Long-noncoding RNAs as epigenetic regulators in neurodegenerative diseases

Paola Ruffo[1], Francesca De Amicis[2], Emiliano Giardina[3, 4], Francesca Luisa Conforti[1, *]

https://doi.org/10.4103/1673-5374.358615

Date of submission: May 31, 2022

Date of decision: August 1, 2022

Date of acceptance: August 19, 2022

Date of web publication: October 24, 2022

From the Contents

Abstract

The growing and rapid development of high-throughput sequencing technologies have allowed a greater understanding of the mechanisms underlying gene expression regulation. Editing the epigenome and epitranscriptome directs the fate of the transcript influencing the functional outcome of each mRNA. In this context, non-coding RNAs play a decisive role in addressing the expression regulation at the gene and chromosomal levels. Long-noncoding RNAs, consisting of more than 200 nucleotides, have been shown to act as epigenetic regulators in several key molecular processes involving neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease. Long-noncoding RNAs are abundantly expressed in the central nervous system, suggesting that their deregulation could trigger neuronal degeneration through RNA modifications. The evaluation of their diagnostic significance and therapeutic potential could lead to new treatments for these diseases for which there is no cure.

Key Words: Alzheimer's disease; amyotrophic lateral sclerosis; epigenetic mechanism; Huntington's disease; long-noncoding RNAs; neurodegenerative disease; non-coding RNAs; Parkinson's disease

Introduction

Genome size in all nucleated cells of an organism is identical but different genetic mechanisms allow the establishment of a differential gene expression. In 1492, C.H. Waddington introduced the term "epigenetic" to describe how the interactions between environment and genes determine phenotype development (Tronick and Hunter, 2016). Genetic mechanisms explain how heritable traits arise from mutations in the DNA sequence, while epigenetic mechanisms describe how phenotypic changes occur independently of the underlying DNA sequence (Egger et al., 2004). Epigenetic changes ensure that differential expression patterns are inherited stably as cells divide by providing a form of cellular memory that is passed on to offspring. Furthermore, these mechanisms can ensure the stable inheritance of an active transcriptional state for some target genes or certain genomic regions. Alternately, they can rearrange the chromatin of some genomic regions adopting a completely condensed and therefore transcriptionally inactive form (Bird, 2007). The most significant mechanisms for epigenetic labeling can be classified into three categories: DNA modifications (DNA methylation and hydroxy-methylation), histone modifications (histone methylation, acetylation, phosphorylation, ubiquitylation), and non-coding-mediated RNA modifications (ncRNA) (Wei et al., 2017).

Several studies have shown that ncRNAs play a decisive role in the epitranscriptomic alterations regulating expression at the gene and chromosomal level with consequent control of cell differentiation (Amaral et al., 2008; Costa, 2008; Peschansky and Wahlestedt, 2014; Wei et al., 2017; **Figure 1**). In particular, microRNA (miRNA) and short-interfering RNA (siRNA) are involved in the silent transcription gene, Piwi-interacting RNA (piRNA) performs the function of transposon repression DNA methylation, and long non-coding RNA (lncRNA) is involved in the genomic imprinting and inactivation of the X chromosome (Wei et al., 2017).

Epitranscriptome and epigenome alterations also play a key role in neuronal aging in a not yet defined way, although the importance of these processes in the genesis of neurons and the consolidation of memory is known (Creighton et al., 2020). Different scientific evidence shows the presence of global and gene-specific epigenetic changes at the peripheral and brain levels in patients with overt neurodegenerative diseases (NDs), such as Alzheimer's disease (AD) (Coppede, 2021), Parkinson's disease (PD) (Rathore et al., 2021) and amyotrophic lateral sclerosis (ALS) (Coppede, 2020). In the tissues of ND patients, both short RNAs and lncRNAs were found to be deregulated (Giulia Gentile 2022), candidates for these molecules as probable therapeutic biomarkers (Huaying et al., 2020). The results of *in vitro* studies on the targeting of epigenetic signs in ND show improvements in synaptic plasticity, reduction of disease progression, and motor and cognitive functions (Coppede, 2022).

LncRNAs are non-coding RNAs longer than 200 nucleotides. They have a specific tissue expression and are copiously expressed in the central neuron system where they participate in various biological processes, such as epigenetic regulation, programmed cell death, synaptic activity, and inflammatory response processes (Ruffo et al., 2021). Misregulation of lncRNAs is directly related to the dysregulation of the pathogenesis of some diseases, including NDs (Zhang and Wang, 2021). Specifically, several lncRNAs have been found to be involved in organ development (Rayner and Liu, 2016), differentiation (Chen and Zhang, 2016), synaptic formation (Maag et al., 2015), learning and memory (Gudenas and Wang, 2015) as well as cell senescence at different stages of the cell cycle (Puvvula, 2019). Several lncRNAs play a role in cellular senescence and organism aging through cell cycle regulation. Among these, many studies have shown that *MALAT1*

[1]Medical Genetics Laboratory, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy; [2]Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy; [3]Genomic Medicine Laboratory UILDM, IRCCS Fondazione Santa Lucia, Rome, Italy; [4]Department of Biomedicine & Prevention, Tor Vergata University of Rome, Rome, Italy

*__Correspondence to:__ Francesca Luisa Conforti, PhD, francescaluisa.conforti@unical.it.

https://orcid.org/0000-0001-8364-1783 (Francesca Luisa Conforti)

Funding: *This work was funded by a special award to the Department of Pharmacy, Health and Nutritional Sciences of University of Calabria (Italy) (Department of Excellence, Italian Law232/2016) from the Italian Ministry of Research and University (MIUR) to FLC.*

How to cite this article: *Ruffo P, De Amicis F, Giardina E, Conforti FL (2023) Long-noncoding RNAs as epigenetic regulators in neurodegenerative diseases. Neural Regen Res 18(6): 1243-1248.*

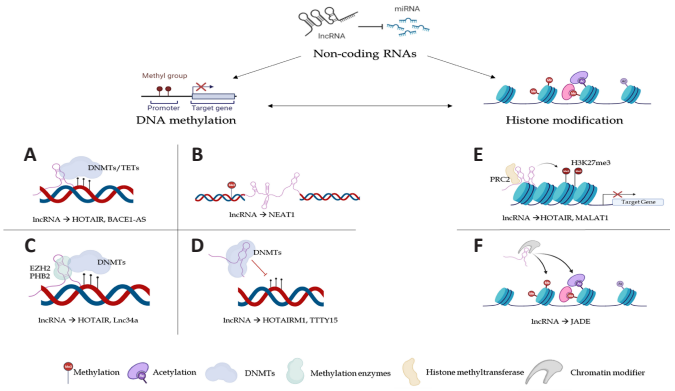

Figure 1 | **Mechanisms for epigenetic labeling: function of ncRNAs.**
(A) LncRNAs directly recruit DNMTs/TETs. (B) DNA methylation sites located at or near lncRNA regulate its expression. (C) LncRNAs indirectly recruit DNMTs via EZH2/PHB2. (D) LncRNAs sequestrate DNMTs. (E) LncRNAs can promote histone H3K27me3 of the promoter region of chromatin via the recruitment of histone complexes such as PRC2, thereby leading to the silencing of gene transcription. (F) LncRNAs recruit different kinds of regulatory proteins which promote histone methylation and acetylation on the chromatin. DNMTs: DNA methyltransferases; EZH2: enhancer of zeste homolog 2; H3K27me3: histone H3 Lys27 trimethylation; PHB2: prohibitin 2; PRC2: polycomb repressive complex 2; TETs: ten-eleven translocation. Created with BioRender.com.

(Metastasis-Associated Lung Adenocarcinoma Transcript 1) is a cell cycle regulator causing cycle arrest in the G1 or G1/S phase by improving the senescence phenotype (Tripathi et al., 2013). Another aging-related lncRNA is *TUG1* (Taurine upregulated gene 1) that blocks p53-mediated growth and apoptosis as well as modifies gene expression of the *HOX* (Homeobox) gene family, resulting in aging (Khalil et al., 2009). LncRNAs are also involved in chromatin modulation leading to senescence and aging process. Among these, *ANRASSF1* is an lncRNA-AS that potentially reduces the transcription of the tumor suppressor gene, Ras-associated domain-containing protein 1A (*RASSF1A*), involved in cell cycle arrest and apoptosis (Beckedorff et al., 2013). Aging is also associated with the production of senescence-associated secretory phenotype factors that facilitate inflammation and the onset of age-related diseases. Many lncRNAs participate in innate immunity such as *FIRRE* (Functional intergenic repeating RNA element), a recently discovered lncRNA controlled by *NF-κB* (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling in macrophages. This lncRNA impacts nuclear architecture through interaction with *hnRNP-U* (Heterogeneous Nuclear Ribonucleoprotein U) and positively regulates several inflammatory genes expression (Lu et al., 2017).

