GWAS) with susceptibility to MS (Hafler et al., 2007). In addition, *Tmevpg1* is another lncRNA that may be involved in MS. It is found in human and mouse immune cells and is transcribed from a cluster of cytokine genes, which includes γ-interferon (Vigneau et al., 2003). In mouse, *Tmevpg1* is believed to play a role in controlling the persistence of Theiler's murine encephalomyelitis virus (TMEV) infection (Vigneau et al., 2003). Notably, TMEV infection serves as an experimental model for MS because it is characterized, in part, by chronic inflammatory demyelination with oligodendrocyte apoptosis and axonal degeneration

(Tsunoda and Fujinami, 2009). These observations suggest that lncRNAs are responsible, at least in part, for mediating immune responses in the CNS.

Neuro-oncological disorders

LncRNAs are implicated in promoting the acquisition and maintenance of cell identity, which are perturbed in cancer, suggesting that some lncRNA species may be important in the process of cellular transformation. In fact, lncRNAs are important for mediating a range of processes that are aberrant in cancer, such as X chromosome inactivation (XCI), genomic imprinting and transcriptional regulation, and a number of systemic cancer phenotypes, including leukemia, colon cancer, prostate cancer, breast cancer and hepatocellular carcinoma, exhbit dysregulation of lncRNAs as a primary feature (Calin et al., 2007; Fu et al., 2006; Guffanti et al., 2009; Lin et al., 2007; Pibouin et al., 2002). Perturbations in lncRNA expression are also associated with CNS tumors.

H19 is an imprinted lncRNA expressed from the maternal allele that is located in a gene cluster, which also includes *IGF2. H19* is expressed during embryogenesis, and subsequent deregulation of *H19* and genes in the imprinted cluster is linked directly to cellular transformation and also associated indirectly with the development of a number of other tumors, including medulloblastomas, meningiomas and gliomas. For example, a study of medulloblastomas and medulloblastoma cell lines showed partial loss of imprinting (LOI) and biallelic expression of *H19* (Albrecht et al., 1996). An examination of meningiomas (World Health Organization grades I-III) demonstrated more robustly that the imprinting status of *H19* is perturbed with LOI in a significant number of these tumors (Muller et al., 2000). Another study performed in $CD133^{+}$ and $CD133^{-}$ glioblastoma derived primary cell lines revealed levels of *H19* expression that were relatively high and low, respectively (Beier et al., 2007). Mechanistically, *H19* is a target of the GLI1 transcription factor, which mediates SHH signaling and is amplified more than 50-fold in human gliomas (Kinzler et al., 1987; Yoon et al., 2002). *H19* has also been linked to the tumor suppressor, p53, which negatively regulates its expression (Dugimont et al., 1998) and the oncogene, *c-myc*, which positively regulates its expression in diverse cell types including T98G human glioblastoma cells (Barsyte-Lovejoy et al., 2006). In addition, *H19* transcription is positively regulated by the cell cycle regulatory factor, E2F1, during the S-phase of growth-stimulated cells (Berteaux et al., 2005). Intriguingly, a lncRNA has recently been described that is transcribed antisense to *H19* but not imprinted, implicated in regulating IGF2, and overexpressed in human cancer cells (Berteaux et al., 2008). The presence of this antisense lncRNA and its deregulation in cancer further highlights the complexity of epigenetic regulation within this gene cluster and may be relevant for CNS tumors.

Similarly, *anti-NOS2A* is a lncRNA that is expressed in meningiomas and glioblastomas from a genomic locus that evolved by duplication of the *NOS2A* gene followed by internal DNA inversion (Korneev et al., 2008). This intronless, non-polyadenylated lncRNA is implicated in negatively regulating the expression of *NOS2A*, which plays a role in neuronal differentiation of ES cells (Korneev et al., 2008). Further, *NOS2A* is induced in human brain tumors including glioblastoma and in glioma cell lines, where it can differentially influence the efficacy of chemotherapeutic agents (Broholm et al., 2003). This example may be particularly important because many other genes that are deregulated in CNS tumors, including oncogenes and tumor suppressor genes, have antisense lncRNAs encoded in the genome (Grinchuk et al., 2010).

