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Long non-coding RNAs in psychiatric disorders

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Abstract

Long non-coding RNAs (lncRNAs) are non-protein coding transcripts longer than 200 nucleotides. Many of these lncRNAs have regulatory functions and have recently emerged as major players in governing fundamental biological processes. Here we review the definition, distribution, identification, databases, analysis, classification and functions of lncRNAs. We also discuss the potential roles of lncRNAs in the etiological processes of psychiatric disorders and the implications for clinical diagnosis and treatment.

Keywords

LncRNAs; psychiatric disorders

Although only 1.2% of the mammalian genome encodes proteins, the genome is almost entirely transcribed, generating an enormous number of non-protein coding RNAs that include tens of thousands of long non-coding RNAs (lncRNAs) (> 200 nt) (Carninci *et al.*, 2005; Mercer *et al.*, 2009; Perkel, 2013). lncRNAs resemble protein-coding messenger RNAs (mRNAs) in sequence, but they can be distinguished based on multiple other features including expression levels, average number of exons, gene length, number of alternatively spliced isoforms, degree of tissue-specificity, signatures of conservation, presence of 5′ caps and polyA tails, rates of degradation/turn-over, etc. Expression of lncRNAs is tissue-, cell

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Conflict of interest

Authors declare no conflict of interest related to this review.

type- and developmental stage-specific (Amaral *et al.*, 2008; Amaral and Mattick, 2008; Mercer *et al.*, 2008). lncRNAs are expressed in various tissues (e.g., livers (Dong *et al.*, 2014)) with over half of all lncRNAs expressed in the brain (Mercer *et al.*, 2008). Most lncRNAs are permanently localized in the nucleus (Kapranov *et al.*, 2007), with exceptions showing functionality in the cytoplasm (Carrieri *et al.*, 2012; Kapranov *et al.*, 2007; Mercer *et al.*, 2009; Qureshi and Mehler, 2013; Taft *et al.*, 2010). This specificity of tissue and subcellular distributions strongly suggests that the expression of lncRNAs is under precise regulatory control. This review summarizes the identification, databases, classification, analysis and functions of lncRNAs and their roles in various psychiatric disorders.

Identification of lncRNAs

Both RNA-Seq and microarray hybridization technologies can be used to identify lncRNAs, each with distinct advantages and limitations. Traditionally, lncRNAs can be identified by sequencing together with mRNAs and other RNAs using whole-transcriptome RNA-Seq technology. However, because lncRNAs tend to be expressed at much lower levels than mRNAs (Cabili *et al.*, 2011; Cawley *et al.*, 2004; Guttman *et al.*, 2010; Kampa *et al.*, 2004), to achieve adequate coverage of lncRNAs, the read depths of mRNAs will have to exceed around 10 times of the normal need in whole-transcriptome sequencing (Cabili *et al.*, 2011; Derrien *et al.*, 2012; Guttman *et al.*, 2010; Yan *et al.*, 2013). In addition, many lncRNAs are still undetectable by whole-transcriptome RNA-Seq even with the increase in overall read depth (Toung *et al.*, 2011). In a word, this technique may not be the most effective to reliably and precisely quantify the low abundance lncRNA expression (Labaj *et al.*, 2011). Instead, targeted RNA-Seq technology may better address these coverage issues, including lncRNA capture or rRNA+PolyA depletion to enrich lncRNAs before sequencing. Alternatively, some special microarrays can be used to identify low-abundance lncRNAs. For example, Arraystar Human LncRNA Microarray V3.0 (www.arraystar.com) has been designed to collect only lncRNAs and proximate mRNAs, so that users can enhance the expression signals of lncRNAs to a sufficient level by increasing the template input, and avoid cost on other unwanted sequences that whole-transcriptome RNA-Seq usually produces. However, the technical limitations of microarrays for the detection of low-abundant transcripts are well known, including low signal-to-noise ratios, and have in the past led to significant over-estimation of the extent and levels of intergenic transcription.

Many lncRNAs overlap with mRNAs, which brings a big challenge for researchers to distinguish between these two classes of transcripts if when the traditionally 3′-biased microarray probes are used, because these probes target the 3′UTRs that are shared by both types of transcripts. Transcript-specific probes that target only the exons or the splice junctions of each lncRNA transcript may enable more reliable and accurate detection of each individual transcript. Alternatively, directional RNA-Seq may also have significant advantages in addressing the issue of overlapping.

Many lncRNAs identified by RNA-Seq and microarray hybridization technologies fail to show conservation, and thus their functions are unclear. On this point, chromatin signature represents a distinct, third approach and may confer advantages (www.arraystar.com). On the basis of exploiting chromatin structure, this method identifies sets of functional large

intergenic non-coding RNAs (lincRNAs) that show a high degree of evolutionary conservation. Mikkelsen et al. (2007) created a genome-wide chromatin-state map using chromatin immunoprecipitation followed by massively parallel sequencing (ChIP-Seq) (Mikkelsen *et al.*, 2007). This map marks the 'K4–K36 domains' from trimethylation of lysine 4 of histoneH3 (H3K4me3) at the promoters to trimethylation of lysine 36 of histone H3 (H3K36me3) along the length of the transcribed genomic regions. Guttman et al. (2009) searched for K4–K36 domains in this genome-wide chromatin-state map that reside outside known protein coding gene loci and do not overlap known miRNAs or endogenous short interfering RNAs (siRNAs), and then systematically revealed 1,675 K4–K36 (1,250 conservatively defined) domains (Guttman *et al.*, 2009). Most of these K4–K36 domains encode functional lincRNAs that are highly conserved in nucleotide sequence and chromatin structure and are implicated in diverse biological processes including transcription of these sites (Guttman *et al.*, 2009).

Databases of lncRNAs

The sequence information for lncRNAs are available in several public databases, including RefSeq release 60, UCSC hg19, GENCODE 17, RNAdb 2.0 (Pang *et al.*, 2007), NRED (Dinger *et al.*, 2009), Valadkhan Lab Functional lncRNA Database, LncRNADisease, lncRNAdb, NONCODE (Bu *et al.*, 2012a) and Ensembl 37.59. Among them, RefSeq, GENCODE, Ensembl and UCSC are gene annotation databases that include varying numbers of annotated lncRNAs; Valadkhan Lab Functional lncRNAs, LncRNADisease and lncRNAdb are lncRNA databases; RNAdb 2.0 and NONCODE are RNA databases including lncRNAs; and NRED is a microarray expression database of lncRNAs. Some databases include unannotated RNAs that are not well defined and might have little or no expression data. To extract effective lncRNAs from these unannotated RNAs, one can screen these databases according to certain computational pipeline. For example, one can filter transcripts of known coding RNAs, structural RNAs (e.g., tRNAs, rRNAs), small ncRNAs, and highly similar sequences, examine whether each transcript contains a significant open reading frame (ORF), and, finally, retain only multiexonic transcripts > 200 nt.