In this review, following a general introduction to the lncRNA epigenetic regulation mechanisms, we will provide a brief overview of the role of lncRNAs whose epigenetic regulatory mechanisms have previously been known in AD, PD, ALS, and Huntington's disease (HD), discussing those eligible as therapeutic markers.

Data Sources

Database: https://pubmed.ncbi.nlm.nih.gov/ (May 20, 2022) was searched. The first research was conducted using keywords: lncRNAs AND neurodegenerative diseases AND Alzheimer's disease AND Parkinson's disease AND amyotrophic lateral sclerosis. Subsequently, we have selected only the papers in which the mechanisms of lncRNAs epigenetic regulation were discovered. Furthermore, the selected lncRNAs underwent a further filter: only those eligible as therapeutical markers were discussed.

Long-Noncoding RNAs Epigenetic Regulation Mechanisms

The ability to be variable, flexible, and structurally changeable makes lncRNAs the main characters of genomic dynamism, thus resulting in significant components in epigenetic regulation. This can occur according to different mechanisms that allow the classification of lncRNAs into several classes: guides, dynamic scaffolds, molecular recall, signal, and enhancers (**Figure 2**; Balas and Johnson, 2018). In particular, lncRNAs classified as guides can bind chromatin-modifying proteins and target complexes formed at specific genomic locations by reprogramming the epigenetic state. By implementing this, lncRNAs change gene expression to cis or trans (**Figure 2A**; Asadi et al., 2021). LncRNAs acting as dynamic scaffolds play a structural role in assembling different complexes and recruiting transcriptional enzymes. Following the assembly phase, one can witness their activation or repression. This underlines the importance of lncRNAs in the transcription process (**Figure 2B**; Fang and Fullwood, 2016). LncRNAs that act as molecular recall are likely negative regulators in both transcriptional processing and chromatin modification. The lncRNAs belonging to this category can sponge miRNAs by creating a competing endogenous RNA network to inhibit their binding to the target mRNA (**Figure 2C**; Asadi et al., 2021). LncRNAs perform a signal function and are expressed at a precise moment and in a specific position in response to external stimuli. Some of these are regulatory, while others are simply products of transcription, with the act of regulatory initiation, elongation, or termination. Signal lncRNAs are known to interact with chromatin-modifying enzymes such as histone methyltransferase to silence their target genes by blocking their transcription or through the formation of heterochromatin (**Figure 2D**; Wang and Chang, 2011). Other lncRNAs exert function as enhancers, i.e., activating gene transcription by serving as the cis-regulatory molecules. Furthermore, recent studies have demonstrated that many enhancer elements can be transcribed and produce RNA molecules, which are termed enhancer RNAs (**Figure 2E**; Kim et al., 2015).

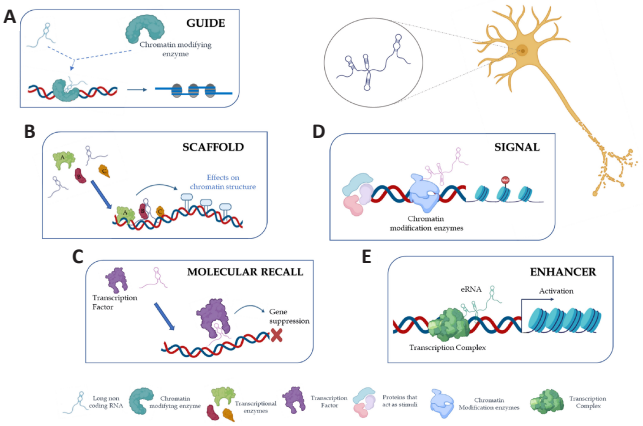

Figure 2 | **Function and mechanism of lncRNAs in transcriptional regulation.**
(A) Guide: lncRNAs arrange transcription factors at specific genomic loci and help to regulate chromatin. (B) Scaffold: lncRNAs help to assemble RNA-protein complexes; their role is to promote or suppress transcription by activating or repressing target genes. (C) Molecular recall: lncRNAs have more affinity for particular regulatory factors; once bound, they lead to transcriptional repression by preventing these regulatory factors from binding to the DNA. (D) Signal: lncRNAs respond to a stimulus and receive the signal to interact with chromatin-modifying enzymes to prevent transcription. (E) Enhancer: enhancer-derived RNAs (eRNAs) regulate enhancer/promoter communication by directly recruiting chromatin modifiers favoring the activation of gene expression. Created with BioRender.com.

LncRNAs, impacting gene function through transcriptional and epigenetic regulation, include also RNA transcribed from the opposite strength of protein-coding genes or sense strand derived mRNA, called lncRNA-AS (antisense lncRNA) (Gagliardi et al., 2018). Precisely this characteristic allows the formation of particular structural configurations capable of addressing the action of lncRNA in a specific and selective manner (MacDonald and Mann, 2020). There are several mechanisms of lncRNA-AS action, but these will not be presented in this review.

Long-Noncoding RNAs as Epigenetic Regulators in Alzheimer's Disease

AD is the most common cause of progressively disabling degenerative dementia with onset in presenile age characterized by the formation of β-amyloid plaques and neurofibrillary tangles resulting in brain atrophy and neuronal death. The etiology of the disease is largely unknown and, in most cases, occurs sporadically. The best-known genetic risk factor is the inheritance of the ε4 allele of Apolipoprotein E (*APO-E*). Between 40% and 60% of people with the disease have at least one APOE-ε4 allele. Although the hereditary genes that cause familial AD are rare, they have been identified as being associated with the processing or production of amyloid-beta (Soria Lopez et al., 2019).

BACE1 (β-site amyloid precursor protein cleavage enzyme 1, chr.11q23.3, OMIM * 604252) encodes for an enzyme responsible for β-amyloid plaque formation through the cleavage of the amyloid beta precursor protein. In mouse models, *BACE1* has been shown to regulate voltage-gated sodium channels that control neuronal activity involved in the pathophysiology of AD. In particular, *BACE1* expression is localized to the presynaptic terminals surrounding the amyloid plaques showing that *BACE1*-deficient mice have a healthy phenotype and suppressed β-amyloid production (Sayad et al., 2022). Deregulation of *BACE1* plays an important role in the initial phase of the disease by initiating the process of toxicity (Hampel et al., 2021). The action of several miRNAs, such as miR-34a-5p, miR-125b-5p, miR-15b, and miR-149, inhibit the expression of *BACE1*, reduce amyloid accumulation and improve neuronal damage (Sayad et al., 2022). *BACE1-AS* (*BACE1* antisense RNA, 11q23.3, OMIM * 614263) lncRNA acts in the post-transcriptional regulation of *BACE1*. *BACE1-AS* is an antisense transcript that appears to be elevated in patients with AD, determines a molecular change promoting β-secretase synthesis, and can function as competing endogenous RNA capable of avoiding the degradation of *BACE1* mRNA (Faghihi et al., 2008). The aggregation and the formation of a duplex between *BACE1-AS* and *BACE1* increase the stability of the transcript, underlining how the lncRNA determines an upregulation of mRNA and BACE1 protein. The *BACE1-AS*/

miR-485-5p/*BACE1* axis demonstrates the involvement of this lncRNA in the pathogenesis of AD through the post-transcriptional regulation of *BACE1* (Faghihi et al., 2010). Furthermore, He and collaborators demonstrated that *BACE1-AS* avoids *BACE1* transcript degradation by acting against miR-29b-3p/miR-107/miR-124-3p/miR-485-5p/miR-761 (He et al., 2020). The *BACE1-AS*/miR-132-3p axis is involved in the neuroprotective process induced by berberine, a protoberberine isoquinoline alkaloid that limits the formation of β-amyloid plaques and intracellular neurofibrillary tangles (Cai et al., 2016). In particular, berberine treatment downregulates *BACE1-AS* in AD, modulating the function of miR-132-3p whose accumulation alleviates the neuronal damage induced by β-amyloid (Ge et al., 2020).