Furthermore, abnormalities in pathways related to lncRNA regulation and function are associated with CNS tumors, supporting the conclusion that lncRNAs are important in modulating cellular transformation. For example, a recent study found a subset of p53 *cis*-regulatory element-associated lncRNAs that are specifically induced in response to DNA damage in p53 wild type cells but not in $p53^{-/-}$ cells (Guttman et al., 2009). These and other

lncRNAs may be involved in the p53-mediated induction of cell-cycle arrest, DNA repair and apoptosis that protect neural cells from DNA damage and transformation (Tedeschi and Di Giovanni, 2009). REST also regulates lncRNA expression, and abnormalities of REST expression and function are associated with the development of medulloblastomas, neuroblastomas and glioblastomas (Qureshi and Mehler, 2009). These observations, coupled with the potential roles of lncRNAs in establishing and maintaining neural cell identity, suggest that REST-mediated lncRNA dysregulation may contribute to the development of these tumors. Disruption of chromatin regulation may be one the potential mechanisms by which lncRNAs play roles in oncogenesis. In fact, many lncRNAs participate in chromatin modulation through interactions with PRC2, and recent evidence suggests that genes epigenetically deregulated in glioblastoma are highly enriched for targets of PRC2 (Martinez et al., 2009). Further, subunits of the PRC2 complex, such as EZH2, are implicated in the development of glioblastomas and maintenance of cancer initiating stem cells (Abdouh et al., 2009). Similarly, many lncRNAs participate in chromatin modulation through interactions with CoREST, which is thought to modulate genes in key pathways responsible for CNS tumors (Abrajano et al., 2009a; Abrajano et al., 2009b).

Other neurological and psychiatric disorders

LncRNAs, such as *BC1/BC200* and *Evf2*, may be involved in mediating the process of epileptogenesis because they modulate neural network plasticity and excitability (Mattick and Mehler, 2008; Mehler, 2008; Mercer et al., 2008a). For example, a recent study showed that $BC1^{-/-}$ animals exhibit neuronal hyperexcitability, significantly elevated gamma frequency oscillations on cortical electroencephalogram (EEG) recordings, and epileptogenesis (Zhong et al., 2009). Similarly, *Evf2* mouse mutants display abnormal development of GABAN circuitry in the hippocampus and dentate gyrus leading to a reduction in inhibitory synaptic activity suggesting a predisposition to neuronal hyperexcitability (Bond et al., 2009).

LncRNAs may also influence the pathogenesis of Restless Legs Syndrome (RLS), a sensorimotor disorder that is associated with abnormal cerebellar activity (Bucher et al., 1997). The leading genetic risk factor for this disorder is variation at the *Meis1* gene locus, which encodes a homeobox protein with roles in development and oncogenesis (Winkelmann et al., 2007). A recent study suggested that the predisposition to RLS results from reduced expression of *Meis1* mediated by intronic *cis*-regulatory elements (Xiong et al., 2009). Intriguingly, in the developing mouse brain, *Meis1* is co-expressed in the developing cerebellar granule cell layer along with a genomically-associated lncRNA *AK042766* (Ponjavic et al., 2009). These observations raise the interesting possibility that lncRNA mediated mechanisms may regulate the expression of the *Meis1* gene during development and adult life, thereby modulating the pathogenesis of this complex disorder.

In addition to neurological diseases, a number of psychiatric disorders have also been associated with lncRNAs. Specifically, the disruption of the *DISC* genomic locus, which encodes both the *DISC1* protein-coding gene and the *DISC2* lncRNA, has been linked in a number of genetic analyses to the risk of developing schizophrenia, schizoaffective disorder, bipolar disorder, major depression, and autistic spectrum disorders (Chubb et al., 2008; Millar et al., 2000; Williams et al., 2009). *DISC2* overlaps *DISC1* and is transcribed in the opposite direction. Like other antisense transcripts, *DISC2* is implicated in regulating the expression of its partner, *DISC1*, which modulates multiple aspects CNS structure and function including embryonic and adult neurogenesis (Brandon et al., 2009). However, *DISC2* may also represent an important candidate gene for psychiatric disease separately from its effects on *DISC1* (Chubb et al., 2008).

Perspectives

Recent studies have dramatically changed our understanding of the genome and the transcriptome, and encouraged us to focus on examining the roles not only of protein-coding genes but also of diverse classes of interleaved ncRNAs to understand biological systems in general, and the sophistication of the CNS in particular. Indeed, RNA molecules have properties that make them uniquely suited to perform a spectrum of regulatory, structural, and catalytic functions. For example, RNAs can efficiently serve as highly sensitive biosensors for interoceptive and environmental signals and can dynamically store, process and integrate information through sequence-specific, digital, and conformational, analog, features (St Laurent and Wahlestedt, 2007). Because of these properties, ncRNAs can specifically regulate the temporal and spatial deployment of genes and functional gene networks by modulating the transcription, post-transcriptional processing, and translation of mRNAs. These functions are critical in the CNS, where ncRNAs also play additional roles in mediating bidirectional axodendritic transport and activity-dependent plasticity. Short ncRNAs, such as miRNAs, have been studied in detail, but in this review we surveyed data that indicates lncRNAs, the most abundant and least studied class of ncRNAs, are similarly important for mediating nervous system development, homeostasis, stress responses, plasticity and the pathophysiology of a spectrum of CNS pathologies including neurodevelopmental, neurodegenerative and neuroimmunological disorders, primary brain tumors, and psychiatric diseases.