Several ground-breaking landmark publications also reported lncRNAs [30,37–50]. These lncRNAs (www.arraystar.com) include: **(1)** LincRNAs (1st set). Khalil et al. identified and characterized 3,289 lincRNAs by searching for intergenic K4-K36 domains in genome-wide chromatin-state maps (Khalil *et al.*, 2009). **(2)** LincRNAs (2nd set). Cabili et al. defined a reference catalog of more than 8,000 lincRNAs using RNA-Seq data and public database information (Cabili *et al.*, 2011). A total of 14,353 transcripts expressed from 4,662 stringently-defined lincRNAs were identified. **(3)** Transcribed Ultra-Conserved Regions encoding lncRNAs (T-UCRs). Ultra-conserved regions (UCRs) are intra- and intergenic sequences with >200nt that are 100% identical among humans, mice, and rats. 481 UCRs were identified by Bejerano et al. (Bejerano *et al.*, 2004). 475 UCRs encode T-UCRs. **(4)** HOX LncRNAs. Rinn et al. identified 407 transcribed regions within the four HOX loci in humans (101 HOX exons, 75 introns and 231 intergenic ncRNA transcripts) (Rinn *et al.*, 2007). **(5)** LncRNAs with Enhancer-like Function (LncRNA-a). Orom et al. identified about 3,000 lncRNAs with lncRNA-a using the GENCODE annotation (Harrow *et al.*, 2006; Orom *et al.*, 2010). **(6)** Finally, some lncRNAs with ORFs. Some sense-overlapping lncRNAs have

an ORF that shares the same start codon as a protein-coding transcript; however, these short ORFs are unlikely to encode a protein for some reasons. About 709 sense-overlapping lncRNAs with such ORF types have been reported (www.arraystar.com). Actually, a large proportion of these lncRNAs have already been deposited into the above databases. Some of the putative lncRNAs lack expression data or have not been characterized in details either, and thus the effective lncRNAs should be extracted using the computational filtering pipelines as described above.

Classification and functions of lncRNAs

LncRNAs have recently emerged as major players in governing fundamental biological processes. Recent evidence suggests that lncRNAs are involved in a wide variety of cellular functions, including epigenetic silencing, transcriptional regulation, RNA processing and modification (Amaral *et al.*, 2008; Mercer *et al.*, 2009; Wang *et al.*, 2008), and implicated in neural plasticity (Sartor *et al.*, 2012), neuropathological process (Bu *et al.*, 2012b), neurotransmission (Qureshi *et al.*, 2010), and stress response (Sartor *et al.*, 2012). A large proportion of lncRNAs may *cis*-regulate their neighboring protein-coding genes, so analyzing the genomic context of lncRNAs can help predict their functional roles. According to the positional relationship between lncRNAs and their associated protein-coding genes, lncRNAs can be classified as intergenic, intronic, antisense, sense overlapping, and bidirectional lncRNAs (www.arraystar.com) (Figure 1). 1. **Intergenic lncRNAs (lincRNAs)** are located between protein-coding genes and are at least 1 kb away from the nearest protein-coding genes. For example, a sense lincRNA, i.e., proliferating cell nuclear antigen pseudogene 1 (*PCNAP1*; 1,055 nt), is located between *ADH4* and *ADH6*. LincRNAs are implicated in diverse biological processes, including embryonic stem cell pluripotency, cell-cycle regulation and immune surveillance. They usually interact with chromatin modifying proteins (PRC2, SCMX and CoREST) to regulate the expression of proximate genes (Khalil *et al.*, 2009). **2. Intronic lncRNAs** are located within the intron of annotated protein coding genes. Most of them show the same tissue expression patterns as the host genes, and may stabilize the host transcripts or regulate their alternative splicing (Nakaya *et al.*, 2007). **3. Sense-overlapping lncRNAs** can be considered transcript isoforms of protein-coding mRNAs, because they overlap with the host gene on the same genomic strand. The majority of these IncRNAs lack substantial open reading frames (ORFs) for protein translation. Some others contain ORFs that share the same start codons as the host transcripts but are unlikely to encode a protein because of non-sense mediated decay (NMD) that limits the translation of mRNAs with premature termination stop codons and triggers NMD-mediated destruction of the mRNA, or because of an upstream alternative ORF which inhibits the translation of the predicted ORF. Some sense-overlapping lncRNAs share stop codons with host mRNAs on the same genomic strand. For example, *IPO11-LRRC70* read-through overlaps *IPO11* mRNA and shares a stop codon on the same genomic strand. This lncRNA is close to the peak association marker rs7445832 ($p=6.2\times10^{-9}$) for alcohol and nicotine codependence in European-Americans and Australians as identified in a GWAS (Zuo *et al.*, 2013). **4. Antisense-overlapping lncRNAs:** Natural antisense transcripts (NATs) are RNA molecules that are transcribed from the opposite strand of many protein coding (sense) genes and overlap in part with well-defined spliced sense or intronless sense mRNAs. NATs bind to

sense RNA and/or proteins to regulate transcription and translation. For example, a large antisense-overlapping lncRNA, i.e., *LOC100507053* (213kb), covers *ADHs* 5, 4, 6 and 1A genes that form a risk genomic region for alcoholism demonstrated by numerous GWASs and candidate gene studies (Gelernter *et al.*, 2009; Li *et al.*, 2011, 2012). This class of lncRNA frequently uses diverse transcriptional and post-transcriptional regulatory mechanisms to fulfill a wide variety of biological roles (Sartor *et al.*, 2012). These lncRNAs usually have a tendency to undergo fewer splicing events and typically show lower abundance than sense transcripts (He *et al.*, 2008). The basal expression levels of antisense-overlapping lncRNAs and sense mRNAs in different tissues and cell lines can be either positively or negatively regulated (Katayama *et al.*, 2005; Okada *et al.*, 2008). **5. Bidirectional lncRNAs** are oriented head to head with a protein-coding gene within 1kb. A bidirectional lncRNA transcript exhibits an expression pattern similar to its host gene, suggesting that they may be subject to shared regulatory pressures. However, discordant expression relationships between bidirectional lncRNAs and protein coding gene pairs have also been identified, challenging the assertion that lncRNA transcription occurs solely to "open" chromatin to promote the expression of neighboring coding genes (Chakalova *et al.*, 2005; Mercer *et al.*, 2008; Struhl, 2007).