SNHG1 (Small Nucleolar RNA Host Gene 1, chr.11q12.3) is an lncRNA involved in neuronal damage induced by the presence of β-amyloid plaques through the axis *SNHG1*/miR-137/*KREMEN1* (Kringle Containing Transmembrane Protein 1) and *SNHG1*/miR-361-3p/*ZNF217* (Zinc Finger Protein 217) (Sabaie et al., 2021). *SNHG1* may play a positive role in the progression of NDs as the *SNHG1* knockdown can promote cell survival mitigating the progression of AD. The study results conducted by Gao et al. (2020) showed that resveratrol exerts a neuroprotective effect by acting on the *SNHG1*/miR-361-3p/*ZNF217* axis. In particular, the expression of *SNHG1* is negatively regulated by resveratrol that inhibits the sponging of miR-361-3p whose overexpression determines *ZNF217* silencing with consequent inhibition of cell injury (Gao et al., 2020).

NEAT1 (Nuclear Paraspeckle Assembly Transcript 1, chr.11q13.1, OMIM # 612769) is an lncRNA involved in epigenetic regulation in AD through chemical modifications of long-term memory formation processes. In particular, *NEAT1* knockdown with siRNA regulates *c-Fos* (human Fos proto-oncogene) promoter methylation by H3K9me2, an epigenetic modification to the DNA packaging protein histone H3, increasing gene expression and improving long-term memory (Butler et al., 2019). Furthermore, upregulated *NEAT1* regulates the interaction between *PINK1* (PTEN-induced kinase 1) and *NEDD4L* (ubiquitin-protein ligase nedd4-like) with consequent ubiquitination and degradation of *PINK1* which causes an increase in the accumulation of β-amyloid and cognitive decline (Huang et al., 2020). This lncRNA acts through the miR-124/*BACE1* axis with consequent promotion of the development of AD (Zhao et al., 2019). In particular, Zhao and collaborators observed that the down-regulation of *NEAT1* expression contributed to the deposition of β-amyloid, inhibiting the expression of multiple endocytosis-related genes, through the interaction with the P300/CBP complex (Zhao et al., 2019).

SOX21-AS1 (SOX21 Antisense Divergent Transcript 1, chr.13q32.1) is an lncRNA that plays a similar role to *NEAT1*: they both act against miR-107 which is found to be deregulated in brain tissue of AD patients. In particular, *SOX21-AS1* knockdown attenuates neuronal apoptosis and mitigates oxidative stress in AD by sponging miR-107, reducing Aβ-induced neuronal damage (Xu et al., 2020). Furthermore, silencing of this lncRNA could act by upregulating the expression of FZD3/5 (frizzled class receptor) and following activation of the Wnt signaling pathway (Zhang et al., 2019a).

LoNA (long nucleolus-specific lncRNA) is a recently discovered lncRNA that works by reducing *NCL* (nucleolin) transcription and 2'-O-methylation rRNA (ribosomal RNA) methylation resulting in a reduction of active *FBL* (fibrillarin), a component of a nucleolar small nuclear ribonucleoprotein (snRNP) particle thought to participate in the first step in processing preribosomal RNA. A downregulation of *LoNA* causes an increase in rRNA concentrations, improving synaptic activity and long-term memory (Asadi et al., 2021). *In vivo* studies suggest that *LoNA* plays a key role in NDs by representing a probable therapeutic target for the treatment of AD (Li et al., 2018).

MALAT1 (metastasis-associated lung adenocarcinoma transcript 1, chr.11q13.1, OMIM * 607924), known as *NEAT2*, regulates neuronal and synaptic activity by modulating the expression of genes involved in the formation and maintenance of synapses (Asadi et al., 2021). Emerging evidence suggests a neuroprotective function of *MALAT1* through the inhibition of neuroinflammation. Indeed, *MALAT1* knockdown promotes neuronal apoptosis and represses neurite growth while the overexpression of this lncRNA determines a modification of the inflammatory picture, favoring neuritic growth and preventing apoptosis in AD, through the interaction with miR-125b (Ma et al., 2019; Lan et al., 2021). In addition, the study conducted by Zhuang and collaborators demonstrated that *MALTA1*/miR-125b can be considered prognostic and predictive markers of AD and that the correlation between this axis and *FOXQ1* (forkhead box Q1), *PTGS2* (prostaglandin-endoperoxide synthase 2) and *CDK5* (cyclin-dependent kinase 5) could provide important information for the therapies of AD (Zhuang et al., 2020).

A newly discovered lncRNA involved in AD is MAPT-AS1, located within the antisense strand of the *MAPT* promoter region, which plays a critical role in the formation and maintenance of microtubules. Several evidences show that *MAPT* upregulation causes an increase in events related to neurodegeneration (Adams et al., 2009). Recently, de Silva et al. (2018) showed that delivery of *MAPT-AS1* vectors into the hippocampus of mouse models via adeno-associated virus, resulted in a decrease in tau levels, suggesting *MAPT-AS1* as a potential therapeutic approach to treating AD (Rohan de Silva, 2006).

Long-Noncoding RNAs as Epigenetic Regulation in Parkinson's Disease

PD is a neurodegenerative disease age-related that predominantly affects dopaminergic neurons in a specific area of the brain: the substantia nigra (Strafella et al., 2021). The etiology of the disease is not entirely clear, although scientists believe that the cause is a combination of genetic and environmental factors. Familial cases of PD can be caused by mutations in the *LRRK2* (Leucine-rich repeat kinase 2), *PARK7* (Parkinsonism associated deglycase), *PINK1* (PTEN-induced kinase 1), *PRKN* (Parkin RBR E3 Ubiquitin Protein Ligase), or *SNCA* (Synuclein Alpha) genes, or by alterations in genes not yet identified (Cherian and Divya, 2020).

SNHG1, also known as *linc00057*, is a recently discovered lncRNA in PD. Several studies have shown that this lncRNA is involved in different molecular and cellular mechanisms directly related to the phenotype of the disease. The main biological function of *SNHG1* is to promote the ubiquitination of α-synuclein and regulate its toxicity through the *SNHG1*-miR15b-5p-SIAH1-linc-p21-miR-1277-5p axis (Xu et al., 2018). Specifically, *SNHG1* promotes the aggregation and toxicity of α-synuclein by targeting miR15b-5p. This interaction activates the gene SIAH1 (Siah E3 Ubiquitin Protein Ligase 1) (Chen et al., 2018) regulated by the lncRNA linc-p21 which, in turn, sponges miR-1277-5p and indirectly increases the expression of α-synuclein to suppress viability and activate apoptosis (Xu et al., 2018). Moreover, *SNHG1* promotes neuroinflammation through the miR-7/*NLRP3* (NLR Family Pyrin Domain Containing 3) axis (Rasheed et al., 2021) and, when upregulated, promotes 1-methyl-4-phenylpyridinium (MPP^+) induced cytotoxicity through miR-153-3p sponging. This positive ion has been related to chemical reactions causing *in vitro* PD-like cytotoxic cellular events (Shishido et al., 2019). *SNHG1* is also involved in the autophagic process by regulating the expression of p27/mTOR (mammalian target of rapamycin kinase) through competitive interaction with miR-221/222 members (Qian et al., 2019).

The above-discussed *NEAT1* is also involved in PD and it has been strengthened by a recent study discussing contradictory results on its upregulation as part of a protective or a damaging mechanism (Boros et al., 2021). Yang et al. (2018) observed that *NEAT1* promotes the autophagic process induced by MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine) by stabilizing *PINK1* (Yan et al., 2018). In a more recent work by Sun et al. (2021), it was observed that downregulated NEAT1 binds miR-1301-3p and inhibits the expression of GJB1 (gap junction protein beta 1) resulting in decreased α-induced NLRP3 inflammation. Zhou et al. (2020) demonstrated that an upregulation of the *NEAT1* lncRNA can contribute to the neuronal damage created by MPP^+ via the *NEAT1*-miR-1277-5p-*ARHGAP26* (Rho GTPase Activating Protein 26) (Zhou et al., 2021a). Despite several studies suggest a protective role of *NEAT1* downregulation in PD progression (Boros et al., 2021), no data from *in vitro* and *in vivo* models studies are available to confirm a direct role of this lncRNA in the pathogenesis of the disease (Boros et al., 2021).

