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Review Article

Long non-coding RNAs in humans: Classification, genomic organization and function

Barbara Chodurska [a,b], Tanja Kunej [a,*]

[a] University of Ljubljana, Biotechnical Faculty, Department of Animal Science, Slovenia
[b] Medical University of Łódź, Faculty of Biomedical Sciences, Poland

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ABSTRACT

Long non-coding RNAs (lncRNAs) regulate numerous biological functions in animals. Despite recent advances in lncRNA research, their structural and functional annotation and classification remain an ongoing challenge. This review provides a comprehensive overview of human lncRNAs, highlighting their genomic organization, mode of action and role in physiological and pathological processes. Subgroups of lncRNA genes are discussed using representative examples and visualizations of genomic organization. The HUGO Gene Nomenclature Committee (HGNC) categorizes lncRNAs into nine subgroups: (1) microRNA non-coding host genes, (2) small nucleolar RNA non-coding host genes, (3) long intergenic non-protein coding RNAs (LINC), (4) antisense RNAs, (5) overlapping transcripts, (6) intronic transcripts, (7) divergent transcripts, (8) long non-coding RNAs with non-systematic symbols and (9) long non-coding RNAs with FAM root systems. Circular RNAs (circRNAs) are a separate class that shares some characteristics with lncRNAs and are divided into exonic, intronic and intronic-exonic types. LncRNAs act as molecular signals, decoys, scaffolds and sponges for microRNAs and often function as competing endogenous RNAs (ceRNAs). LncRNAs are involved in various physiological and pathological processes, such as cell differentiation, p53-mediated DNA damage response, glucose metabolism, inflammation and immune functions. They are associated with several diseases, including various types of neoplasms, Alzheimer's disease and autoimmune diseases. A clear classification system for lncRNA is essential for understanding their biological role and for facilitating practical applications in biomedical research. Future studies should focus on drug development and biomarker discovery. As important regulators of various biological processes, lncRNAs represent promising targets for innovative therapies.

1. Introduction

Long non-coding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides (nt) that are generally not translated. They are usually capped, polyadenylated and spliced. The origins of lncRNAs are diverse, including pre-existing protein-coding sequences, chromosomal rearrangements, retrotranspositions, tandem duplications and insertions of transposable elements. LncRNAs are transcribed from various genomic regions, including promoter upstream regions, enhancers, intergenic regions and the reverse strand of protein-coding genes [1]. LncRNAs are categorized into sense, antisense, bidirectional, intronic and intergenic lncRNAs based on their genomic location [2]. The classification has recently been extended to nine subgroups by the HUGO Gene Nomenclature Committee (HGNC) [3].

LncRNAs regulate cell differentiation and development in mammals. They play roles in physiological processes such as the p53-mediated DNA damage response, immune cell recombination, cytokine expression, endotoxic shock, inflammation, and neuropathic pain, cholesterol biosynthesis and homeostasis, growth hormone and prolactin production, glucose metabolism, cellular signal transduction and transport pathways, synapse function and learning. LncRNAs have been associated with cell membranes and ribozymes [4]. Sequence variants and changes in lncRNA expression are associated with various human diseases such as cancer, cardiovascular diseases and neurodegenerative diseases [2,4–6].

Circular RNAs (circRNAs) share some properties with lncRNAs and play crucial roles in RNA functions. CircRNAs can be categorized into three types: exonic, intronic, and exonic-intronic. CircRNAs and ncRNAs

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* Corresponding author.
E-mail addresses: barbara.chodurska@wp.pl (B. Chodurska), tanja.kunej@bf.uni-lj.si (T. Kunej).

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compete for binding to shared microRNAs (miRNAs) and cross-regulate each other at the post-transcriptional level [7].

In lncRNA research, perspectives on classification have evolved over time. While lncRNAs are generally defined as transcripts longer than 200 nt, some studies propose using a threshold of 500 nt, as certain RNAs between 200 and 500 nt, such as 7SK (~330 nt) and 7SL (~300 nt), exhibit coding functions [4]. Research on lncRNAs is rapidly increasing; however, their classification is complicated by inconsistencies between databases, reflecting the rapid evolution of research in this field. These inconsistencies highlight the major challenges in the discovery and characterization of lncRNAs and point to a crucial gap in our current understanding.

The aim of this review was to provide a comprehensive overview of human lncRNA. We have presented examples of lncRNA from different subgroups, their mode of action and function. In this review, lncRNAs are categorized into nine subgroups, which illustrates their diversity. Numerous studies have investigated disease-relevant lncRNAs in humans and gained insights into their structural features, expression profiles and biological functions. By summarizing these findings, we highlight various functions of lncRNAs and their importance in human biology.

The data for lncRNA examples were extracted from the HGNC database [3] (last update: 2024-12-06). The Ensembl genome browser (release 113) was used to visualize the genomic organization [8], while the genomic positions were extracted from Ensembl and NCBI databases [9]. Gene Ontology (GO) terms, including cellular components, biological processes and molecular functions, were extracted from Ensembl [8]. Gene descriptions were obtained from Gene Cards [10] and PubMed. CircRNA data and disease associations were obtained from the PubMed and LncRNADisease v3.0 database [11]. The terms "MIR" and "miR" refer to miRNA gene loci and mature miRNAs, respectively.

A graphical summary of the review is shown in Fig. 1 and includes lncRNA classification and functions.

2. LncRNA subgroups according to HGNC classification

Classification of lncRNAs is mostly based on their genomic organization and provides information about their spatial relationships to nearby genes and their genomic arrangement, which may be critical for determining their potential regulatory functions and interactions within the genome [2]. Two subgroups (non-systematic symbols and FAM root system) are additional categories not strictly defined by genomic