Additionally, some lncRNAs may *trans*-regulate distant protein-coding genes. RNA Immunoprecipitation sequencing (RIP-Seq) or microarray (RIP-Chip) technology has identified many lncRNAs that interact with specific RNA binding proteins (RBPs) (Zhao *et al.*, 2010). LncRNAs may function by interacting with these RBPs.

Roles of lncRNAs in psychiatric disorders

Recent findings that suggest a functional role of lncRNAs in various aspects of cell biology have increased awareness of their potential to contributing towards diseases. To determine which lncRNAs are related to various diseases becomes the logical and necessary next step in identifying the missing regulatory pathways following a long history of attention to the coding regions and small ncRNAs like miRNAs. For instance, by analyzing the differential expression, fold change of expression, classification, and regulatory effects of lncRNAs, many association studies have identified lncRNAs in association with Alzheimer's disease, substance dependence, schizophrenia, bipolar disorder, depression, autism spectrum disorder (ASD) and panic disorder.

Alzheimer's disease

Alzheimer's disease (AD) is the main cause of dementia in the elderly population worldwide. Adult neurogenesis appears to be upregulated very early in AD pathogenesis in response to some specific aggregates of beta-amyloid (Aβ) peptides, exhausting the neuronal stem cell pools in the brain. LncRNAs exhibit aberrant expression in AD. Recently, it has been demonstrated that an antisense lncRNA, *BACEAS*, exhibited elevated expression in several brain regions in individuals with AD. *BACEAS* regulates the expression of the sense beta-secretase-1 (*BACE1*) gene, a crucial enzyme in AD etiology (Faghihi *et al.*, 2008; Modarresi *et al.*, 2011). Upon exposure to various cell stressors including beta-amyloid 1-42 (Aβ 1-42), expression of *BACE1-AS* becomes elevated, increasing *BACE1* mRNA stability

and generating additional Aβ 1-42 through a post-transcriptional feed-forward mechanism. Alternatively, alteration of the expression for *BACE1-AS* may also mediate changes at an epigenetic level to effect gene expression and contribute to disease etiology, suggesting that this lncRNA may serve as an attractive drug target candidate for AD (Faghihi *et al.*, 2008) (www.arraystar.com).

Recent studies indicated that sortilin-related receptor 1 (*SORL1*) is a risk gene for late-onset AD. An antisense-overlapping lncRNA, *51A*, maps in intron 1 of *SORL1* gene and is frequently upregulated in expression in the cerebral cortices of individuals with AD. *51A* expression drives a splicing shift of *SORL1* from the synthesis of the canonical long protein variant A to an alternatively spliced protein form. This process, resulting in a decreased synthesis of *SORL1* variant A, is associated with impaired processing of amyloid precursor protein (APP), leading to increased Aβ formation that is implicated in neurodegeneration. (Ciarlo *et al.*, 2013)

Another lncRNA, Brain Cytoplasmic RNA 200-Alpha (*BC200*), a human analog of brain cytoplasmic RNA 1 (*BC1*), is a translational regulator that is selectively targeted to somatodendritic domains of neurons. It modulates local protein synthesis in postsynaptic dendritic microdomains, contributing to the maintenance of long-term synaptic plasticity. Dysfunctional plasticity has been posited as a starting point for the neurodegenerative changes as observed in AD. BC200 was significantly up-regulated in AD brains, specifically in Brodmann's area 9 and the hippocampus, regions that frequently are involved in the disease. Relative BC200 levels in these brain areas are correlated with the disease severity. In more advanced stages of the disease, BC200 is 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 in both early and later stages of AD. (Mus *et al.*, 2007)

Other lncRNAs implicated in the etiology of AD include *GDNF-AS1* (Airavaara *et al.*, 2011), *CDKN2B-AS1* (Zuchner *et al.*, 2008), *HAR1A* (Harries, 2012), *HAR1B* (Harries, 2012), *SNHG3* and *SOX2-OT* (Arisi *et al.*, 2011).

Substance dependence

Dysregulation of many lncRNAs has been reported to contribute to substance use disorders including alcohol, nicotine, heroin and cocaine dependence. For example, nuclear enriched abundant transcript 2 (*NEAT2*), an lncRNA regulating synapse formation (Bernard *et al.*, 2010), was up-regulated in alcoholics' brain (Kryger *et al.*, 2012); *NEAT2, NEAT1,* myocardial infarction associated transcript (*MIAT*) and maternally expressed 3 transcript (*MEG3*) were up-regulated in the nucleus accumbens (NAc) of heroin abusers (Michelhaugh *et al.*, 2011); and *NEAT2, MIAT, MEG3* and empty spiracles homeobox 2 opposite strand transcript (*EMX2OS*) were elevated in the NAc of cocaine abusers (Michelhaugh *et al.*, 2011). Smokers had dramatically elevated imprinted maternally expressed transcript (*H19*) expression in airway epithelium (Kaplan *et al.*, 2003); demethylation of *H19* was correlated to chronic alcohol use in males (Ouko *et al.*, 2009); and many lncRNAs were reported to be involved in cocaine-induced neural plasticity in the NAc and in risk for cocaine dependence (Bu *et al.*, 2012b).