HOTAIR (Hox Transcript Antisense RNA, chr.12q13.13, OMIM * 611400) is an lncRNA whose functional role is well known in oncogenetic processes while its role in PD is unclear. This lncRNA is associated with human *HOX* loci and, by targeting the repressive *PRC2*, can modify the status of methylation of H3K27me, and manipulate gene expression patterns throughout the genome. The molecular pathogenesis of PD is hypothesized to be associated with mitochondrial dysfunction and activation of the apoptotic cascade. MPP^+-induced neuronal death, mediated by loss of mitochondrial membrane potential, is attenuated by *HOTAIR* knockdown, through the reduction of the cell death protease activity of Caspase 3 (Wang et al., 2017). Zhao and collaborators demonstrated that *HOTAIR* sponging miR-874-5p is involved in the neuronal damage generated by MPP^+ (Zhao et al., 2020). In the same year, a study by Zhang and collaborators showed that *HOTAIR* inhibits the activation of *NLRP3*-mediated pyroptosis, a form of lytic and inflammatory cell death, in mouse models of PD through the miR-326/*ELAVL1* (ELAV Like RNA Binding Protein 1) axis (Zhao et al., 2020; Zhang et al., 2021). Furthermore, this lncRNA tagged miR-126-5p and *RAB3IP* (RAB3A Interacting Protein) resulting in increased disease progression (Rasheed et al., 2021).

SNHG14 (Small Nucleolar RNA Host Gene 14, chr.15q11.2, OMIM * 616259) is a lncRNA potentially involved in the loss of dopaminergic neurons, capable of regulating miR-133b which, in turn, can control the expression of α-synuclein. The *SNHG14*/miR-133b complex determines a downregulation of α-synuclein and, therefore, could mitigate the symptoms (Zhang et al., 2019b). Since α-synuclein is the major component of Lewy bodies, then changes in α-synuclein influence the development of PD. In addition, *SNHG14* sponge miR-214-3p tags *KLF4* (Kruppel Like Factor 4) (Zhou et al., 2020). The latter favors the effects of MPP^+ by delaying cell proliferation and programmed cell death (Chen et al., 2013). Based on these findings, the *SNHG14*/miR-214-3p/*KLF4* axis could therefore be considered a therapeutic target (Zhou et al., 2020).

The expression of α-synuclein is also regulated by the lncRNA *TP53COR1* (Tumor Protein P53 Pathway Corepressor 1, Chr. 6p21.2, OMIM * 616343), also known as *lincRNA-p21*. Specifically, this lncRNA sponges miR-1277-5p and determines the activation of α-synuclein with consequent promotion of programmed cell death and repression of cell viability (Xu et al., 2018). Furthermore, the *lincRNA-p21*/miR-625 axis determines the inhibition of the neuronal damage generated by MPP^+ (Ding et al., 2019).

AL049437 is an lncRNA with evident neuroprotective functions. As demonstrated by Zhang et al., this lncRNA reduces the presence of *TNF-α* (Tumor necrosis factor α), *IL-6* (Interleukin 6), and reactive oxygen species in MPP^+ models (Zhang et al., 2020). Transcriptomic analysis performed by Ni et

al. (2017), highlighted a high number of deregulated lncRNAs in PD patients, underlining that the lncRNAs *AL049437* and *AK021630* are involved in the pathogenetic mechanisms of the disease (Ni et al., 2017). To our knowledge, no other studies have investigated the role of *AL049437* in PD and further research is needed to understand the *AL049437* mechanism of action in the pathogenesis of the disease.

Long-Noncoding RNAs as Epigenetic Regulation in Amyotrophic Lateral Sclerosis

ALS is a neurodegenerative disease caused by the progressive loss of motor neurons resulting in weakness and paralysis of the voluntary muscles. The main clinical feature of ALS is the involvement of upper and lower motor neurons in multiple regions of the brain stem and spinal cord. Although important progress has been made in recent times in understanding etiopathology, ALS still remains an unknown disease in many respects (Masrori and Van Damme, 2020). 10% of individuals affected by this pathology show a genetic driver that allows the distinction between familial ALS and sporadic ALS cases (Wijesekera and Leigh, 2009). There is extensive heterogeneity in the genetic causes of familial ALS, but the forms of familial ALS and sporadic ALS have similarities in their pathological and clinical characteristics, suggesting a convergence of cellular and molecular events leading to motor neuron degeneration (Grad et al., 2017). To date, more than 100 genes have been associated with ALS (https://alsod.ac.uk/), but only four of them are linked to a significant percentage of ALS cases including *SOD1* (superoxide dismutase 1), *C9orf72*, *TARDBP* (TAR DNA Binding Protein), and *FUS* (fused in sarcoma) (Ungaro et al., 2021).

NEAT1_2 is a lncRNA with an important structural role in nuclear paraspeckles (Fox et al., 2002). TDP-43 and FUS proteins bind *NETA1_2* to properly create these structures. Mutations in these proteins result in functional defects in nuclear paraspeckles. Furthermore, the role of *NEAT1_2* as a disease biomarker is highlighted as it is poorly expressed in motor neurons of healthy subjects while it is highly expressed in motor neurons of ALS patients (Nishimoto et al., 2013). However, stresses can cause NEAT1_2-induced paraspeckle formation in the nucleus, but it is not yet known the mechanism involved in *NEAT1_2* lncRNA upregulation during the early phase of ALS (Nishimoto et al., 2013). *NEAT1_2* can bind RBPs (RNA binding protein) in the nuclei of motor neurons by regulating their expression (Nishimoto et al., 2013) and allowing a greater understanding of lncRNAs in ALS as both prognostic and therapeutic markers.

C9Orf72-AS is an lncRNA-AS that contains the reverse repeat sequence of the causative hexanucleotide of ALS disease. The function of the *C9Orf72* sense transcript is better known than that of the antisense transcript which could lead to the formation of polypeptides and RNA foci (Freibaum and Taylor, 2017; Mizielinska et al., 2017). The production of these foci causes the RBPs sequester and an indirect regulation of gene expression. Greater knowledge of these transcripts may prove to be an alternative strategy for targeting repeated *C9Orf72* expansions and reversing the transcriptional changes typical of the disease (Chen and Chen, 2020).

Long-Noncoding RNAs as Epigenetic Regulation in Huntington's Disease

HD is an autosomal dominant neurodegenerative disease clinically characterized by movement disorders, progressive dementia, and psychiatric and behavioral disorders. An increase in the copy number of CAG trinucleotide repeats in the first exon of the HTT (Huntingtin) gene, that encodes polyglutamine, causes HD (Jimenez-Sanchez et al., 2017). Specifically, an increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. The stretched protein is cut into smaller, more toxic fragments that bind and build up in neurons, disrupting the normal functions of these cells. Dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of pathology (Walker, 2007).

TUG1 (Taurine Upregulated Gene 1, 22q12.2, OMIM * 614971), highly expressed in the mammalian brain, appears to be involved in neurodegenerative diseases in various physiological processes such as those regulating genes at epigenetic, post-transcriptional, and post-translational regulation (Guo et al., 2020). A study conducted by Khalil et al. (2009), showed that *TUG1* binds to the PRC2 epigenetic regulatory complex and its knockdown causes widespread changes in gene expression and in particular in the upregulation of cell cycle genes. Interestingly in the HD context, *TUG1* serves as a direct downstream transcriptional repressor of p53 (known to be up-regulated in HD), acting as a survival factor in neurons (Khalil et al., 2009). However, further studies are needed to identify the mechanism of action of this lncRNA at the neuronal level. Different other lncRNAs, such as *MEG3* (Maternally Expressed Gene 3, 14q32.2, OMIM *605636), *NEAT1*, and *XIST* (X Inactivation-Specific Transcript, Xq13.2, OMIM *314670), have shown to contribute to HD pathogenesis. Some studies suggest that these lncRNAs can interact with many miRNAs as miR-9, miR-125b, miR-132, miR-146a, miR-150, miR-221, and miR-222, potentially reducing the efficiency of binding to their target mRNAs and thus promoting the development of the disease (Zhou et al., 2021b).