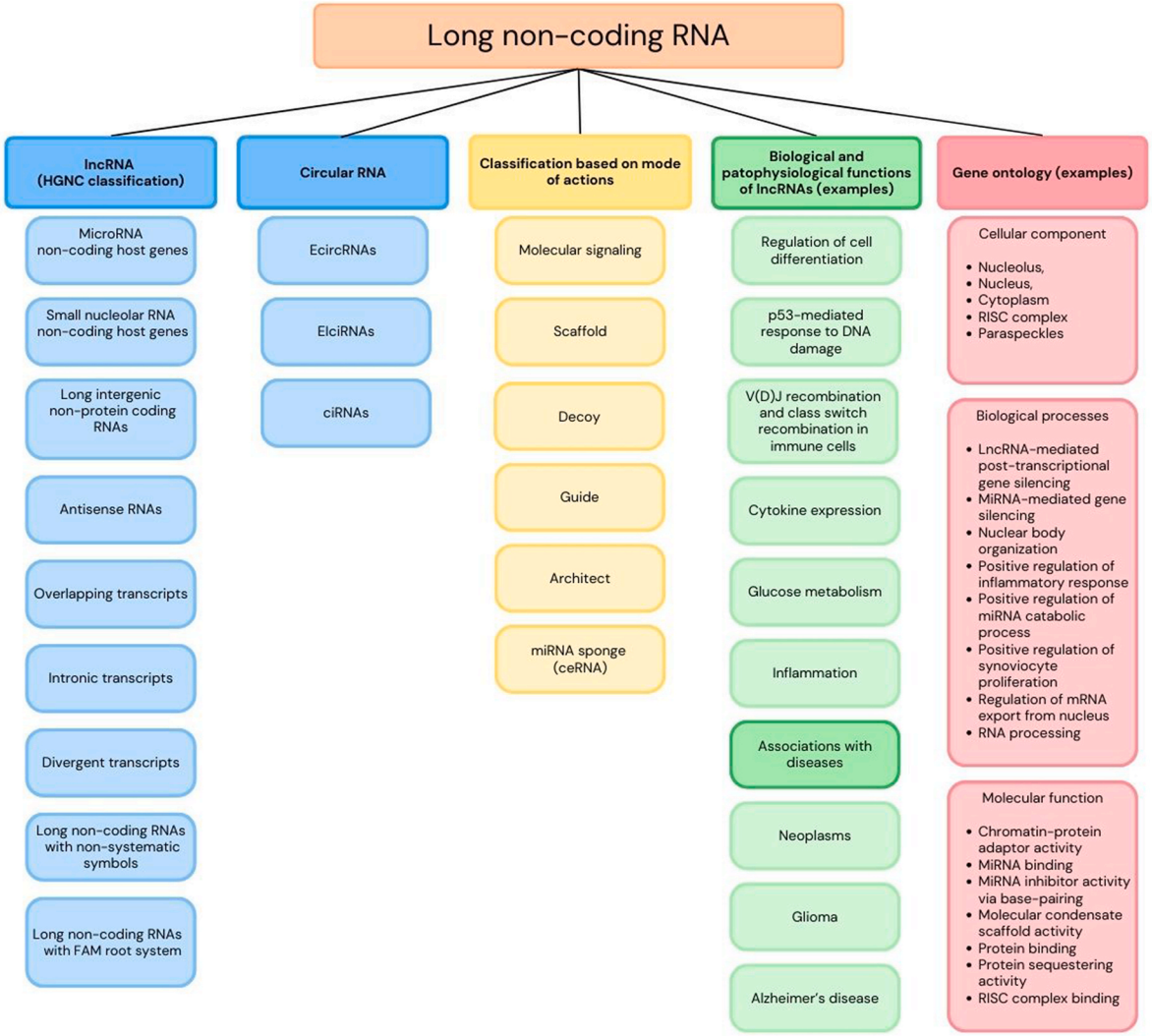

Fig. 1. Classification of lncRNA subgroups according to HGNC and their functions. Circular RNAs, as a distinct class of ncRNAs, are presented with an overview of their types. Although most circRNAs are non-coding, some can retain coding potential.
HGNC – Human Gene Nomenclature Committee, EcircRNAs – exonic circular RNAs, EIciRNAs – exonic-intronic circular RNAs, ciRNAs – intronic circular RNAs, ceRNA – competing endogenous RNAs, VDJ – variable, diversity and joining gene segments involved in immune cell recombination, FAM root system – family with sequence similarity root system, RISC – RNA-induced silencing complex.

context. The lncRNA subgroups with gene examples are listed in Table 1.

Fig. 2 provides an overview of nine lncRNA subgroups, summarizing their key characteristics and visualizing their genomic organization. LncRNAs encompass a broad spectrum of genes that have been the focus of extensive research, including prominent examples such as *HOTAIR*, *PANDAR*, *XIST* as well as *CERNA1* and *CERNA2*. Some lncRNA genes are categorized into more than one subgroup. *H19*, for example, belongs to the non-coding miRNA host genes and the long non-coding RNAs with non-systematic symbols. *DANCR* belongs to three groups: miRNA non-coding host genes, snoRNA non-coding host genes and the long non-coding RNAs with non-systematic symbols.

Some protein-coding genes are linked to specific lncRNAs. For example, the *GABPB1* gene is linked to two lncRNAs: an antisense lncRNA named *GABPB1-AS1* and an intronic lncRNA named *GABPB1-IT1*. Table 1 also shows the number of genes within each lncRNA subgroup based on the HGNC data. The largest number of genes is found in the LINC, antisense and divergent transcript lncRNA subgroups. As of 12/2024, the HGNC database contains 5751 lncRNA genes, while Ensembl contains 35,076. These numbers are likely to increase in the future.

The number of PubMed publications illustrates the most intensively studied lncRNA genes; however, these publications are not evenly distributed across the lncRNA subclasses. Most studies focus on miRNA non-coding miRNA host genes, snoRNA non-coding host genes and long non-coding RNAs with non-systematic symbols. For each lncRNA subgroup, we provide a brief description of five lncRNA examples, including their genomic positions and main functions. Figs. 3–11 show graphical visualizations of the genomic locations of lncRNAs from nine HGNC subclasses. The genomic visualizations are from Ensembl and in some cases have been simplified for clarity without changing the original information.

Table 1
Subgroups of lncRNAs: HGNC classification, gene examples and publication count in PubMed.

Subgroups of lncRNA	No. of genes within the group (HGNC)[1]	Examples of lncRNAs genes[2]	Number of publications (PubMed)[3]
MicroRNA non-coding host genes (miRNA non-coding host genes)	99 (1.7 %)	*H19*	4438
		DANCR	247
		MEG3	1449
		NEAT1	1540
		MIR17HG	272
Small nucleolar RNA non-coding host genes (snoRNA non-coding host genes)	37 (0.6 %)	*SNHG1*	351
		ZFAS1	261
		SNHG3	175
		SNHG5	145
		SNHG14	157
		DANCR	247
Long intergenic non-protein coding RNAs (LINC)	2299 (40 %)	*LINC00092*	19
		LINC00657	46
		LINC00312	38
		LINC00114	8
		LINC00028	2
Antisense RNAs (-AS1)	1957 (34 %)	*ABCA9-AS1*	3
		AGAP2-AS1	83
		CD27-AS1	12
		DLX6-AS1	124
		FBXL19-AS1	29
		GABPB1-AS1	23
Overlapping transcripts (-OT)	21 (0.4 %)	*SOX1-OT*	4
		SOX2-OT	65
		TGFB2-OT1	8
		C21orf91-OT1	1
		SPANXA2-OT1	1
Intronic transcripts (-IT1)	137 (2.4 %)	*SPRY4-IT1*	117
		RUNX1-IT1	23
		ALMS1-IT1	12
		FTO-IT1	2
		GABPB1-IT1	5
Divergent transcripts (-DT)	609 (10.6 %)	*EIF3J-DT*	6
		ITGB1-DT	12
		KDM7A-DT	3
		BARX1-DT	2
		CHKB-DT	2
Long non-coding RNAs with non-systematic symbols	491 (8.5 %)	*BANCR*	119
		ELDR	15
		LCDR	62
		CYTOR	109
		DBET	17
		DANCR	247
		H19	4438
		HOTAIR	1981
		XIST	2335
		PANDAR	68
		CERNA1	8
		CERNA2	5
		CERNA3	1
Long non-coding RNAs with FAM root system (FAM [number])	101 (1.8 %)	*FAM30A*	17
		FAM99A	10
		FAM215A	7
		FAM230A	2
		FAM239A	2
	Sum: 5751		

Legend: [1] Number of genes within the group and their percentage relative to all lncRNA genes in the HGNC database (n = 5751). [2] Some genes are classified into multiple lncRNA classes. [3] Query performed using official (HGNC) lncRNA gene symbol.

2.1. MicroRNA non-coding host genes

This subgroup includes lncRNA genes that contain a miRNA gene either within an intron or an exon on the same strand. Five examples from this group are described below: *H19*, *DANCR*, *MEG3*, *NEAT1*, and *MIR17HG*. Of these, *H19* is located on the reverse strand, while the other four lncRNA genes are located on the forward strand.

2.1.1. H19 (H19 imprinted maternally expressed transcript)

H19, located on the reverse strand of chromosome 11, hosts the miRNA gene *MIR675* (Fig. 3) [10], and it has 46 transcripts [8]. *H19* belongs to two lncRNA groups, besides the group of miRNA non-coding host genes also to the lncRNAs with no systematic symbol [3]. It also shares a partial position with two novel miscellaneous RNAs (miscRNA) transcripts – *ENST00000617997* and *ENST00000620857* [8]. *H19* is located downstream of insulin-like growth factor 2 (*IGF2*), and the two are often co-regulated. *H19* is expressed on the maternally inherited chromosome, while *IGF2* is expressed on the paternally inherited chromosome. This expression pattern is a hallmark of genomic imprinting, in which the expression of a gene is determined by its parental origin and not by the standard two-allele model. Variations in these genes have been associated with Beckwith-Wiedemann syndrome and Wilms tumor, a rare kidney cancer that primarily affects children, with both genes playing an important role in the development and progression of this disease [10]. In acute kidney injury, *H19* is also involved in reducing cell death and inflammation [12].