It also appears increasingly likely that ncRNAs may be the primary substrate for environment-epigenome interactions mediated by RNA editing, especially in the brain. There are two classes of RNA editing/DNA recoding enzymes in animals, which function by deamination to catalyze adenosine-to-inosine (A-I) and cytidine-to-uridine (C-U) conversions (adenosine deaminases acting on RNAs [ADARs] and apolipoprotein B mRNA editing enzymes, catalytic polypeptide-like [APOBECs], respectively) (Bass, 2002; Navaratnam and Sarwar, 2006; Valente and Nishikura, 2005). ADARs are highly expressed in brain and ADAR3 is both vertebrate- and brain-specific. There is extensive A-I editing of RNAs in the brain, which is far more intensive in humans than mouse and mostly occurs in noncoding transposon-derived transcribed sequences (Athanasiadis et al., 2004; Blow et al., 2004; Kim et al., 2004; Levanon et al., 2004; Levanon et al., 2005; Neeman et al., 2006). The APOBEC C-U editing enzymes are vertebrate-specific and have expanded greatly in mammals and especially in the primates, where the APOBEC3 subfamily shows strong signatures of positive selection (Sawyer et al., 2004; Zhang and Webb, 2004). The functions of the various orthologs of the APOBEC C-U editing enzymes are not well understood, but they are, in part at least, variously involved in the class switch recombination and somatic hypermutation of immunoglobulins (see (Navaratnam and Sarwar, 2006)) and the control of the movement of retroviral sequences and transposable elements such as LINEs (Aguiar and Peterlin, 2008; Schumann, 2007). These sequences are differentially expressed during development (Faulkner et al., 2009), including in the brain where they have been suggested to contribute to somatic neuronal diversity (Coufal et al., 2009). Given that the locus-specificity of epigenetic marks appears to be regulated by lncRNAs (Mattick et al., 2009), this raises the prospect that the editing of these transcripts modulates the epigenetic trajectories that underpin brain development and function (Mattick, 2009b; Mattick et al., 2009) and that the expansion of RNA editing, concomitant with the selection of responsive cassettes spread by retrotransposition, was central to the evolution of higher order brain function and cognition (Mattick and Mehler, 2008). If so, variation in, and/or dysregulation, of this system and its target repertoire of protein-coding and regulatory RNAs may play a significant role in psychological and cognitive variation, as well as various disorders. Indeed there is evidence that aberrant RNA editing is associated with an increased risk of neurodevelopmental, neurodegenerative and neuropsychiatric diseases (Maas et al., 2006; Valente and Nishikura, 2005) as well as primary brain tumors (Cenci et al., 2008).

A raft of transcriptomic and functional studies are now needed to poll the full range of lncRNAs expressed in different parts of the CNS and to further elucidate the epigenetic and other functional contributions made by lncRNAs and RNA editing to the complexity of CNS structure and function, as well as to characterize their roles in disease processes. Indeed, GWAS have been performed for many CNS disorders and revealed a number of susceptibility loci but only a paucity of disease-causing protein-coding genes (Simon-Sanchez and Singleton, 2008). Because a significant percentage of disease association signals map to non-protein-coding regions of the genome and because of the abundance of antisense and other lncRNAs encoded by the genome, it is important to consider whether these previously identified disease association signals are linked to lncRNAs, although it is a challenging problem to determine the causative variation in such sequences, in contrast to identifying nonsense or missense mutations in protein-coding exons (Mattick, 2009a). In addition, therapeutic strategies that target endogenous mRNA molecules, such as those employing RNA interference (RNAi) and other customized oligonucleotide approaches with the capacity to reprogram disease-associated mRNAs, are now being developed (Wood et al., 2007). These approaches may readily be adapted to target lncRNAs whose sequence or expression may be aberrant in CNS disorders. Together, these observations suggest that lncRNAs represent a versatile class of factors that are centrally important to the modulation of diverse CNS processes and may represent the major layer underlying the genetic programming of brain development and its ability to learn, which may potentially be utilized for developing novel diagnostic and therapeutic strategies to combat CNS disorders.