Long-Noncoding RNAs as Targets: Current Challenges in Alzheimer's Disease/Parkinson's Disease/Amyotrophic Lateral Sclerosis/ Huntington's Disease Therapy

To date, the studies performed on lncRNAs leave open the possibility of using these as new biomarkers for the diagnosis and clinical therapy of NDs. In the clinical context, the detection of circulating lncRNA has been widely described in many body fluids (plasma, urine, saliva, blood, and CSF samples) from NDs patients, indicating their potential role as prognostic and diagnostic biomarkers (Feng et al., 2018; Gagliardi et al., 2018; Fan et al., 2019; Fotuhi et al., 2019; Cheng et al., 2021; Yu et al., 2022). However, limitations due to the lncRNA detection and/or disease-specificity limit their use for early disease diagnosis.

lncRNAs can be targeted by multiple approaches in the nucleus and cytoplasm including: knockdown of pathogenic RNAs by using siRNAs or antisense oligonucleotides, modulation of lncRNA genes by steric blockade of the promoter or by using genome-editing techniques as CRISPR/Cas9. Another interesting approach involves the use of natural antisense transcripts (NATs): lncRNAs that act as repressors of specific genomic loci. In particular, so-called "antagoNATs", antisense oligonucleotides that target NATs have shown exciting results for gene reactivation in the CNS (Modarresi et al., 2012).

Currently, various siRNA or antisense oligonucleotide-based therapies involved in pathogenesis have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (Winkle et al., 2021). Despite nobody lncRNA-based therapeutics having entered the clinic, there are many ongoing studies for the evaluation of lncRNAs as targets and/or therapeutic systems, especially in oncological pathologies (Zhou et al., 2021b). In our context, several lncRNAs with key roles in NDs could be considered therapeutic targets. In **Additional Table 1**, we provide a detailed list of the lncRNAs, previously described in the text, associated with AD/PD/ALS/HD.

Despite lncRNAs targeting are receiving considerable attention, understanding of their function and effects is incomplete, and there are still some limitations to their clinical application. First, the sensitive detection and tissue disease-specificity of lncRNA are challenging and require more comprehensive studies in the future. Moreover, clinical trial results about lncRNAs are lacking so far and many questions still need to be answered beyond the identification and the choice of the disease-specific lncRNA reference, from the system used to deliver lncRNA in targeting NDs to the safety of its application in the human body.

Conclusion

In recent decades, thanks to advances in high-throughput sequencing technologies and whole-genome and transcriptome studies, it has been possible to discover new mechanisms of variability involved in the regulation of gene expression.

In recent years, various research groups have pointed out that lncRNAs play a major role in central nervous system development through epigenetic and translational modifications. The emerging role of lncRNAs in NDs (**Additional Table 1**), suggests that their dysregulation could trigger neuronal death through as yet unexplored RNA-based regulatory mechanisms that deserve further investigation. The evaluation of their diagnostic significance and their therapeutic potential could also address the development of new treatments for diseases for which a cure is not yet available.

Author contributions: *Conceptualization: PR, EG, FLC; methodology, resources, writing—original draft preparation: PR; writing—review and editing: PR, FDA, EG, and FLC. All authors have read and agreed to the published version of the manuscript.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Availability of data and materials: *All data generated or analyzed during this study are included in this published article and its supplementary information files.*
Open access statement: *This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.*
Additional file:
Additional Table 1: *List of lncRNAs associated with the pathogenesis of NDs and eligible as therapeutic targets.*

References

Adams SJ, Crook RJ, Deture M, Randle SJ, Innes AE, Yu XZ, Lin WL, Dugger BN, McBride M, Hutton M, Dickson DW, McGowan E (2009) Overexpression of wild-type murine tau results in progressive tauopathy and neurodegeneration. Am J Pathol 175:1598-1609.

Ahmadi S, Zobeiri M, Bradburn S (2020) Molecular mechanisms underlying actions of certain long noncoding RNAs in Alzheimer's disease. Metab Brain Dis 35:681-693.

Amaral PP, Dinger ME, Mercer TR, Mattick JS (2008) The eukaryotic genome as an RNA machine. Science 319:1787-1789.

Asadi MR, Hassani M, Kiani S, Sabaie H, Moslehian MS, Kazemi M, Ghafouri-Fard S, Taheri M, Rezazadeh M (2021) The perspective of dysregulated lncRNAs in Alzheimer's disease: a systematic scoping review. Front Aging Neurosci 13:709568.

Balas MM, Johnson AM (2018) Exploring the mechanisms behind long noncoding RNAs and cancer. Noncoding RNA Res 3:108-117.

Beckedorff FC, Ayupe AC, Crocci-Souza R, Amaral MS, Nakaya HI, Soltys DT, Menck CF, Reis EM, Verjovski-Almeida S (2013) The intronic long noncoding RNA ANRASSF1 recruits PRC2 to the RASSF1A promoter, reducing the expression of RASSF1A and increasing cell proliferation. PLoS Genet 9:e1003705.

Bhattacharyya N, Pandey V, Bhattacharyya M, Dey A (2021) Regulatory role of long non coding RNAs (lncRNAs) in neurological disorders: from novel biomarkers to promising therapeutic strategies. Asian J Pharm Sci 16:533-550.

Bird A (2007) Perceptions of epigenetics. Nature 447:396-398.

Boros FA, Vecsei L, Klivenyi P (2021) NEAT1 on the field of Parkinson's disease: offense, defense, or a player on the bench? J Parkinsons Dis 11:123-138.

Butler AA, Johnston DR, Kaur S, Lubin FD (2019) Long noncoding RNA NEAT1 mediates neuronal histone methylation and age-related memory impairment. Sci Signal 12:eaaw9277.

Cai Z, Wang C, Yang W (2016) Role of berberine in Alzheimer's disease. Neuropsychiatr Dis Treat 12:2509-2520.

Chen J, Wang X, Yi X, Wang Y, Liu Q, Ge R (2013) Induction of KLF4 contributes to the neurotoxicity of MPP + in M17 cells: a new implication in Parkinson's disease. J Mol Neurosci 51:109-117.

Chen KW, Chen JA (2020) Functional roles of long non-coding RNAs in motor neuron development and disease. J Biomed Sci 27:38.

Chen L, Zhang S (2016) Long noncoding RNAs in cell differentiation and pluripotency. Cell Tissue Res 366:509-521.

Chen Y, Lian YJ, Ma YQ, Wu CJ, Zheng YK, Xie NC (2018) LncRNA SNHG1 promotes alpha-synuclein aggregation and toxicity by targeting miR-15b-5p to activate SIAH1 in human neuroblastoma SH-SY5Y cells. Neurotoxicology 68:212-221.

Cheng J, Duan Y, Zhang F, Shi J, Li H, Wang F, Li H (2021) The role of lncRNA TUG1 in the Parkinson disease and its effect on microglial inflammatory response. Neuromolecular Med 23:327-334.

Cherian A, Divya KP (2020) Genetics of Parkinson's disease. Acta Neurol Belg 120:1297-1305.

Coppede F (2020) Epigenetics of neuromuscular disorders. Epigenomics 12:2125-2139.

Coppede F (2021) Epigenetic regulation in Alzheimer's disease: is it a potential therapeutic target? Expert Opin Ther Targets 25:283-298.

Coppede F (2022) Targeting the epigenome to treat neurodegenerative diseases or delay their onset: a perspective. Neural Regen Res 17:1745-1747.

Costa FF (2008) Non-coding RNAs, epigenetics and complexity. Gene 410:9-17.

Coupland KG, Kim WS, Halliday GM, Hallupp M, Dobson-Stone C, Kwok JB (2016) Role of the long non-coding RNA MAPT-AS1 in regulation of microtubule associated protein Tau (MAPT) expression in Parkinson's disease. PLoS One 11:e0157924.

Creighton SD, Stefanelli G, Reda A, Zovkic IB (2020) Epigenetic mechanisms of learning and memory: implications for aging. Int J Mol Sci 21:6918.

Ding XM, Zhao LJ, Qiao HY, Wu SL, Wang XH (2019) Long non-coding RNA-p21 regulates MPP(+)-induced neuronal injury by targeting miR-625 and derepressing TRPM2 in SH-SY5Y cells. Chem Biol Interact 307:73-81.

Egger G, Liang G, Aparicio A, Jones PA (2004) Epigenetics in human disease and prospects for epigenetic therapy. Nature 429:457-463.

Faghihi MA, Zhang M, Huang J, Modarresi F, Van der Brug MP, Nalls MA, Cookson MR, St-Laurent G, 3rd, Wahlestedt C (2010) Evidence for natural antisense transcript-mediated inhibition of microRNA function. Genome Biol 11:R56.

Faghihi MA, Modarresi F, Khalil AM, Wood DE, Sahagan BG, Morgan TE, Finch CE, St Laurent G, 3rd, Kenny PJ, Wahlestedt C (2008) Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of beta-secretase. Nat Med 14:723-730.