2.1.2. DANCR (differentiation antagonizing non-protein coding RNA)

DANCR is located on the forward strand of chromosome 4. It hosts the miRNA gene *MIR4449* and partially overlaps with the lncRNA gene *ENSG00000286161* and the snoRNA gene *SNORA26*. *DANCR* has 14 transcripts and is categorized into three lncRNA groups: miRNA non-coding host gene, snoRNA non-coding host gene, and lncRNA with non-systematic symbols [3,8]. *DANCR* is transcribed in the same genomic region as *LINC01618*, a lincRNA associated with colorectal cancer [10]. *DANCR* functions as a negative regulator of cell differentiation. This transcript interacts with the enhancer of zeste homolog 2 (EZH2) to repress the expression of the runt-related transcription factor 2 (*RUNX2*) gene. Increased expression of this transcript is associated with cancer [10].

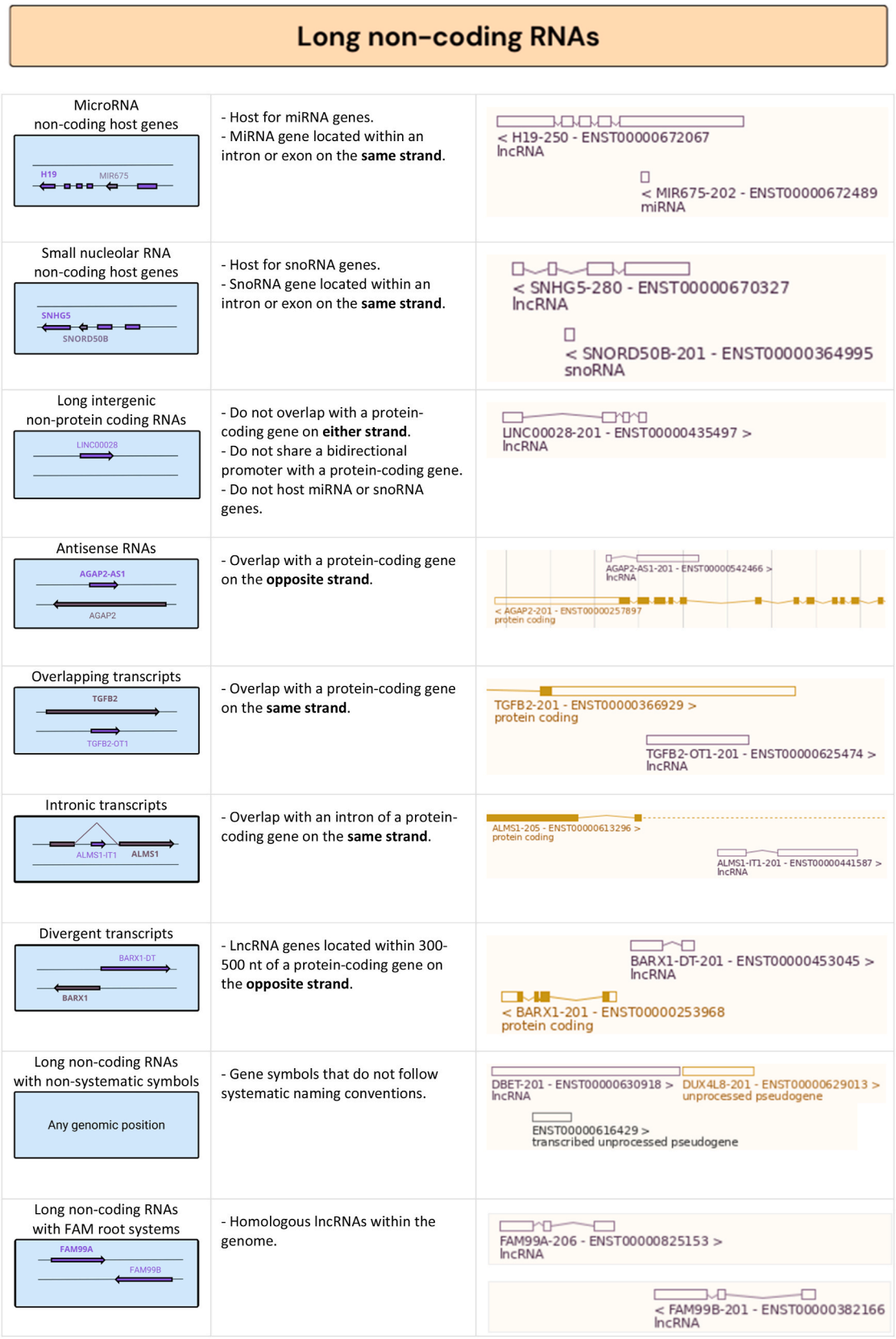

Fig. 2. LncRNA subgroups: characteristics and genomic organization.
Legend: FAM: family with sequence similarity. Genomic visualizations were obtained from Ensembl and presented in a simplified form to increase clarity without altering the original information.

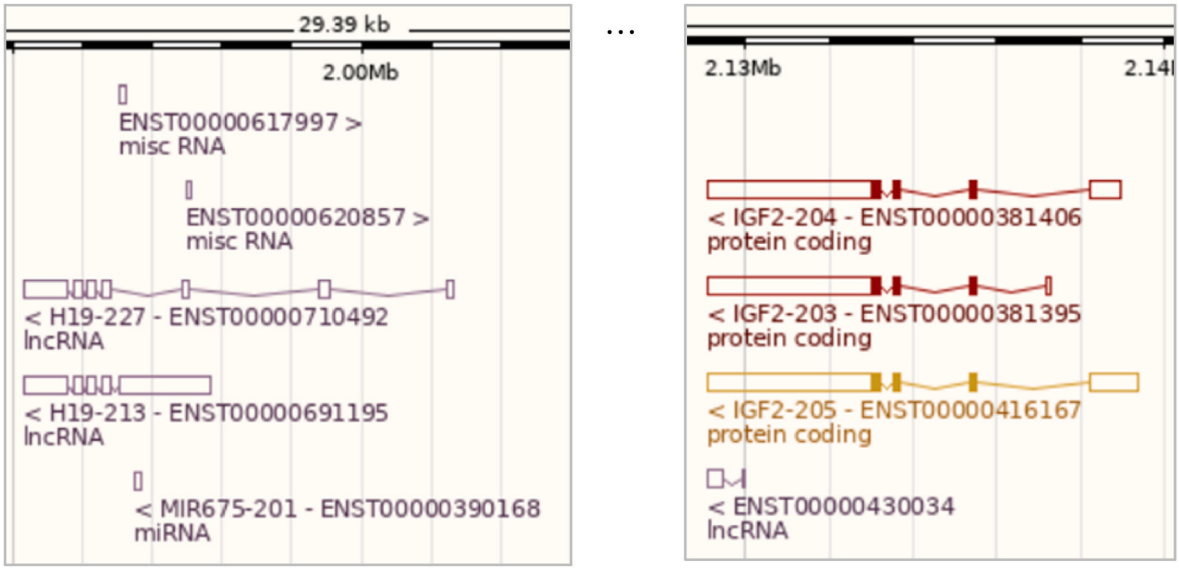

Fig. 3. Genomic organization of the *H19* locus.

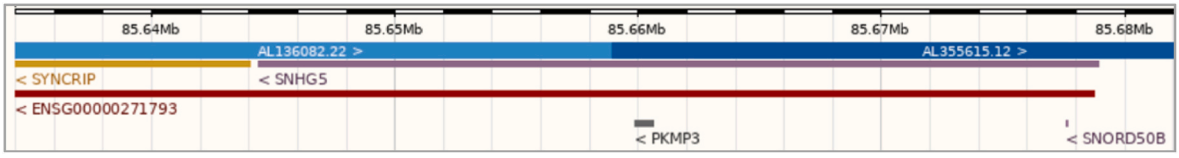

Fig. 4. Genomic organization of the *SNHG5* locus.