Brain-derived neurotrophic factor (*BDNF*) gene, a gene known to be involved in substance dependence, e.g., cocaine dependence (Ghitza *et al.*, 2010), is controlled by a conserved antisense lncRNA, i.e., *BDNF-AS* (Modarresi *et al.*, 2012). *BDNF-AS* suppresses *BDNF* mRNA expression by altering chromatin structure at the *BDNF* gene locus. Inhibiting *BDNF-AS* by siRNA or other methods robustly increased BDNF mRNA and protein expression and enhanced neuronal outgrowth. *BDNF-AS* is dysregulated in response to chronic drug use and contributes to drug-seeking behaviors. (Sartor *et al.*, 2012)

Schizophrenia

Alternative splicing of some mRNAs is associated with the pathology of schizophrenia (SZ). Many disease-associated genes displayed aberrant splicing patterns. Gomafu is an lncRNA highly regulated by neural activity. It binds directly to splicing factors, and is significantly downregulated in the cortex of SZ patients. Modulation of Gomafu expression alters splicing patterns of at least two SZ-associated genes. Knockdown of Gomafu resulted in the upregulation of SZ pathology-related splice variants of *DISC1* and *ERBB4*, consistent with the observation that overexpression of these same splice variants are associated with SZ. In contrast, Gomafu overexpression produced significant downregulation of the same disease-associated splice variants of both genes (Barry *et al.*, 2014). This suggests that the lncRNA Gomafu may contribute to the pathogenic splicing pattern of these key SZ genes. (Guennewig and Cooper, 2014)

DLG2AS, aka *PSZA11q14*, is an antisense-overlapping lncRNA to *DLG-2* gene, located within the first intron of *DLG-2*. It acts as an antisense regulator of *DLG-2*, which controls the assembly of functional N-methyl-D-aspartate (NMDA) receptors. Its expression was reduced in the brains of SZ patients, specifically in Brodmann's areas 9, 21 and 22 and in the hippocampus, indicating that it may be involved in at least some cases of SZ (Polesskaya *et al.*, 2003). Schizophrenia spectrum disorders have also been linked to the reelin (*RELN*) gene and its antisense transcript *HAR1* (Tamura *et al.*, 2007). Other lncRNAs have been reported to be implicated in SZ, including *C6UAS* (Morelli *et al.*, 2000) and *LINC00271* (Amann-Zalcenstein *et al.*, 2006).

Autism spectrum disorders

Autism spectrum disorders (ASDs) include various developmental disorders, including autism, pervasive developmental disorder not otherwise specified (PDD-NOS), Rett syndrome, Fragile X syndrome and the Asperger syndrome. Common symptoms of the various ASDs include problems of reciprocal social interactions, verbal and non-verbal communication, and rigid and stereotyped behaviors. ASD is a clinically and etiologically heterogeneous disorder with a complex genetic architecture. In the last decade, several studies reported aberrant expression of lncRNAs, suggesting that lncRNAs contributed to ASD risk. Recently, Ziats and Rennert (2013) showed that over 200 lncRNAs were differentially expressed in a microarray of postmortem prefrontal cortex and cerebellum tissue of ASD patients (Ziats and Rennert, 2013).

(1) Autism—Vincent et al. (2002) identified a novel autism locus, which includes the gene *RAY1/ST7* (Vincent *et al.*, 2002). This locus contains at least four lncRNAs, i.e., *ST7OT1-4*,

both on the sense and antisense strands that potentially regulate *RAY1/ST7*. Additionally, moesin regulates neuronal architecture and the lncRNA *MSNP1AS*, transcribed in antisense to a moesin pseudogene, is 94% identical and antisense to moesin and can bind moesin mRNA (Kerin *et al.*, 2012; Le Meur *et al.*, 2005). Overexpression of *MSNP1AS* in cultured cells led to decreased moesin levels while *MSNP1AS* transcript levels were 12-fold higher in postmortem brain samples from autism cases (Kerin *et al.*, 2012). High levels of the *MSNP1AS* transcript were associated with the presence of an autism risk SNP and thus *MSNP1AS* is strongly positioned to be an lncRNA risk factor for autism (Kerin *et al.*, 2012). Finally, mutations in the X-chromosome *PTCHD1* gene have been reported to involve X-linked intellectual disability (ID) and autism (Filges *et al.*, 2011; Noor *et al.*, 2010). Several lines of evidence suggest that *PTCHD1* might have a causative role in a subset of ID and/or autism patients (Filges *et al.*, 2011). On the antisense strand of the *PTCHD1* gene, several overlapping lncRNAs (*PTCHD1AS1*, *PTCHD1AS2* and *PTCHD1AS3*) were detected, which may serve as regulators for *PTCHD1*.

(2) Rett syndrome—Rett syndrome is a rare, severe, “girls only” form of autism, usually identified in the first two years of life. It is characterized by arrested development between 6 and 18 months of age, regression of acquired skills, loss of speech, stereotypical movements, seizures, and ID. Mutations in the methyl CpG binding protein 2 (MECP2), which binds methylated CpGs and can both activate and repress transcription, were first described to be the cause of the disorder (Amir *et al.*, 1999). While assessing the transcriptome of male Mecp2 hemizygous knockout mouse brains (Petazzi *et al.*, 2013), it was revealed that the lncRNAs AK081227 and AK087060 were both significantly upregulated as compared to wild-type littermates. Importantly, overexpression of AK08127 was associated with the downregulation of its host coding protein gene, the GABA receptor subunit Rho 2. This suggests that transcriptional dysregulation of lncRNAs may have the capacity to contribute to the etiology of Rett syndrome.

(3) Fragile X Syndrome—Fragile X syndrome (FXS) is the most common known single gene cause of ASD. It is inherited via an X-linked dominant pattern and characterized by moderate to severe mental retardation, macroorchidism, and distinct facial features. The disorder is caused by an unstable expansion of a CGG repeat in the fragile X mental retardation 1 gene (*FMR1*), that leads to the silencing of the gene by methylation of the repeat and the promoter (Sutcliffe *et al.*, 1992), resulting in decreased fragile X mental retardation protein (FMRP) levels in the brain (Devys *et al.*, 1993). Accumulating evidence suggests that the etiology of the disorder is influenced by lncRNAs. FMRP, the protein encoded by *FMR1*, acts as a translational repressor of specific mRNAs at the synapse and is associated with the dendritic lncRNA and *BC1* (Zalfa *et al.*, 2003). BC1 enables the interaction of FMRP with the target mRNAs; and FMRP can directly bind to BC1 and its human analog BC200 via its N-terminus. Of note, the 5′ stem loop of BC1 is involved in FMRP recognition and this region is complementary to FMRP target mRNAs (Zalfa *et al.*, 2005). Taken together, the studies suggested that *BC1* is a lncRNA that is essential for the repression of mRNAs via FMRP and loss of this repression in FXS patients could result in synaptic dysfunction.