Fan Y, Li J, Yang Q, Gong C, Gao H, Mao Z, Yuan X, Zhu S, Xue Z (2019) Dysregulated long non-coding RNAs in Parkinson's disease contribute to the apoptosis of human neuroblastoma cells. Front Neurosci 13:1320.

Fang Y, Fullwood MJ (2016) Roles, functions, and mechanisms of long non-coding RNAs in cancer. Genomics Proteomics Bioinformatics 14:42-54.

Feng L, Liao YT, He JC, Xie CL, Chen SY, Fan HH, Su ZP, Wang Z (2018) Plasma long non-coding RNA BACE1 as a novel biomarker for diagnosis of Alzheimer disease. BMC Neurol 18:4.

Fotuhi SN, Khalaj-Kondori M, Hoseinpour Feizi MA, Talebi M (2019) Long non-coding RNA BACE1-AS may serve as an Alzheimer's disease blood-based biomarker. J Mol Neurosci 69:351-359.

Fox AH, Lam YW, Leung AK, Lyon CE, Andersen J, Mann M, Lamond AI (2002) Paraspeckles: a novel nuclear domain. Curr Biol 12:13-25.

Freibaum BD, Taylor JP (2017) The role of dipeptide repeats in C9ORF72-related ALS-FTD. Front Mol Neurosci 10:35.

Gagliardi S, Pandini C, Garofalo M, Bordoni M, Pansarasa O, Cereda C (2018) Long non coding RNAs and ALS: Still much to do. Noncoding RNA Res 3:226-231.

Gao Y, Zhang N, Lv C, Li N, Li X, Li W (2020) lncRNA SNHG1 knockdown alleviates amyloid-beta-induced neuronal injury by regulating ZNF217 via sponging miR-361-3p in Alzheimer's disease. J Alzheimers Dis 77:85-98.

Ge Y, Song X, Liu J, Liu C, Xu C (2020) The combined therapy of berberine treatment with lncRNA BACE1-AS depletion attenuates Abeta25-35 induced neuronal injury through regulating the expression of miR-132-3p in neuronal cells. Neurochem Res 45:741-751.

Gentile G, Morello G, La Cognata V, Guarnaccia M, Conforti FL, Cavallaro S (2022) Dysregulated miRNAs as biomarkers and therapeutical targets in neurodegenerative diseases. J Pers Med 12:770.

Grad LI, Rouleau GA, Ravits J, Cashman NR (2017) Clinical spectrum of amyotrophic lateral sclerosis (ALS). Cold Spring Harb Perspect Med 7:a024117.

Gudenas BL, Wang L (2015) Gene coexpression networks in human brain developmental transcriptomes implicate the association of long noncoding RNAs with intellectual disability. Bioinform Biol Insights 9:21-27.

Guo C, Qi Y, Qu J, Gai L, Shi Y, Yuan C (2020) Pathophysiological functions of the lncRNA TUG1. Curr Pharm Des 26:688-700.

Hampel H, Vassar R, De Strooper B, Hardy J, Willem M, Singh N, Zhou J, Yan R, Vanmechelen E, De Vos A, Nisticò R, Corbo M, Imbimbo BP, Streffer J, Voytyuk I, Timmers M, Tahami Monfared AA, Irizarry M, Albala B, Koyama A, et al. (2021) The β-secretase BACE1 in Alzheimer's disease. Biol Psychiatry 89:745-756.

He J, Xuan X, Jiang M, Li J, Li N, Nie T (2021) Long non-coding RNA SNHG1 relieves microglia activation by downregulating miR-329-3p expression in an in vitro model of cerebral infarction. Exp Ther Med 22:1148.

He W, Chi S, Jin X, Lu J, Zheng W, Yan J, Zhang D (2020) Long non-coding RNA BACE1-AS modulates isoflurane-induced neurotoxicity to Alzheimer's disease through sponging miR-214-3p. Neurochem Res 45:2324-2335.

Huang Z, Zhao J, Wang W, Zhou J, Zhang J (2020) Depletion of lncRNA NEAT1 rescues mitochondrial dysfunction through NEDD4L-dependent PINK1 degradation in animal models of Alzheimer's disease. Front Cell Neurosci 14:28.

Huaying C, Xing J, Luya J, Linhui N, Di S, Xianjun D (2020) A signature of five long non-coding RNAs for predicting the prognosis of Alzheimer's disease based on competing endogenous RNA networks. Front Aging Neurosci 12:598606.

Jimenez-Sanchez M, Licitra F, Underwood BR, Rubinsztein DC (2017) Huntington's disease: mechanisms of pathogenesis and therapeutic strategies. Cold Spring Harb Perspect Med 7:a024240.

Katsel P, Roussos P, Fam P, Khan S, Tan W, Hirose T, Nakagawa S, Pletnikov MV, Haroutunian V (2019) The expression of long noncoding RNA NEAT1 is reduced in schizophrenia and modulates oligodendrocytes transcription. NPJ Schizophr 5:3.

Khalil AM, Guttman M, Huarte M, Garber M, Raj A, Rivea Morales D, Thomas K, Presser A, Bernstein BE, van Oudenaarden A, Regev A, Lander ES, Rinn JL (2009) Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. Proc Natl Acad Sci U S A 106:11667-11672.

Kim TK, Hemberg M, Gray JM (2015) Enhancer RNAs: a class of long noncoding RNAs synthesized at enhancers. Cold Spring Harb Perspect Biol 7:a018622.

Lan Z, Chen Y, Jin J, Xu Y, Zhu X (2021) Long non-coding RNA: insight into mechanisms of Alzheimer's disease. Front Mol Neurosci 14:821002.

Li D, Zhang J, Wang M, Li X, Gong H, Tang H, Chen L, Wan L, Liu Q (2018) Activity dependent LoNA regulates translation by coordinating rRNA transcription and methylation. Nat Commun 9:1726.

Lu Y, Liu X, Xie M, Liu M, Ye M, Li M, Chen XM, Li X, Zhou R (2017) The NF-kappaB-responsive long noncoding RNA FIRRE regulates posttranscriptional regulation of inflammatory gene expression through interacting with hnRNPU. J Immunol 199:3571-3582.

Ma P, Li Y, Zhang W, Fang F, Sun J, Liu M, Li K, Dong L (2019) Long non-coding RNA MALAT1 inhibits neuron apoptosis and neuroinflammation while stimulates neurite outgrowth and its correlation with MiR-125b mediates PTGS2, CDK5 and FOXQ1 in Alzheimer's disease. Curr Alzheimer Res 16:596-612.

Maag JL, Panja D, Sporild I, Patil S, Kaczorowski DC, Bramham CR, Dinger ME, Wibrand K (2015) Dynamic expression of long noncoding RNAs and repeat elements in synaptic plasticity. Front Neurosci 9:351.