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Abbreviations

Aβ	amyloid β
AD	Alzheimer’s disease
ADAR	adenosine deaminases acting on RNAs
ALS	amyotrophic lateral sclerosis
APOBEC	apolipoprotein B mRNA editing enzymes, catalytic polypeptide-like
APP	amyloid precursor protein
AS	Angelman syndrome
BIC	B-cell integration cluster
CNS	central nervous system
DM1	myotonic dystrophy
DS	Down syndrome
EEG	electroencephalogram
ES	embryonic stem
FXS	fragile X syndrome
FXTAS	fragile X-associated tremor and ataxia syndrome
GABAN	GABAergic neuron

GAT4	GABA-A transporter 4
GWAS	genome wide association study
HD	Huntington's disease
lncRNA	long non-coding RNA
LOI	loss of imprinting
miRNA	microRNA
MS	multiple sclerosis
NPC	neural precursor cell
NSC	neural stem cell
ncRNA	non-coding RNA
OL	oligodendrocyte
PASR	promoter-associated small RNA
PcG	Polycomb group
piRNA	piwiRNA
PWS	Prader-Willi syndrome
RBP	RNA binding protein
RE1/NRSE	repressor element 1/neuron restrictive silencer element
REST/NRSF	repressor element-1 silencing transcription factor/neuron-restrictive silencer factor
RNAi	RNA interference
RLS	restless legs syndrome
rRNA	ribosomal RNA
SCA8	spinocerebellar ataxia 8
SHH	Sonic hedgehog
siRNA	short interfering RNA
snoRNA	small nucleolar RNA
TEA	T early α
tiRNA	transcription initiation RNA
TMEV	Theiler's murine encephalomyelitis virus
tRNA	transfer RNA
TSA	trichostatin A
UTR	untranslated region
VCFS	velocardiofacial syndrome
XCI	X chromosome inactivation
XLMR	X-linked mental retardation

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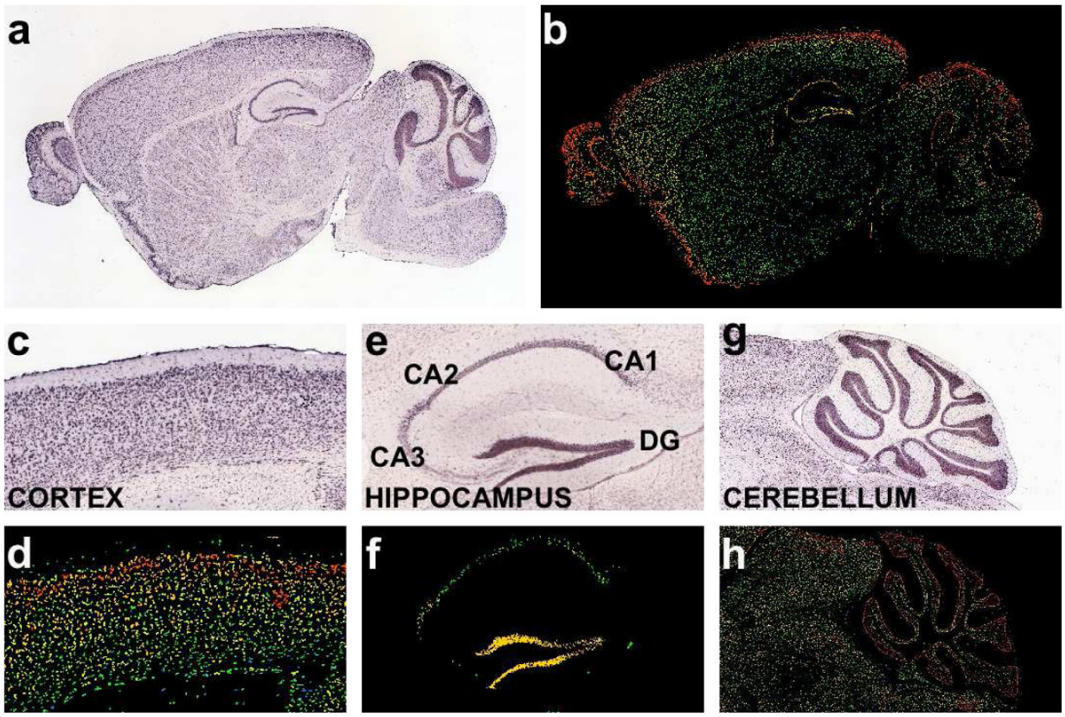

Figure 1. Illustrative examples of regionally enriched long non-coding RNA expression profiles in adult mouse brain

(a) In situ hybridization and (b) expression views displaying expression levels (red - high, yellow - medium, green - low) for *AK019375*, which is broadly but preferentially expressed in the olfactory bulb, hippocampus, and cerebellar cortex. (c) In situ hybridization and (d) expression views for *AK017599*, which is enriched in multiple layers of the cerebral cortex. (e) In situ hybridization and (f) expression views for *AK157548*, which is enriched in hippocampal CA1-3 subregions and the dentate gyrus (DG). (g) In situ hybridization and (h) expression views for *AK050124*, which is enriched in the granule cell and Purkinje cell layers of the cerebellum *(Images courtesy of the Allen Brain Atlas - Allen Institute for Brain Science, Seattle).*