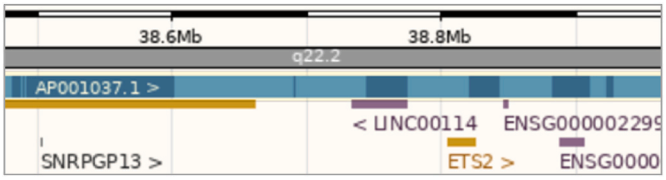

Fig 5. Genomic organization of the *LINC00114* locus.

2.1.3. *MEG3 (maternally expressed 3)*

MEG3 is located on the forward strand of chromosome 14 and hosts *MIR2392* and partially shares location on the forward strand with another miRNA host gene *MIR493HG*. *MEG3* has 71 transcripts [8] and is a maternally expressed imprinted gene. Disorders associated with *MEG3* include Kagami-Ogata syndrome, a rare imprinting disorder with phenotypic overlap that complicates diagnosis, and liver disease. While *MEG3* is expressed in normal tissues, it is repressed in various cancer cell lines from different tissues. *MEG3* inhibits tumor cell proliferation *in vitro* and interacts with the tumor suppressor p53, thereby regulating its expression [10].

2.1.4. *NEAT1 (nuclear paraspeckle assembly transcript 1)*

NEAT1 is located on chromosome 11 on the forward strand. It shares part of its location with two miscRNAs: *ENST00000620525* and *ENST00000613347*, which are also located on the forward strand. *NEAT1* has 16 annotated transcripts [8]. *NEAT1* is transcribed from the multiple endocrine neoplasia (MEN) type 1 locus. This lncRNA remains mainly in the nucleus and serves as a primary structural component of the paraspeckle suborganelles. *NEAT1* functions as a transcriptional

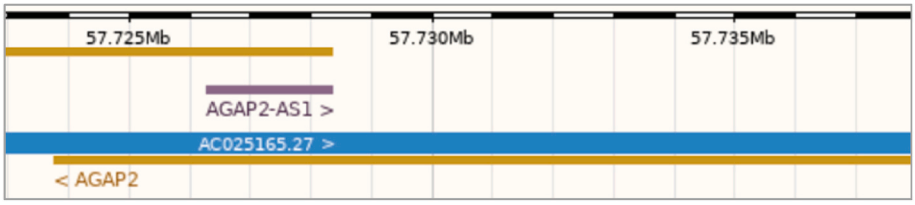

Fig. 6. Genomic organization of the *AGAP2-AS1* locus.

Fig. 7. Genomic organization of the *TGFB2-OT1* locus.

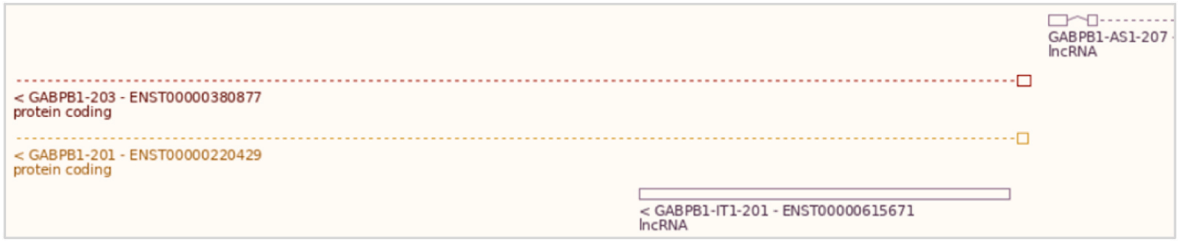

Fig. 8. Genomic organization of the *GABPB1-IT1* locus.

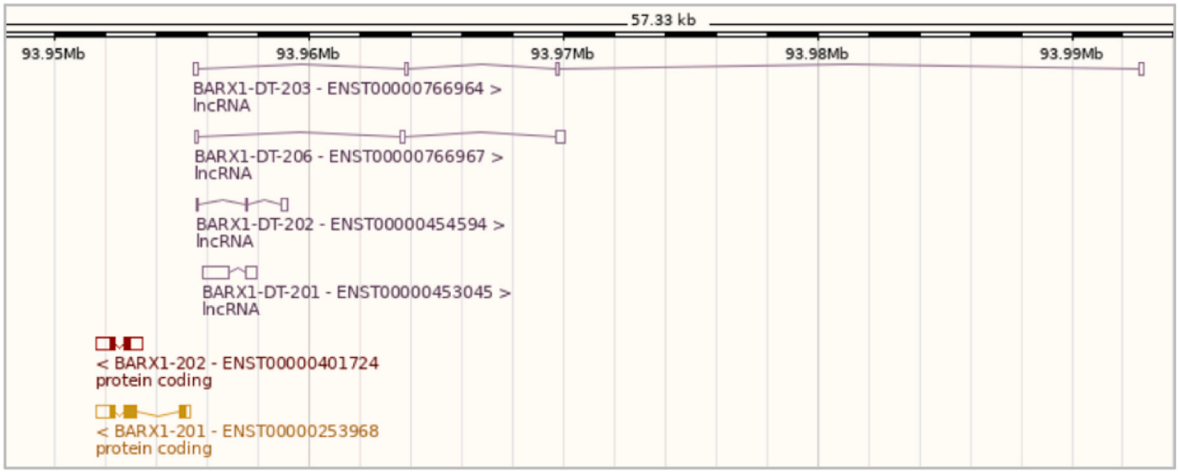

Fig. 9. Genomic organization of the *BARX1-DT* locus.

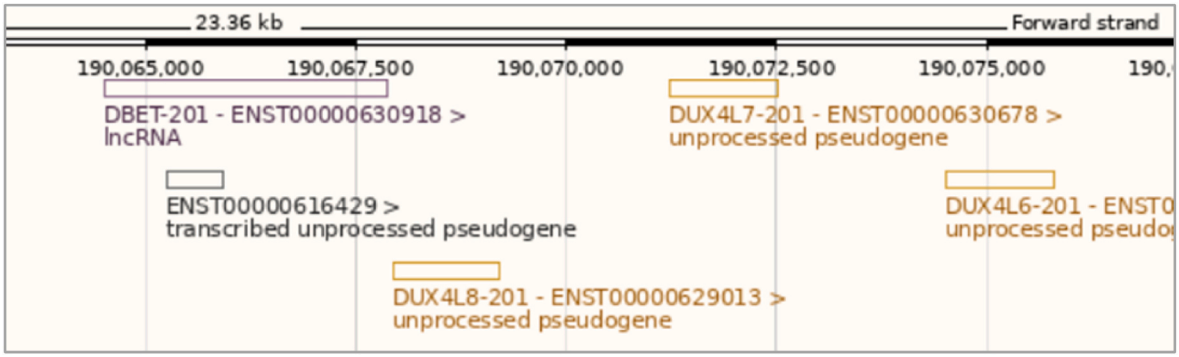

Fig. 10. Genomic organization of the *DBET* locus.

Fig. 11. Genomic organization of the *FAM99A* and *FAM99B* loci.

regulator for several genes, including those involved in cancer progression [10].

2.1.5. *MIR17HG (miR-17-92a-1 cluster host gene)*

MIR17HG is located on chromosome 13 on the forward strand. It has 20 transcripts and it hosts *MIR17-92* cluster, which includes at least six miRNAs (miR-17, miR-18a, miR-19a, miR-19b, miR-20a and miR-92a) [13]. It partially shares location with the lncRNAs *ENST00000710739* and *ENST00000710738* [8]. Several studies have described that the *MIR17-92* cluster affects cell survival, proliferation, differentiation and angiogenesis [13]. Amplification of this gene has been observed in various lymphomas and solid tumors [10].