The promoter of FMR1 is bidirectional and can also give rise to the lncRNA *FMR4* (*FMR1AS1* or *ASFMR1*), a gene transcribed in the antisense orientation and overlaps the CGG repeat region. *FMR4* is similar to *FRM1* in being silenced in FXS patients. Alternative splicing of *FMR4* seems to exhibit premutation specific profiles and is upregulated in premutation carriers (Khalil *et al.*, 2008; Ladd *et al.*, 2007). Following siRNA knockdown of *FMR4*, alterations in cell cycle and apoptosis were reported. Conversely, overexpression of *FMR4* resulted in increased cell proliferation. Additionally, knockdown of *FMR4* did not influence *FMR1* expression and vice versa, suggesting an independent mechanism from *FMR1* (Khalil *et al.*, 2008). Together, these findings point toward a contribution of *FMR4* in the pathology of FXS.

Recently, Pastori et al. (2014) discovered two new lncRNAs in the *FMR1* gene locus: *FMR5* and *FMR6*. *FMR5* was similarly expressed in brain regions from unaffected and premutation individuals and full mutation patients, whereas *FMR6* was silenced in full mutation and premutation carriers. According to the authors, this might suggest an abnormal transcription or chromatin remodeling prior to transition to the full mutation. In addition to the finding that both *FMR5* and *FMR6* are expressed in blood leukocytes, these lncRNAs are potentially useful as biomarkers in FXS. (Pastori *et al.*, 2014)

Multiple mental illnesses

Some lncRNAs have been suggested to be involved in multiple mental illnesses. Disruption of the 'disrupted in schizophrenia-1' (*DISC1*) locus has been linked to the development of schizophrenia, schizoaffective disorder, bipolar disorder, major depression and autistic spectrum disorders (Brandon *et al.*, 2009; Chubb *et al.*, 2008). *DISC1* is regulated by lncRNA *DISC2* (Millar *et al.*, 2000), which may also represent an excellent candidate for susceptibility to these disorders (Taylor *et al.*, 2003). Additionally, lncRNA *DAOA-AS1* (*G72/G30*) has been associated with schizophrenia (Ma *et al.*, 2006; Yue *et al.*, 2006), bipolar disorders (Hattori *et al.*, 2003) and panic disorders (Schumacher *et al.*, 2005).

In summary, lncRNAs are a diverse group of non-coding RNAs that play critical roles in many cellular processes. Accumulating evidence suggests that they are involved in many psychiatric disorders. Having a better understanding of lncRNAs' roles in psychiatric disorders will not only enrich functional annotation of the non-coding regions of human genome, but also have tremendous potential to advance our understanding of specific regulatory pathways for the risk DNA variants to affect the development of psychiatric disorders. These studies have the potential to discover novel biomarkers and drug targets that can be used to facilitate the diagnosis, treatment and prognosis of psychiatric disorders.

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References

Airavaara M, Pletnikova O, Doyle ME, Zhang YE, Troncoso JC, Liu QR. Identification of novel GDNF isoforms and cis-antisense GDNFOS gene and their regulation in human middle temporal gyrus of Alzheimer disease. J Biol Chem. 2011; 286:45093–45102. [PubMed: 22081608]

Amann-Zalcenstein D, Avidan N, Kanyas K, Ebstein RP, Kohn Y, Hamdan A, et al. AHI1, a pivotal neurodevelopmental gene, and C6orf217 are associated with susceptibility to schizophrenia. Eur J Hum Genet. 2006; 14:1111–1119. [PubMed: 16773125]

Amaral PP, Dinger ME, Mercer TR, Mattick JS. The eukaryotic genome as an RNA machine. Science. 2008; 319:1787–1789. [PubMed: 18369136]

Amaral PP, Mattick JS. Noncoding RNA in development. Mamm Genome. 2008; 19:454–492. [PubMed: 18839252]

Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet. 1999; 23:185–188. [PubMed: 10508514]

Arisi I, D'Onofrio M, Brandi R, Felsani A, Capsoni S, Drovandi G, et al. Gene expression biomarkers in the brain of a mouse model for Alzheimer's disease: mining of microarray data by logic classification and feature selection. J Alzheimers Dis. 2011; 24:721–738. [PubMed: 21321390]

Barry G, Briggs JA, Vanichkina DP, Poth EM, Beveridge NJ, Ratnu VS, et al. The long non-coding RNA Gomafu is acutely regulated in response to neuronal activation and involved in schizophrenia-associated alternative splicing. Mol Psychiatry. 2014; 19:486–494. [PubMed: 23628989]

Bejerano G, Pheasant M, Makunin I, Stephen S, Kent WJ, Mattick JS, et al. Ultraconserved elements in the human genome. Science. 2004; 304:1321–1325. [PubMed: 15131266]

Bernard D, Prasanth KV, Tripathi V, Colasse S, Nakamura T, Xuan Z, et al. A long nuclear-retained non-coding RNA regulates synaptogenesis by modulating gene expression. EMBO J. 2010; 29:3082–3093. [PubMed: 20729808]

Brandon NJ, Millar JK, Korth C, Sive H, Singh KK, Sawa A. Understanding the role of DISC1 in psychiatric disease and during normal development. J Neurosci. 2009; 29:12768–12775. [PubMed: 19828788]

Bu D, Yu K, Sun S, Xie C, Skogerbo G, Miao R, et al. NONCODE v3.0: integrative annotation of long noncoding RNAs. Nucleic Acids Res. 2012a; 40:D210–215. [PubMed: 22135294]

Bu Q, Hu Z, Chen F, Zhu R, Deng Y, Shao X, et al. Transcriptome analysis of long non-coding RNAs of the nucleus accumbens in cocaine-conditioned mice. J Neurochem. 2012b; 123:790–799. [PubMed: 22957495]

Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A, et al. Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes Dev. 2011; 25:1915–1927. [PubMed: 21890647]

Carninci P, Kasukawa T, Katayama S, Gough J, Frith MC, Maeda N, et al. The transcriptional landscape of the mammalian genome. Science. 2005; 309:1559–1563. [PubMed: 16141072]

Carrieri C, Cimatti L, Biagioli M, Beugnet A, Zucchelli S, Fedele S, et al. Long non-coding antisense RNA controls Uchl1 translation through an embedded SINEB2 repeat. Nature. 2012; 491:454–457. [PubMed: 23064229]