MacDonald WA, Mann MRW (2020) Long noncoding RNA functionality in imprinted domain regulation. PLoS Genet 16:e1008930.
Masrori P, Van Damme P (2020) Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol 27:1918-1929.
Mizielinska S, Ridler CE, Balendra R, Thoeng A, Woodling NS, Grasser FA, Plagnol V, Lashley T, Partridge L, Isaacs AM (2017) Bidirectional nucleolar dysfunction in C9orf72 frontotemporal lobar degeneration. Acta Neuropathol Commun 5:29.
Modarresi F, Faghihi MA, Lopez-Toledano MA, Fatemi RP, Magistri M, Brothers SP, van der Brug MP, Wahlestedt C (2012) Inhibition of natural antisense transcripts in vivo results in gene-specific transcriptional upregulation. Nat Biotechnol 30:453-459.
Ni Y, Huang H, Chen Y, Cao M, Zhou H, Zhang Y (2017) Investigation of long non-coding RNA expression profiles in the Substantia Nigra of Parkinson's disease. Cell Mol Neurobiol 37:329-338.
Nishimoto Y, Nakagawa S, Okano H (2021) NEAT1 lncRNA and amyotrophic lateral sclerosis. Neurochem Int 150:105175.
Nishimoto Y, Nakagawa S, Hirose T, Okano HJ, Takao M, Shibata S, Suyama S, Kuwako K, Imai T, Murayama S, Suzuki N, Okano H (2013) The long non-coding RNA nuclear-enriched abundant transcript 1_2 induces paraspeckle formation in the motor neuron during the early phase of amyotrophic lateral sclerosis. Mol Brain 6:31.
Peschansky VJ, Wahlestedt C (2014) Non-coding RNAs as direct and indirect modulators of epigenetic regulation. Epigenetics 9:3-12.
Puvvula PK (2019) LncRNAs regulatory networks in cellular senescence. Int J Mol Sci 20:2615.
Qi X, Shao M, Sun H, Shen Y, Meng D, Huo W (2017) Long non-coding RNA SNHG14 promotes microglia activation by regulating miR-145-5p/PLA2G4A in cerebral infarction. Neuroscience 348:98-106.
Qian C, Ye Y, Mao H, Yao L, Sun X, Wang B, Zhang H, Xie L, Zhang H, Zhang Y, Zhang S, He X (2019) Downregulated lncRNA-SNHG1 enhances autophagy and prevents cell death through the miR-221/222 /p27/mTOR pathway in Parkinson's disease. Exp Cell Res 384:111614.
Rasheed M, Liang J, Wang C, Deng Y, Chen Z (2021) Epigenetic regulation of neuroinflammation in Parkinson's disease. Int J Mol Sci 22:4956.
Rathore AS, Birla H, Singh SS, Zahra W, Dilnashin H, Singh R, Keshri PK, Singh SP (2021) Epigenetic modulation in Parkinson's disease and potential treatment therapies. Neurochem Res 46:1618-1626.
Rayner KJ, Liu PP (2016) Long noncoding RNAs in the heart: the regulatory roadmap of cardiovascular development and disease. Circ Cardiovasc Genet 9:101-103.
Rohan de Silva JZP, Almeida F, Svenningsson P, Warner T, Simone R (2006) A gene therapy approach for reduction of Tau by Tau long non-codING RNA gene (MAPT-AS1) natural antisense transcript. Alzheimers Dement 14:1547-1548.
Ruffo P, Strafella C, Cascella R, Caputo V, Conforti FL, Ando S, Giardina E (2021) Deregulation of ncRNA in neurodegenerative disease: focus on circRNA, lncRNA and miRNA in amyotrophic lateral sclerosis. Front Genet 12:784996.
Sabaie H, Amirinejad N, Asadi MR, Jalaiei A, Daneshmandpour Y, Rezaei O, Taheri M, Rezazadeh M (2021) Molecular insight into the therapeutic potential of long non-coding RNA-associated competing endogenous RNA axes in Alzheimer's disease: a systematic scoping review. Front Aging Neurosci 13:742242.
Sayad A, Najafi S, Hussen BM, Abdullah ST, Movahedpour A, Taheri M, Hajiesmaeili M (2022) The emerging roles of the beta-secretase BACE1 and the long non-coding RNA BACE1-AS in human diseases: a focus on neurodegenerative diseases and cancer. Front Aging Neurosci 14:853180.
Shishido T, Nagano Y, Araki M, Kurashige T, Obayashi H, Nakamura T, Takahashi T, Matsumoto M, Maruyama H (2019) Synphilin-1 has neuroprotective effects on MPP(+)-induced Parkinson's disease model cells by inhibiting ROS production and apoptosis. Neurosci Lett 690:145-150.
Soria Lopez JA, Gonzalez HM, Leger GC (2019) Alzheimer's disease. Handb Clin Neurol 167:231-255.
Strafella C, Caputo V, Termine A, Assogna F, Pellicano C, Pontieri FE, Macchiusi L, Minozzi G, Gambardella S, Centonze D, Bossu P, Spalletta G, Caltagirone C, Giardina E, Cascella R (2021) Immune system and neuroinflammation in idiopathic Parkinson's disease: association analysis of genetic variants and miRNAs interactions. Front Genet 12:651971.
Sun Q, Zhang Y, Wang S, Yang F, Cai H, Xing Y, Chen Z, Chen J (2021) NEAT1 decreasing suppresses Parkinson's disease progression via acting as miR-1301-3p sponge. J Mol Neurosci 71:369-378.
Tripathi V, Shen Z, Chakraborty A, Giri S, Freier SM, Wu X, Zhang Y, Gorospe M, Prasanth SG, Lal A, Prasanth KV (2013) Long noncoding RNA MALAT1 controls cell cycle progression by regulating the expression of oncogenic transcription factor B-MYB. PLoS Genet 9:e1003368.
Tronick E, Hunter RG (2016) Waddington, dynamic systems, and epigenetics. Front Behav Neurosci 10:107.
Ungaro C, Sprovieri T, Morello G, Perrone B, Spampinato AG, Simone IL, Trojsi F, Monsurro MR, Spataro R, La Bella V, Ando S, Cavallaro S, Conforti FL (2021) Genetic investigation of amyotrophic lateral sclerosis patients in south Italy: a two-decade analysis. Neurobiol Aging 99:99.e97-99.e14.
Walker FO (2007) Huntington's disease. Lancet 369:218-228.
Wang KC, Chang HY (2011) Molecular mechanisms of long noncoding RNAs. Mol Cell 43:904-914.
Wang S, Zhang X, Guo Y, Rong H, Liu T (2017) The long noncoding RNA HOTAIR promotes Parkinson's disease by upregulating LRRK2 expression. Oncotarget 8:24449-24456.
Wang Z, Zhao Y, Xu N, Zhang S, Wang S, Mao Y, Zhu Y, Li B, Jiang Y, Tan Y, Xie W, Yang BB, Zhang Y (2019) NEAT1 regulates neuroglial cell mediating Abeta clearance via the epigenetic regulation of endocytosis-related genes expression. Cell Mol Life Sci 76:3005-3018.
Wei JW, Huang K, Yang C, Kang CS (2017) Non-coding RNAs as regulators in epigenetics (Review). Oncol Rep 37:3-9.
Wijesekera LC, Leigh PN (2009) Amyotrophic lateral sclerosis. Orphanet J Rare Dis 4:3.
Winkle M, El-Daly SM, Fabbri M, Calin GA (2021) Noncoding RNA therapeutics-challenges and potential solutions. Nat Rev Drug Discov 20:629-651.
Xu W, Li K, Fan Q, Zong B, Han L (2020) Knockdown of long non-coding RNA SOX21-AS1 attenuates amyloid-beta-induced neuronal damage by sponging miR-107. Biosci Rep 40:BSR20194295.
Xu X, Zhuang C, Wu Z, Qiu H, Feng H, Wu J (2018) LincRNA-p21 inhibits cell viability and promotes cell apoptosis in Parkinson's disease through activating alpha-synuclein expression. Biomed Res Int 2018:8181374.
Yan W, Chen ZY, Chen JQ, Chen HM (2018) LncRNA NEAT1 promotes autophagy in MPTP-induced Parkinson's disease through stabilizing PINK1 protein. Biochem Biophys Res Commun 496:1019-1024.
Yu Y, Pang D, Li C, Gu X, Chen Y, Ou R, Wei Q, Shang H (2022) The expression discrepancy and characteristics of long non-coding RNAs in peripheral blood leukocytes from amyotrophic lateral sclerosis patients. Mol Neurobiol 59:3678-3689.
Zhang J, Wang R (2021) Deregulated lncRNA MAGI2-AS3 in Alzheimer's disease attenuates amyloid-beta induced neurotoxicity and neuroinflammation by sponging miR-374b-5p. Exp Gerontol 144:111180.
Zhang L, Fang Y, Cheng X, Lian YJ, Xu HL (2019a) Silencing of long noncoding RNA SOX21-AS1 relieves neuronal oxidative stress injury in mice with Alzheimer's disease by upregulating FZD3/5 via the Wnt signaling pathway. Mol Neurobiol 56:3522-3537.
Zhang L, Wang J, Liu Q, Xiao Z, Dai Q (2020) Knockdown of long non-coding RNA AL049437 mitigates MPP+-induced neuronal injury in SH-SY5Y cells via the microRNA-205-5p/MAPK1 axis. Neurotoxicology 78:29-35.
Zhang LM, Wang MH, Yang HC, Tian T, Sun GF, Ji YF, Hu WT, Liu X, Wang JP, Lu H (2019b) Dopaminergic neuron injury in Parkinson's disease is mitigated by interfering lncRNA SNHG14 expression to regulate the miR-133b/ alpha-synuclein pathway. Aging (Albany NY) 11:9264-9279.
Zhang Q, Huang XM, Liao JX, Dong YK, Zhu JL, He CC, Huang J, Tang YW, Wu D, Tian JY (2021) LncRNA HOTAIR promotes neuronal damage through facilitating NLRP3 mediated-pyroptosis activation in Parkinson's disease via regulation of miR-326/ ELAVL1 axis. Cell Mol Neurobiol 41:1773-1786.
Zhang X, Zhao X, Li Y, Zhou Y, Zhang Z (2019c) Long noncoding RNA SOX21-AS1 promotes cervical cancer progression by competitively sponging miR-7/VDAC1. J Cell Physiol 234:17494-17504.
Zhao J, Li H, Chang N (2020) LncRNA HOTAIR promotes MPP+-induced neuronal injury in Parkinson's disease by regulating the miR-874-5p/ATG10 axis. EXCLI J 19:1141-1153.
Zhao MY, Wang GQ, Wang NN, Yu QY, Liu RL, Shi WQ (2019) The long-non-coding RNA NEAT1 is a novel target for Alzheimer's disease progression via miR-124/BACE1 axis. Neurol Res 41:489-497.
Zhou S, Zhang D, Guo J, Zhang J, Chen Y (2020) Knockdown of SNHG14 alleviates MPP(+)-induced injury in the cell model of Parkinson's disease by targeting the miR-214-3p/ KLF4 axis. Front Neurosci 14:930.
Zhou S, Zhang D, Guo J, Chen Z, Chen Y, Zhang J (2021a) Deficiency of NEAT1 prevented MPP(+)-induced inflammatory response, oxidative stress and apoptosis in dopaminergic SK-N-SH neuroblastoma cells via miR-1277-5p/ARHGAP26 axis. Brain Res 1750:147156.
Zhou S, Yu X, Wang M, Meng Y, Song D, Yang H, Wang D, Bi J, Xu S (2021b) Long non-coding RNAs in pathogenesis of neurodegenerative diseases. Front Cell Dev Biol 9:719247.
Zhuang J, Cai P, Chen Z, Yang Q, Chen X, Wang X, Zhuang X (2020) Long noncoding RNA MALAT1 and its target microRNA-125b are potential biomarkers for Alzheimer's disease management via interactions with FOXQ1, PTGS2 and CDK5. Am J Transl Res 12:5940-5954.