2.2. Small nucleolar RNA non-coding host genes (snoRNA non-coding host genes; SNHG)

LncRNA genes that host small nucleolar RNA (snoRNA) genes in an intron or exon on the same strand are marked with the root symbol: SNHG, which stands for "small nucleolar RNA host gene", followed by a sequential number, such as *SNHG1* for "small nucleolar RNA host gene 1". The HGNC database currently contains 37 snoRNA host genes, 29 of which have the SNHG root, the others have individual names: *CCT6P1*, *CCT6P3*, *DANCR*, *EPB41L4A-AS1*, *GAS5*, *MEG8*, *RPL32P3*. Five examples from this group are described: *SNHG5*, *SNHG1*, *ZFAS1*, *SNHG3* and *SNHG14*. *SNHG5* and *SNHG1* are located on the reverse strand, while the other three genes are located on the forward strand.

2.2.1. SNHG5 (small nucleolar RNA host gene 5)

SNHG5 is located on chromosome 6 on the reverse strand. It hosts the snoRNA *SNORD50B* and partially shares its location on the same strand with the pseudogene *PKMP3* (Fig. 4). *SNHG5* has 116 transcripts [8]. *SNHG5* has been described to regulate gene expression by acting as a sponge for miRNAs. This transcript can also stabilize mRNAs by inhibiting their degradation through interaction with *STAU1*. *SNHG5* has been associated with lung diseases, including chronic obstructive pulmonary disease, as well as lymphoma [10].

2.2.2. SNHG1 (small nucleolar RNA host gene 1)

SNHG1 is located on chromosome 11 on the reverse strand. *SNHG1* hosts snoRNA genes *SNORD22*, *SNORD28* and *SNORD30* and has 363 transcripts [8]. It is upregulated in malignant tumors and has been reported to increase cell proliferation. The functions of this gene include RNA binding and neutral L-amino acid transmembrane transporter activity. This lncRNA inhibits tumor suppressor genes such as *TP53*, and its expression has been shown to be an indicator of tumor development. Diseases associated with *SNHG1* include lung squamous cell carcinoma and multiple pterygium syndrome - Escobar variant [10].

2.2.3. ZFAS1 (ZNFX1 antisense RNA 1)

ZFAS1 is located on chromosome 20 on the forward strand, where it hosts the snoRNA gene *SNORD12*. It partially shares its location on the same strand with miscRNAs *ENST00000610973* and *ENST00000615977* and is transcribed in the opposite direction to ZNFX1. It has 47 annotated transcripts [8]. Increased expression or amplification of *ZFAS1* is associated with cancer progression and metastasis. This transcript regulates the expression of genes involved in differentiation and acts as a molecular sponge for miRNAs. *ZFAS1* is associated with diseases such as breast ductal carcinoma and ovarian epithelial cancer [10].

2.2.4. SNHG3 (small nucleolar RNA host gene 3)

SNHG3 is located on chromosome 1 on the forward strand. *SNHG3* hosts *SNORA73* and partially shares location with the protein-coding *RCC1* gene, and it has three transcripts [8]. *SNHG3* often functions as a ceRNA that sponges miRNAs to control the expression of various genes. In gastric cancer, *SNHG3* sponges miR-326 to increase tumor cell proliferation, migration and invasion [14], and it interacts with proteins such as EZH2, leading to the epigenetic silencing of genes involved in tumor suppression [15]. *SNHG3* is associated with Alzheimer's disease and hepatocellular carcinoma [10].

2.2.5. SNHG14 (small nucleolar RNA host gene 14)

SNHG14 is located on chromosome 15 on the forward strand. *SNHG14* is a host for *SNORD115* and *SNORD116* and has 158 transcripts [8]. Only the paternal allele of the *SNHG14* gene locus is expressed, suggesting that the gene plays a role in the development of Prader-Willi syndrome (PWS) [16]. Although it is highly expressed in the brain, it is also present in a variety of tissues. Paternal deletions of the locus, particularly those affecting transcripts of the *SNORD116* locus, are associated with the genetic disorder PWS, although the function of an active *SNHG14* lncRNA has not yet been determined [16].

2.3. Long intergenic non-protein coding RNAs (LINC)

Long intergenic non-protein-coding RNA genes do not overlap on either strand, share a bidirectional promoter with a protein-coding gene, and do not contain snoRNA or miRNA genes [3]. LINC has characteristics of the other lncRNA families and accounts for more than half of human lncRNA transcripts [17], although it currently represents about 40 % of lncRNAs in the HGNC database. Five examples from this group are described: *LINC00114*, *LINC00941*, *LINC00092*, *LINC00312* and *LINC00028*. *LINC00941*, *LINC00312*, and *LINC00028* are on the forward strand, the other two lincRNA genes are on the reverse strand.

2.3.1. LINC00114 (long intergenic non-protein coding RNA 114)

LINC00114 is located on chromosome 21 on the reverse strand (Fig. 5) and has 16 transcripts [8]. It has been shown to contribute to nasopharyngeal carcinoma development and radioresistance by regulating the ERK/JNK signaling pathway and mediating miR-203 [18]. *LINC00114* promotes tumor progression by enhancing H3K27 trimethylation through its interaction with EZH2 at the promoters of target genes. This histone modification, which is associated with gene silencing, suppresses tumor suppressor genes such as *DLC1* and thus promotes cancer growth and metastasis [19].

2.3.2. LINC00941 (long intergenic non-protein coding RNA 941)

LINC00941 is located on chromosome 12 on the forward strand and has 22 annotated transcripts [8]. *LINC00941* is associated with lung cancer susceptibility 3 and hepatocellular carcinoma [10]. In lung cancer, increased *LINC00941* expression has been associated with the activation of the PI3K-AKT signaling pathway [20].

2.3.3. LINC00092 (long intergenic non-protein coding RNA 92)

LINC00092 is located on chromosome 9 on the reverse strand and has eight annotated transcripts [8]. *LINC00092* influences glycolysis, which is an important process for energy synthesis in cells. By interacting with the glycolytic enzyme PFKFB2, it contributes to the maintenance of glycolytic activity of cancer-associated fibroblasts and thus promotes the proliferation potential of cancer cells [21]. *LINC0092* is associated with ovarian cancer [10] and thyroid cancer [22].

2.3.4. LINC00312 (long intergenic non-protein coding RNA 312)

LINC00312 is located on chromosome 3 on the forward strand [9]. This gene encodes a transcript that functions as a tumor suppressor. The transcript is downregulated in nasopharyngeal cancer and inhibits estrogen receptor signaling. A common polymorphism of this transcript results in the creation of a 94-aa protein in some individuals, which can directly interact with estrogen receptor 1. This open reading frame (ORF) is absent in the reference genome haplotype and is predicted to function through a non-coding RNA product [10].

2.3.5. LINC00028 (long intergenic non-protein coding RNA 28)

LINC00028 is located on chromosome 20 on the forward strand and has three transcripts [8]. It is involved in proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), fibrosis, and autophagy by competitively targeting miR-204-5p. This interaction promotes the production of human trabecular meshwork fibroblasts (HTFs), highlighting *LINC00028* as a promising biomarker and potential therapeutic target for glaucoma treatment [23]. It is also associated with cerebral palsy [10] and osteosarcoma [24].

2.4. Antisense RNAs (AS-lncRNA)

Antisense RNAs are lncRNA genes that are located on the opposite strand of a protein-coding gene and overlap its coding, intronic and untranslated regions (UTRs) [3]. We have described five examples of

antisense RNAs: *CD27-AS1*, *DLX6-AS1* and *FBXL19-AS1*, which are located on the reverse strand, and *AGAP2-AS1* and *ABCA9-AS1*, which are located on the forward strand.