Cawley S, Bekiranov S, Ng HH, Kapranov P, Sekinger EA, Kampa D, et al. Unbiased mapping of transcription factor binding sites along human chromosomes 21 and 22 points to widespread regulation of noncoding RNAs. Cell. 2004; 116:499–509. [PubMed: 14980218]

Chakalova L, Debrand E, Mitchell JA, Osborne CS, Fraser P. Replication and transcription: shaping the landscape of the genome. Nat Rev Genet. 2005; 6:669–677. [PubMed: 16094312]

Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK. The DISC locus in psychiatric illness. Mol Psychiatry. 2008; 13:36–64. [PubMed: 17912248]

Ciarlo E, Massone S, Penna I, Nizzari M, Gigoni A, Dieci G, et al. An intronic ncRNA-dependent regulation of SORL1 expression affecting Abeta formation is upregulated in post-mortem Alzheimer's disease brain samples. Dis Model Mech. 2013; 6:424–433. [PubMed: 22996644]

Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res. 2012; 22:1775–1789. [PubMed: 22955988]

Devys D, Lutz Y, Rouyer N, Bellocq JP, Mandel JL. The FMR-1 protein is cytoplasmic, most abundant in neurons and appears normal in carriers of a fragile X premutation. Nat Genet. 1993; 4:335–340. [PubMed: 8401578]

Dinger ME, Pang KC, Mercer TR, Crowe ML, Grimmond SM, Mattick JS. NRED: a database of long noncoding RNA expression. Nucleic Acids Res. 2009; 37:D122–126. [PubMed: 18829717]

Dong R, Jia D, Xue P, Cui X, Li K, Zheng S, et al. Genome-wide analysis of long noncoding RNA (lncRNA) expression in hepatoblastoma tissues. PLoS One. 2014; 9:e85599. [PubMed: 24465615]

Faghihi MA, Modarresi F, Khalil AM, Wood DE, Sahagan BG, Morgan TE, et al. Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of beta-secretase. Nat Med. 2008; 14:723–730. [PubMed: 18587408]

Filges I, Rothlisberger B, Blattner A, Boesch N, Demougin P, Wenzel F, et al. Deletion in Xp22.11: PTCHD1 is a candidate gene for X-linked intellectual disability with or without autism. Clin Genet. 2011; 79:79–85. [PubMed: 21091464]

Gelernter J, Kranzler HR, Panhuysen C, Weiss RD, Brady K, Poling J, et al. Dense genomewide linkage scan for alcohol dependence in African Americans: significant linkage on chromosome 10. Biol Psychiatry. 2009; 65:111–115. [PubMed: 18930185]

Ghitza UE, Zhai H, Wu P, Airavaara M, Shaham Y, Lu L. Role of BDNF and GDNF in drug reward and relapse: a review. Neurosci Biobehav Rev. 2010; 35:157–171. [PubMed: 19914287]

Guennewig B, Cooper AA. The central role of noncoding RNA in the brain. Int Rev Neurobiol. 2014; 116:153–194. [PubMed: 25172475]

Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature. 2009; 458:223–227. [PubMed: 19182780]

Guttman M, Garber M, Levin JZ, Donaghey J, Robinson J, Adiconis X, et al. Ab initio reconstruction of cell type-specific transcriptomes in mouse reveals the conserved multi-exonic structure of lincRNAs. Nat Biotechnol. 2010; 28:503–510. [PubMed: 20436462]

Harries LW. Long non-coding RNAs and human disease. Biochem Soc Trans. 2012; 40:902–906. [PubMed: 22817756]

Harrow J, Denoeud F, Frankish A, Reymond A, Chen CK, Chrast J, et al. GENCODE: producing a reference annotation for ENCODE. Genome Biol. 2006; 7(Suppl 1):S4, 1–9. [PubMed: 16925838]

Hattori E, Liu C, Badner JA, Bonner TI, Christian SL, Maheshwari M, et al. Polymorphisms at the G72/G30 gene locus, on 13q33, are associated with bipolar disorder in two independent pedigree series. Am J Hum Genet. 2003; 72:1131–1140. [PubMed: 12647258]

He Y, Vogelstein B, Velculescu VE, Papadopoulos N, Kinzler KW. The antisense transcriptomes of human cells. Science. 2008; 322:1855–1857. [PubMed: 19056939]

Kampa D, Cheng J, Kapranov P, Yamanaka M, Brubaker S, Cawley S, et al. Novel RNAs identified from an in-depth analysis of the transcriptome of human chromosomes 21 and 22. Genome Res. 2004; 14:331–342. [PubMed: 14993201]

Kaplan R, Luettich K, Heguy A, Hackett NR, Harvey BG, Crystal RG. Monoallelic up-regulation of the imprinted H19 gene in airway epithelium of phenotypically normal cigarette smokers. Cancer Res. 2003; 63:1475–1482. [PubMed: 12670893]

Kapranov P, Cheng J, Dike S, Nix DA, Duttagupta R, Willingham AT, et al. RNA maps reveal new RNA classes and a possible function for pervasive transcription. Science. 2007; 316:1484–1488. [PubMed: 17510325]

Katayama S, Tomaru Y, Kasukawa T, Waki K, Nakanishi M, Nakamura M, et al. Antisense transcription in the mammalian transcriptome. Science. 2005; 309:1564–1566. [PubMed: 16141073]

Kerin T, Ramanathan A, Rivas K, Grepo N, Coetzee GA, Campbell DB. A noncoding RNA antisense to moesin at 5p14.1 in autism. Sci Transl Med. 2012; 4:128ra140.