C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y

Additional Table 1 List of lncRNAs associated with the pathogenesis of NDs and eligible as therapeutic targets

Disease	lncRNAs	Molecular mechanism	Target	Pathology related changes	Cellular localization	Expression pattern	Disease models used for the study	Mouse model phenotype	Reference
AD	*BACE1-AS*	lncRNA-AS	BACE1	β-Secretase synthesis	Nucleus/ Chromatin	Glia and cortical neurons	*in vivo* and *in vitro* mouse and human brains	Transgenic mice	Faghihi et al., 2008
	SNHG1	Guide, scaffold, and sponge	miR-137/KREMEN1 and miR-361-3p/ZNF217	Neuronal apoptosis	Nuclear	Microglia cells	*in vivo* and *in vitro* mouse and human cell assay	Knockout mice	Qi et al., 2017
	NEAT1	Guide, scaffold, sponge, and signal	PINK1, NEDD4L, miR-124/*BACE1, miR-1301-3p*	Tau phosphorylation	Nuclear	Cerebrocortical regions, astrocytic	*in vivo* and *in vitro* mouse and human brains	Transgenic mice	Katsel et al., 2019; Wang et al., 2019
	SOX21-AS1	lncRNA-AS	miR-107	Neuronal oxidative stress	Subcellular localization	Neurogenic regions	*in vitro* mouse and human cell assay	Transgenic mice	Zhang et al., 2019c
	LoNA	Guide, scaffold, and sponge	*NCL, FBL*	Synaptic activity and long-term memory	Nuclear	Neuronal soma	*in vitro* cell assay	Transgenic mice	Bhattacharyya et al., 2021
	MALAT1	Guide, scaffold, and sponge	miR-125b, FOXQ1, CDK5	Neuroinflammation and apoptosis	Nuclear	Neurons	*in vitro* mouse and human cell assay	Transgenic mice	Zhuang et al., 2020
	MAPT-AS1	lncRNA-AS	MAPT	Neurodegenerative process	Nuclear	Putamen, anterior cingulate, visual cortices, and cerebellum	*in vivo* and *in vitro* human brains	Knockout and/or transgenic mice	Coupland et al., 2016; Ahmadi et al., 2020
PD	*SNHG1*	Scaffold and sponge	miR-153-3p , miR-7/NLRP3 , miR-221/222/p27/mTOR	Neuronal autophagy and cell death	Nuclear or cytoplasm	Microglia cells	*in vivo* and *in vitro* mouse and human cell assay	Knockout mice	He et al., 2021
	NEAT1	Guide, scaffold, sponge, and signal	PINK1 , NEDD4L, miR-124/*BACE1, miR-1301-3p*	Autophagic process and neural damage	Nuclear	Cerebrocortical regions, astrocytic	*in vivo* and *in vitro* mouse and human brains	Transgenic mice	Boros et al., 2021; He et al., 2021
	HOTAIR	Scaffold, sponge, and enhancer	NLRP3, miR-326 / ELAVL1 , miR-126-5p, RAB3IP and miR-874-5p	Neuroinflammation and apoptosis	Nuclear	Glia neurons	*in vitro* cell assay	Knockout and/or transgenic mice	Zhao et al., 2020; Rasheed et al., 2021

	SNHG14	Scaffold and sponge	miR-133b, miR-214-3p, KLF4	Neuroinflammation and α-synuclein expression	Cytoplasm	(not specified)	*in vitro* cell assay	Knockout mice	Zhou et al., 2020
	TP53COR1	Sponge and enhancer	miR-1277-5p	α-Synuclein modulation and programmed cell death	Nuclear	Microglia cells	*in vitro* cell assay	Knockout mice	Xu et al., 2018
	AL049437	Scaffold and sponge	TNF-α, IL-6	Neuroinflammation and oxidative stress	Cytoplasm	Substantia nigra	*in vivo* and *in vitro* mouse cell assay	Transgenic mice	Ni et al., 2017 Zhang et al., 2020
ALS	*C9Orf72-AS*	lncRNA-AS	C9Orf72	Polypeptide and RNA foci formation	Nuclear	Frontal cortex, cerebellum, and spinal cord	*in vivo* and *in vitro* animal and human brains	Knockout mice	Chen and Chen, 2020
	NEAT1_2	Scaffold, sponge, and signal	TDP-43 and FUS	Formation of paraspeckles, inflammation, cell cycle triggering, and apoptosis	Nuclear	Spinal cord and spinal ventral horn	*in vivo* and *in vitro* mouse and human brains	Transgenic mice	Nishimoto et al., 2021
HD	*TUG1*	Not specified	PRC2	Cell cycle and cytotoxicity	Cytoplasm	Not specified	*in vitro* cell assay	Transgenic mice	Khalil et al., 2009

BACE1: β-Site amyloid precursor protein cleaving enzyme 1; *BACE1-AS*: BACE1 antisense RNA; *C9Orf72*: chromosome 9 open reading frame 72; *C9Orf72-AS*: C9Orf72 antisense RNA; *CDK5*: cyclin-dependent kinase 5; *ELAVL1*: ELAV like RNA binding protein 1; *FBL*: fibrillarin; *FOXQ1*: forkhead box Q1; *FUS*: fused in sarcoma; *HOTAIR*: Hox transcript antisense RNA; *IL-6*: interleukin 6; *KLF4*: Kruppel like factor 4; *KREMEN1*: Kringle containing transmembrane protein 1; *LoNA*: long nucleolus-specific lncRNA; *MALAT1*: metastasis-associated lung adenocarcinoma transcript 1; *MAPT*: microtubule-associated protein tau; *MAPT-AS1*: MAPT antisense RNA 1; *mTOR*: mammalian target of rapamycin kinase; *NCL*: neuronal ceroid lipofuscinoses; *NEAT1*: nuclear paraspeckle assembly transcript 1; *NEDD4L*: Neural precursor cell expressed developmentally downregulated gene 4-like; *NLRP3*: NLR family Pyrin domain containing 3; *PINK1*: PTEN-induced kinase 1; *RAB3IP*: RAB3A interacting protein; *SNHG1*: small nucleolar RNA host gene 1; *SNHG14*: small nucleolar RNA host gene 14; *SOX21-AS1*: SOX21 antisense divergent transcript 1; *TDP-43*: TAR DNA-binding protein 43; *TNF-α*: tumor necrosis factor α; *TP53COR1*: tumor protein P53 pathway corepressor 1; *TUG1*: taurine upregulated gene 1; *ZNF217*: zinc finger protein 217.