2.4.1. AGAP2-AS1 (AGAP2 antisense RNA 1)

AGAP2-AS1 is located on chromosome 12 on the forward strand and overlaps with the genomic location of the *AGAP2* gene, which is located on the reverse strand (Fig. 6) [8]. *AGAP2-AS1* has one transcript. This gene is located in an evolutionarily conserved region as it contains several constraint elements. *AGAP2-AS1* has been reported to promote proliferation, motility and invasion of anaplastic glioma cells, and its knockdown has been shown to increase apoptotic cell rate [25]. It is also associated with malignant astrocytomas and gastric cancer [10].

2.4.2. ABCA9-AS1 (ABCA9 antisense RNA 1)

ABCA9-AS1 is located on chromosome 17 on the forward strand. It partially shares its genomic location with the protein-coding gene *ABCA9* and has eight transcripts [8]. *ABCA9* belongs to the ATP-binding cassette transporter (ABC) superfamily. The encoded protein has two transmembrane domains and two nucleotide-binding folds. ABC proteins transport chemicals through extracellular and intracellular membranes [10].

2.4.3. CD27-AS1 (CD27 antisense RNA 1)

CD27-AS1 is located on chromosome 12 on the reverse strand. It partially shares its genomic location with the protein-coding gene *CD27* and it has 36 annotated transcripts [8]. Diseases associated with *CD27-AS1* include lymphoproliferative syndrome 2 and combined T- and B-cell immunodeficiency [10].

2.4.4. DLX6-AS1 (DLX6 antisense RNA 1)

DLX6-AS1 is located on chromosome 7 on the reverse strand. It shares part its genomic location with the protein-coding gene *DLX6*, a member of the homeobox transcription factor gene family. *DLX6-AS1* has 38 annotated transcripts [8,10]. It is predicted play a role in the positive regulation of transcription by RNA polymerase II and is likely localized in the nucleus. *DLX6-AS1* has been associated with neuropathy and split-hand/foot malformation 2 [10].

2.4.5. FBXL19-AS1 (FBXL19 antisense RNA 1)

FBXL19-AS1 is located on chromosome 16, on the reverse strand, and partially shares the genomic location with the protein-coding gene *FBXL19*. It has one annotated transcript [8]. *FBXL19* encodes a member of the Skp1-cullin-F-box family of E3 ubiquitin ligases. The encoded protein interacts with the transmembrane receptor interleukin 1 receptor-like 1 (IL1RL1) and regulates its ubiquitination and degradation. This protein is associated with the regulation of lung inflammation and psoriasis [10]. Diseases associated with *FBXL19-AS1* include rheumatoid arthritis and glioma susceptibility 1 [9].

2.5. Overlapping transcripts

Overlapping transcripts are lncRNA genes that overlap with a protein-coding gene on the same strand [3]. We present five examples of this lncRNA subclass: *TGFB2-OT1*, *SOX1-OT*, *SOX2-OT* and *SPANXA2-OT1*, which are all located on the forward strand, and *C21orf91-OT1*, which is located on the reverse strand.

2.5.1. TGFB2-OT1 (TGFB2 overlapping transcript 1)

TGFB2-OT1 is located on chromosome 1 on the forward strand and overlaps with the *TGFB2* gene (Fig. 7). It has one transcript and is located in an evolutionarily conserved region [8]. *TGFB2-OT1* regulates autophagy in vascular endothelial cells (VECs) [26]. In addition, it functions as an alternative activator of the Wnt/β-catenin pathway and promotes angiogenesis and hepatocellular carcinoma (HCC) development by preventing β-catenin phosphorylation [27]. Diseases associated with *TGFB2-OT1* include septic myocarditis and retinitis pigmentosa [10].

2.5.2. SOX1-OT (SOX1 overlapping transcript)

SOX1-OT is located on chromosome 13 on the forward strand. It overlaps with the *SOX1* gene, partially shares its location with the novel lncRNA transcript *ENST00000567967* and has 29 transcripts [8]. *SOX1-OT1* inhibits the binding of *HDAC10* to the *SOX1* promoter, thereby maintaining histone acetylation and promoting *SOX1* expression. *SOX1* is an intronless gene encoding a transcription factor belonging to the *SOX* (SRY-related HMG-box) family. This family of transcription factors plays a key role in the regulation of embryonic development and cell fate determination. When the SOX1 protein forms a complex with other proteins, it acts as a transcriptional activator and enhances gene expression [10]. In addition, *SOX1* stimulates the expression of *ASCL1*, which promotes the development of dorsal cortical neurons and ventral GABAergic neurons [28].

2.5.3. SOX2-OT (SOX2 overlapping transcript)

SOX2-OT is located on chromosome 3 on the forward strand. It overlaps with protein-coding genes such as *SOX2*, *FXR1* and *DNAJC19*, as well as pseudogenes such as *RNU6-4P* and *RPL7AP25*. *SOX2-OT* has 214 annotated transcripts [8]. Its expression is increased in tumor cells and shows a positive correlation with *SOX2* gene expression. Overexpression of these transcripts is suggested to promote cell growth [10].

2.5.4. C21orf91-OT1 (C21orf91 overlapping transcript 1)

C21orf91-OT1 is located on chromosome 21 on the reverse strand and has four transcripts. This gene overlaps with the protein-coding gene *C21orf91*, which is thought to play an important role in the cerebral cortex neuron differentiation and dendritic spine development [8, 10]. Diseases associated with *C21orf91* include enterokinase deficiency and ulcerative blepharitis [10].

2.5.5. SPANXA2-OT1 (SPANXA2 overlapping transcript 1)

SPANXA2-OT1 is located on chromosome X on the forward strand and has eight transcripts. It overlaps with *SPANXA2*, *SPANXA1*, *SPANXC*, and the pseudogene *RBMX* [8]. It is also located in the region of *LDOC*, a regulator of NFKB signaling. *SPANXA1*, *SPANXA2* and *SPANXC* belong to the *SPANX* family of cancer/testis-associated genes, which are clustered on chromosome X and encode testis-specific proteins [10].

2.6. Intronic transcripts

Intronic transcripts are lncRNA genes located within an intron on the same strand as a protein-coding gene [6]. Although thousands of putative intronic lncRNAs have been identified, determining their functionality remains challenging. It is also challenging to determine which of them are independently transcribed or are by-products of pre-mRNA processing. Some intronic lncRNAs have been characterized in the context of cancer [29]. Five examples from this group are described below: *GABPB1-IT1*, *ALMS1-IT1*, *SPRY4-IT1*, *FTO-IT1* and *RUNX1-IT1*. *GABPB1-IT1*, *SPRY4-IT1* and *RUNX1-IT1* are located on the reverse strand, while *ALMS1-IT1* and *FTO-IT1* are located on the forward strand.

2.6.1. GABPB1-IT1 (GABPB1 intronic transcript)

GABPB1-IT1 is located on chromosome 15 on the reverse strand (Fig. 8) and is encoded within an intron of the protein-coding gene *GABPB1* (GA binding protein transcription factor subunit beta 1). It has a single transcript. *GABPB1-IT1* is located downstream of *GABPB1-AS1*, an antisense lncRNA that is also associated with the protein-coding gene *GABPB1* [8]. In non-small cell lung cancer (NSCLC), *GABPB1-IT1* is downregulated and its reduced expression is associated with poor prognosis. It is proposed to function as a tumor suppressor, with higher levels of *GABPB1-IT1* correlating with improved overall survival and

disease-free survival in NSCLC patients [27].