Khalil AM, Faghihi MA, Modarresi F, Brothers SP, Wahlestedt C. A novel RNA transcript with antiapoptotic function is silenced in fragile X syndrome. PLoS One. 2008; 3:e1486. [PubMed: 18213394]

Khalil AM, Guttman M, Huarte M, Garber M, Raj A, Rivea Morales D, et al. Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. Proc Natl Acad Sci U S A. 2009; 106:11667–11672. [PubMed: 19571010]

Kryger R, Fan L, Wilce PA, Jaquet V. MALAT-1, a non protein-coding RNA is upregulated in the cerebellum, hippocampus and brain stem of human alcoholics. Alcohol. 2012; 46:629–634. [PubMed: 22560368]

Labaj PP, Leparc GG, Linggi BE, Markillie LM, Wiley HS, Kreil DP. Characterization and improvement of RNA-Seq precision in quantitative transcript expression profiling. Bioinformatics. 2011; 27:i383–391. [PubMed: 21685096]

Ladd PD, Smith LE, Rabaia NA, Moore JM, Georges SA, Hansen RS, et al. An antisense transcript spanning the CGG repeat region of FMR1 is upregulated in premutation carriers but silenced in full mutation individuals. Hum Mol Genet. 2007; 16:3174–3187. [PubMed: 17921506]

Le Meur E, Watrin F, Landers M, Sturny R, Lalande M, Muscatelli F. Dynamic developmental regulation of the large non-coding RNA associated with the mouse 7C imprinted chromosomal region. Dev Biol. 2005; 286:587–600. [PubMed: 16126194]

Li D, Zhao H, Gelernter J. Strong association of the alcohol dehydrogenase 1B gene (ADH1B) with alcohol dependence and alcohol-induced medical diseases. Biol Psychiatry. 2011; 70:504–512. [PubMed: 21497796]

Li D, Zhao H, Gelernter J. Further clarification of the contribution of the ADH1C gene to vulnerability of alcoholism and selected liver diseases. Hum Genet. 2012; 131:1361–1374. [PubMed: 22476623]

Ma J, Qin W, Wang XY, Guo TW, Bian L, Duan SW, et al. Further evidence for the association between G72/G30 genes and schizophrenia in two ethnically distinct populations. Mol Psychiatry. 2006; 11:479–487. [PubMed: 16402132]

Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. Nat Rev Genet. 2009; 10:155–159. [PubMed: 19188922]

Mercer TR, Dinger ME, Sunkin SM, Mehler MF, Mattick JS. Specific expression of long noncoding RNAs in the mouse brain. Proc Natl Acad Sci U S A. 2008; 105:716–721. [PubMed: 18184812]

Michelhaugh SK, Lipovich L, Blythe J, Jia H, Kapatos G, Bannon MJ. Mining Affymetrix microarray data for long non-coding RNAs: altered expression in the nucleus accumbens of heroin abusers. J Neurochem. 2011; 116:459–466. [PubMed: 21128942]

Mikkelsen TS, Ku M, Jaffe DB, Issac B, Lieberman E, Giannoukos G, et al. Genome-wide maps of chromatin state in pluripotent and lineage-committed cells. Nature. 2007; 448:553–560. [PubMed: 17603471]

Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, et al. Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum Mol Genet. 2000; 9:1415–1423. [PubMed: 10814723]

Modarresi F, Faghihi MA, Lopez-Toledano MA, Fatemi RP, Magistri M, Brothers SP, et al. Inhibition of natural antisense transcripts in vivo results in gene-specific transcriptional upregulation. Nat Biotechnol. 2012; 30:453–459. [PubMed: 22446693]

Modarresi F, Faghihi MA, Patel NS, Sahagan BG, Wahlestedt C, Lopez-Toledano MA. Knockdown of BACE1-AS Nonprotein-Coding Transcript Modulates Beta-Amyloid-Related Hippocampal Neurogenesis. Int J Alzheimers Dis. 2011; 2011:929042. [PubMed: 21785702]

Morelli C, Magnanini C, Mungall AJ, Negrini M, Barbanti-Brodano G. Cloning and characterization of two overlapping genes in a subregion at 6q21 involved in replicative senescence and schizophrenia. Gene. 2000; 252:217–225. [PubMed: 10903453]

Mus E, Hof PR, Tiedge H. Dendritic BC200 RNA in aging and in Alzheimer's disease. Proc Natl Acad Sci U S A. 2007; 104:10679–10684. [PubMed: 17553964]

Nakaya HI, Amaral PP, Louro R, Lopes A, Fachel AA, Moreira YB, et al. Genome mapping and expression analyses of human intronic noncoding RNAs reveal tissue-specific patterns and

enrichment in genes related to regulation of transcription. Genome Biol. 2007; 8:R43. [PubMed: 17386095]

Noor A, Whibley A, Marshall CR, Gianakopoulos PJ, Piton A, Carson AR, et al. Disruption at the PTCHD1 Locus on Xp22.11 in Autism spectrum disorder and intellectual disability. Sci Transl Med. 2010; 2:49ra68.

Okada Y, Tashiro C, Numata K, Watanabe K, Nakaoka H, Yamamoto N, et al. Comparative expression analysis uncovers novel features of endogenous antisense transcription. Hum Mol Genet. 2008; 17:1631–1640. [PubMed: 18283053]

Orom UA, Derrien T, Beringer M, Gumireddy K, Gardini A, Bussotti G, et al. Long noncoding RNAs with enhancer-like function in human cells. Cell. 2010; 143:46–58. [PubMed: 20887892]

Ouko LA, Shantikumar K, Knezovich J, Haycock P, Schnugh DJ, Ramsay M. Effect of alcohol consumption on CpG methylation in the differentially methylated regions of H19 and IG-DMR in male gametes: implications for fetal alcohol spectrum disorders. Alcohol Clin Exp Res. 2009; 33:1615–1627. [PubMed: 19519716]

Pang KC, Stephen S, Dinger ME, Engstrom PG, Lenhard B, Mattick JS. RNAdb 2.0--an expanded database of mammalian non-coding RNAs. Nucleic Acids Res. 2007; 35:D178–182. [PubMed: 17145715]

Pastori C, Peschansky VJ, Barbouth D, Mehta A, Silva JP, Wahlestedt C. Comprehensive analysis of the transcriptional landscape of the human FMR1 gene reveals two new long noncoding RNAs differentially expressed in Fragile X syndrome and Fragile X-associated tremor/ataxia syndrome. Hum Genet. 2014; 133:59–67. [PubMed: 24005575]

Perkel JM. Visiting “noncodarnia”. Biotechniques. 2013; 54:301, 303–304. [PubMed: 23750541]

Petazzi P, Sandoval J, Szczesna K, Jorge OC, Roa L, Sayols S, et al. Dysregulation of the long non-coding RNA transcriptome in a Rett syndrome mouse model. RNA Biol. 2013; 10:1197–1203. [PubMed: 23611944]