2.6.2. ALMS1-IT1 (ALMS1 intronic transcript 1)

ALMS1-IT1 is located on chromosome 2 on the forward strand and is transcribed from an intronic region of the protein-coding gene *ALMS1* (*ALMS1* centrosome and basal body associated protein). It has a single annotated transcript [8]. High *ALMS1-IT1* expression levels are associated with poor outcome of certain malignancies. By controlling the pentose phosphate pathway (PPP), which is essential for the production of NADPH and degradation of disulfide bonds to promote cell survival and cancer progression, it contributes to the modulation of cell death under glucose deprivation conditions. In head and neck cancer (HNSCC), *ALMS1-IT1* plays a role in disulfidptosis, a novel cell death process in which it regulates the formation of disulfide bonds between proteins of the actin cytoskeleton under stress conditions such as glucose deprivation. This regulation is essential for maintaining cell structure and function in such situations, and provides a link between *ALMS1-IT1* and cellular stress responses and cancer cell survival [30].

2.6.3. SPRY4-IT1 (SPRY4 intronic transcript 1)

SPRY4-IT1 is located on chromosome 5 [9] and is transcribed from an intronic region of the protein-coding gene *SPRY4* (sprouty RTK signaling antagonist 4). It produces non-coding RNA, that is elevated in a variety of cancers, including melanoma, breast and prostate cancer cells. This transcript is suggested to regulate cell growth, proliferation and apoptosis. It modulates lipin-2 levels and may therefore play a role in lipid production [10].

2.6.4. FTO-IT1 (FTO intronic transcript 1)

FTO-IT1 is located on chromosome 16 [9] and is transcribed from an intronic region of the protein-coding gene *FTO* (FTO alpha-ketoglutarate dependent dioxygenase). It is upregulated in HCC and is associated with a poor prognosis. *FTO-IT1* promotes tumor cell proliferation and glycolysis by regulating *FTO*-mediated N6-methyladenosine (m6A) modification of key glycolytic enzymes, including GLUT1 and PKM2. Elevated expression of *FTO-IT1* enhances the glycolytic capacity of HCC cells, contributing to their rapid growth and development [31]. The *FTO* gene is an m6A demethylase that regulates RNA stability and processing by removing methyl groups from mRNA. This activity impacts various biological processes, such as energy metabolism and adipogenesis, linking *FTO* to obesity, type 2 diabetes, and cardiovascular disease [32].

2.6.5. RUNX1-IT1 (RUNX1 intronic transcript 1)

RUNX1-IT1 is located on chromosome 21 [9] and is transcribed from an intronic region of the gene *RUNX1* (RUNX family transcription factor 1). It plays a role in gene regulation, particularly in hematopoiesis and leukemia. *RUNX1-IT1* has been identified as a regulator of the *RUNX1* gene, which is necessary for the normal growth and differentiation of blood cells. In acute myeloid leukemia (AML), *RUNX1-IT1* is often dysregulated, which leads to the disease pathogenesis by altering the *RUNX1* expression and activity [33].

2.7. Divergent transcripts

Divergent transcripts (DT) are defined as lncRNA genes that are within 300–500 nt of a protein-coding gene on the opposite strand [3]. We have described five examples from this group: *BARX1-DT*, *EIF3J-DT*, *ITGB1-DT*, *KDM7A-DT*, *CHKB-DT*. Among these *EIF3J-DT* is located on the reverse strand, while the other four are located on the forward strand.

2.7.1. BARX1-DT (BARX1 divergent transcript)

BARX1-DT is located on chromosome 9 on the forward strand and it is named after the *BARX1* (*BARX homeobox 1*) gene, which is located on the opposite strand (Fig. 9). It has seven annotated transcripts [8]. In several malignancies, including laryngeal squamous cell carcinoma (LSCC), *BARX1-DT* functions as an oncogenic lncRNA. It also regulates immune responses and interacts with other ncRNAs [34].

2.7.2. EIF3J-DT (EIF3J divergent transcript)

EIF3J-DT is located on chromosome 15 on the reverse strand and is transcribed in the opposite direction to the protein-coding gene *EIF3J* (*eukaryotic translation initiation factor 3 subunit J*). It partially overlaps with the *CTDSPL2* (CTD small phosphatase like 2) gene and has 16 annotated transcripts [8]. *EIF3J-DT* acts as an autoregulator in gastric cancer cells and increases their resistance to chemotherapy by upregulating ATG14 protein expression. It acts by stabilizing *ATG14* mRNA and blocking its degradation by competitively binding to miRNA *MIR188-3p* [35].

2.7.3. ITGB1-DT (ITGB1 divergent transcript)

ITGB1-DT is located on chromosome 10 on the forward strand on the opposite strand of the *ITGB1* (integrin subunit beta 1) gene. It shares the genomic location with four processed pseudogenes, including *MTND4LP11*, as well as miscRNAs. *ITGB1-DT* has 38 transcripts [8]. *ITGB1-DT* is associated with breast cancer [10]. *ITGB1-DT* has been shown to accelerate the progression of various malignancies, including lung adenocarcinoma (LUAD) and colon adenocarcinoma (COAD) [36, 37]. In LUAD, *ITGB1-DT* creates a positive feedback loop with the ITGB1/Wnt/β-catenin/MYC signaling pathway, accelerating oncogenic processes [36].

2.7.4. KDM7A-DT (KDM7A divergent transcript)

KDM7A-DT is located on chromosome 7 on the forward strand. It is located on the opposite strand of the gene *KDM7A* (lysine demethylase 7A), and it has three transcripts [8]. *KDM7A-DT* functions as important regulator in aggressive cancers, particularly breast cancer subtypes, by modulating DNA damage response pathways, inhibiting apoptosis, and promoting cell cycle arrest [38].

2.7.5. CHKB-DT (CHKB divergent transcript)

CHKB-DT is located on chromosome 22 on the forward strand, opposite the *CHKB* (choline kinase beta) gene. It has 11 annotated transcripts [8]. *CHKB-DT* plays a crucial role in energy metabolism, maintains cardiac function by regulating mitochondrial activity and protects against cardiac dilatation and dysfunction in dilated cardiomyopathy (DCM) [39]. Additionally, *CHKB-DT* is associated with periarthritis [10].

2.8. Long non-coding RNAs with non-systematic symbols

This group of lncRNAs is named using non-systematic symbols, reflecting their context of discovery or their functional associations rather than a standardized nomenclature. Five examples from this group are described: *DBET*, *BANCR*, *ELDR*, *LCDR* and *CYTOR*. Among them, *DBET*, *LCDR* and *CYTOR* are located on the forward strand, while *BANCR* and *ELDR* are on the reverse strand.

2.8.1. DBET (D4Z4 binding element transcript)

DBET is located on chromosome 4 on the forward strand (Fig. 10). It partially shares the location with the pseudogene *ENST00000616429* and has a single annotated transcript [8]. It is associated with facioscapulohumeral muscular dystrophy 1 and muscular dystrophy, Duchenne type [10].

2.8.2. BANCR (BRAF-activated non-protein coding RNA)

BANCR is located on chromosome 9 on the reverse strand, and it has 11 transcripts [8]. It stimulates the MAP kinase signaling pathway and promotes tumor growth and the epithelial-mesenchymal transition [10]. *BANCR* has been found to be overexpressed in numerous malignancies, including melanoma, non-small cell lung cancer (NSCLC), colorectal cancer and retinoblastoma [40].

2.8.3. ELDR (EGFR long non-coding downstream RNA)

ELDR is located on chromosome 7 on the reverse strand. It partially overlaps with the pseudogene *ENST00000425993* and has 16 transcripts [8]. *ELDR* plays a role in the regulation of gene expression [10]. ELDR stimulates cell proliferation and tumor growth in oral cancer by stabilizing key cell cycle proteins and interacting with miRNAs. Its overexpression is associated with increased tumor aggressiveness and poor prognosis, making it a promising therapeutic target. Inhibition of *ELDR in vivo* has been shown to inhibit tumor growth, highlighting its importance in cancer progression [41].

2.8.4. LCDR (lysosome cell death regulator)

LCDR is located on chromosome 20 on the forward strand. It partially shares the genomic location with lincRNA *LINC00652* and has three transcripts [8]. *LCDR* is required for cell survival as well as for integrity of lysosomal membrane. To prevent lysosomal membrane permeabilization and cell death, it binds to hnRNP K and stabilizes the *LAPTM5* transcript. The *LCDR*/hnRNP K/*LAPTM5* axis has been found to be overexpressed in lung cancer tissues [42].