Polesskaya OO, Haroutunian V, Davis KL, Hernandez I, Sokolov BP. Novel putative nonprotein-coding RNA gene from 11q14 displays decreased expression in brains of patients with schizophrenia. J Neurosci Res. 2003; 74:111–122. [PubMed: 13130513]

Qureshi IA, Mattick JS, Mehler MF. Long non-coding RNAs in nervous system function and disease. Brain Res. 2010; 1338:20–35. [PubMed: 20380817]

Qureshi IA, Mehler MF. Long Non-coding RNAs: Novel Targets for Nervous System Disease Diagnosis and Therapy. Neurotherapeutics. 2013; 10:632–646. [PubMed: 23817781]

Rinn JL, Kertesz M, Wang JK, Squazzo SL, Xu X, Brugmann SA, et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell. 2007; 129:1311–1323. [PubMed: 17604720]

Sartor GC, St Laurent G 3rd, Wahlestedt C. The Emerging Role of Non-Coding RNAs in Drug Addiction. Front Genet. 2012; 3:106. [PubMed: 22737160]

Schumacher J, Abou Jamra R, Becker T, Klopp N, Franke P, Jacob C, et al. Investigation of the DAOA/G30 locus in panic disorder. Mol Psychiatry. 2005; 10:428–429. [PubMed: 15477870]

Struhl K. Transcriptional noise and the fidelity of initiation by RNA polymerase II. Nat Struct Mol Biol. 2007; 14:103–105. [PubMed: 17277804]

Sutcliffe JS, Nelson DL, Zhang F, Pieretti M, Caskey CT, Saxe D, et al. DNA methylation represses FMR-1 transcription in fragile X syndrome. Hum Mol Genet. 1992; 1:397–400. [PubMed: 1301913]

Taft RJ, Pang KC, Mercer TR, Dinger M, Mattick JS. Non-coding RNAs: regulators of disease. J Pathol. 2010; 220:126–139. [PubMed: 19882673]

Tamura Y, Kunugi H, Ohashi J, Hohjoh H. Epigenetic aberration of the human REELIN gene in psychiatric disorders. Mol Psychiatry. 2007; 12:519, 593–600. [PubMed: 17310238]

Taylor MS, Devon RS, Millar JK, Porteous DJ. Evolutionary constraints on the Disrupted in Schizophrenia locus. Genomics. 2003; 81:67–77. [PubMed: 12573262]

Toung JM, Morley M, Li M, Cheung VG. RNA-sequence analysis of human B-cells. Genome Res. 2011; 21:991–998. [PubMed: 21536721]

Vincent JB, Petek E, Thevarkunnel S, Kolozsvari D, Cheung J, Patel M, et al. The RAY1/ST7 tumor-suppressor locus on chromosome 7q31 represents a complex multi-transcript system. Genomics. 2002; 80:283–294. [PubMed: 12213198]

Wang X, Arai S, Song X, Reichart D, Du K, Pascual G, et al. Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature. 2008; 454:126–130. [PubMed: 18509338]

Yan L, Yang M, Guo H, Yang L, Wu J, Li R, et al. Single-cell RNA-Seq profiling of human preimplantation embryos and embryonic stem cells. Nat Struct Mol Biol. 2013; 20:1131–1139. [PubMed: 23934149]

Yue W, Liu Z, Kang G, Yan J, Tang F, Ruan Y, et al. Association of G72/G30 polymorphisms with early-onset and male schizophrenia. Neuroreport. 2006; 17:1899–1902. [PubMed: 17179866]

Zalfa F, Adinolfi S, Napoli I, Kuhn-Holsken E, Urlaub H, Achsel T, et al. Fragile X mental retardation protein (FMRP) binds specifically to the brain cytoplasmic RNAs BC1/BC200 via a novel RNA-binding motif. J Biol Chem. 2005; 280:33403–33410. [PubMed: 16006558]

Zalfa F, Giorgi M, Primerano B, Moro A, Di Penta A, Reis S, et al. The fragile X syndrome protein FMRP associates with BC1 RNA and regulates the translation of specific mRNAs at synapses. Cell. 2003; 112:317–327. [PubMed: 12581522]

Zhao J, Ohsumi TK, Kung JT, Ogawa Y, Grau DJ, Sarma K, et al. Genome-wide identification of polycomb-associated RNAs by RIP-seq. Mol Cell. 2010; 40:939–953. [PubMed: 21172659]

Ziats MN, Rennert OM. Aberrant expression of long noncoding RNAs in autistic brain. J Mol Neurosci. 2013; 49:589–593. [PubMed: 22949041]

Zuchner S, Gilbert JR, Martin ER, Leon-Guerrero CR, Xu PT, Browning C, et al. Linkage and association study of late-onset Alzheimer disease families linked to 9p21.3. Ann Hum Genet. 2008; 72:725–731. [PubMed: 18761660]

Zuo L, Zhang XY, Wang F, Li CS, Lu L, Ye L, et al. Genome-wide significant association signals in IPO11-HTR1A region specific for alcohol and nicotine codependence. Alcohol Clin Exp Res. 2013; 37:730–739. [PubMed: 23216389]

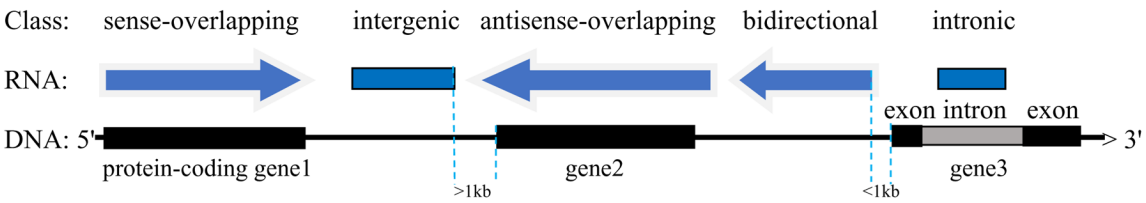

Figure 1. Classification of LncRNAs

[Sense, LncRNAs are transcribed from the same genomic strand as the protein-coding mRNAs; Intergenic, located between two protein-coding genes and at least 1 kb away from these genes; Antisense, transcribed from the antisense strand; Intronic, located within the intron of protein coding genes; Bidirectional, oriented head to head with a protein-coding gene within 1kb. Arrow direction: 5′ → 3′]