2.8.5. CYTOR (cytoskeleton regulator RNA)

CYTOR is located on chromosome 2 on the forward strand. It partially shares location with *LINC01943* and the pseudogene *PAFAH1B1P1* and has 39 transcripts [8]. It binds to the EZH2 enhancer and contributes to silencing tumor suppressor genes by transcription. It acts as a sponge for miRNAs. *CYTOR* is overexpressed in cancer cells, and promotes cell proliferation and epithelial-mesenchymal transition [10].

2.9. LncRNAs with FAM# root symbol

Homologous lncRNA genes are grouped under the root symbol FAM (family with sequence similarity), a term that is also used for protein-coding genes. The number of members varies between the different families, for example the FAM99 family comprises the genes *FAM99A* and *FAM99B*, while the FAM230 family comprises ten members, from *FAM230A* to *FAM230J* [3,8]. Five representative examples from this group, all located on the forward strand, are described below: *FAM99A*, *FAM30A*, *FAM215A*, *FAM230A* and *FAM239A*.

2.9.1. FAM99A (family with sequence similarity 99 member A)

FAM99A is located on chromosome 11 on the forward strand and encodes seven transcripts. It is part of the FAM99 family, which also includes *FAM99B* (Fig. 11) [3,8]. It acts as a tumor suppressor in HCC by inhibiting cell invasion, migration and proliferation. Although the expression of *FAM99A* is significantly downregulated in HCC tissue, its overexpression is associated with a better prognosis [43].

2.9.2. FAM30A (family with sequence similarity 30 member A)

FAM30A is located on chromosome 14 on the forward strand and partially shares the location with genes from the *IGHD* (immunoglobulin heavy constant delta) family. *FAM30A* has 14 annotated transcripts [8] and belongs to the FAM30 gene family, which also includes *FAM30B* and *FAM30C* [3]. This gene family plays a role in antigen binding, immunoglobulin receptor binding and the positive regulation of interleukin-1 production. Diseases associated with *FAM30A* include gallbladder cancer [10].

2.9.3. FAM215A (family with sequence similarity 215 member A)

FAM215A is located on chromosome 17 on the forward strand and partially shares its genomic location with novel lncRNA transcripts in antisense orientation. *FAM215A* has two annotated transcripts [8] and belongs to the FAM215 gene family, which also includes *FAM215B*. *FAM215A* has been associated with glioma susceptibility 1 and ovarian cancer [10].

2.9.4. FAM230A (family with sequence similarity 230 member A)

FAM230A is located on chromosome 22 on the forward strand and partially shares its genomic location with unannotated lncRNAs, such as *ENST00000614584*. *FAM230A* has 12 transcripts and its gene family includes ten paralogs, named from *FAM230A* to *FAM230J* [8]. This gene is associated with retinitis pigmentosa [10].

2.9.5. FAM239A (family with sequence similarity 239 member A)

FAM239A is located on chromosome X [9] and is member of the FAM239 gene family, which also includes *FAM239B* and *FAM239C* [3]. *FAM239A* increases the proliferation and migration of tumor cells in HNSCC by upregulating the expression of *SHP2* (Src homology 2 domain-containing phosphatase 2). This modulation promotes the proliferation of cancer cells and their metastatic potential [44].

3. Circular RNA (circRNA)

In contrast to linear lncRNAs, which are primarily classified according to their genomic location in relation to other genes, circRNAs represent a separate class of RNAs. CircRNAs are single-stranded RNA molecules with a covalently closed circular structure [45,46]. This structure makes circRNAs more resistant to RNA exonucleases, which makes them promising candidates as biomarkers or therapeutic targets. Based on their structure and biogenesis, circRNAs are categorized into three main types: exonic (EcircRNA), circular intronic (ciRNA) and exon-intron circRNAs (EIciRNA) [46] (Fig. 12).

EcircRNAs consist of one or more exons and are produced through a splicing process known as "head-to-tail" or "backsplicing". They are predominantly found in the cytoplasm [47,48]. CircRNA can retain coding potential and may be translated into peptides or proteins [48]. EcircRNAs can be generated by mechanisms such as lariat-driven and intron-pairing-driven circularization models [48]. An example of an EcircRNA is *circHIPK3*, derived from the *HIPK3* gene, which has been linked to carcinogenesis due to its role in regulating cell proliferation [49].

CiRNAs are formed from intron lariats that escape debranching and degradation. Their production depends on specific sequence motifs, such as a GU-rich sequence at the 5′ splice site and the C-rich motif near the branch point [50]. An example of a ciRNA is *ciANKRD52*, which promotes the transcription of its host gene *ANKRD52* by interacting with RNA polymerase II [51].

EIciRNA are mainly located in the nucleus and are formed by circularization of exons while retaining introns. Complementary sequences, such as Alu elements, may be involved in their production [48,

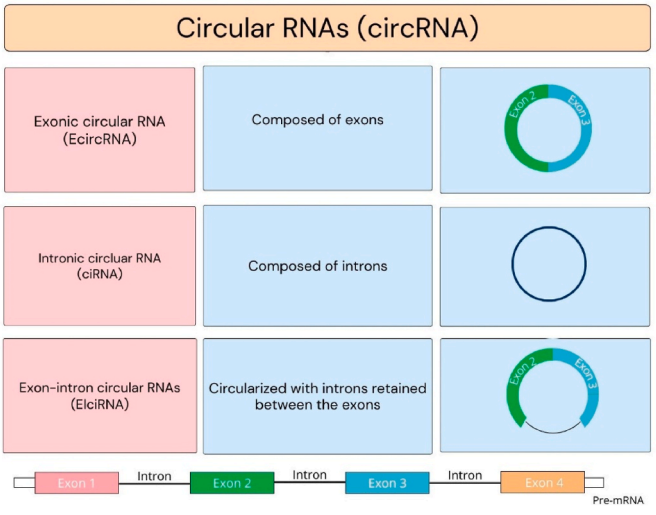

Fig. 12. Subgroups of circular RNAs.

50]. Examples include *circEIF3J* and *circPAIP2*, which enhance the transcription of their host genes by interacting with RNA polymerase II and other components of the transcription machinery [52].

4. Mode of action of lncRNA

LncRNAs regulate gene expression through various cis- and trans-mechanisms, influencing diverse biological processes and complex molecular signaling networks. They play multiple roles in gene regulation, such as molecular signals, scaffolds, decoys, guides, organizers of chromatin architecture and miRNA sponges. These versatile strategies demonstrate the complexity and adaptability of lncRNAs in cellular processes and the regulation of gene expression.

4.1. Molecular signaling

LncRNAs can function as molecular signals in response to specific cellular stimuli. For example, they recruit chromatin-modifying enzymes to specific target genes, leading to changes in chromatin structure that result in the repression of certain genes [53]. A well-known example is HOX transcript antisense RNA (*HOTAIR*), a lncRNA produced by the *HoxC* gene cluster. *HOTAIR* inhibits the transcription of genes at the *HoxD* locus in trans by interacting with the histone demethylase LSD1 and the polycomb repressor complex 2 (PRC2). These interactions demonstrate how lncRNAs can act as molecular signals to regulate gene expression across chromatin domains [54].

4.2. Scaffold

LncRNA can act as molecular scaffolds, that connect multiple proteins or protein complexes to facilitate their interaction at specific sites. This function often involves histone modifications that influence chromatin structure and gene expression. For example, lncRNAs can interact with RNA-binding factors such as hnRNPs to form RNA-protein complexes (RNPs). These RNPs can enhance transcription by recruiting essential proteins to the promoters of target genes or repress it by binding to transcriptional repressors. A well-known example is *NEAT1*, which acts as a scaffold in paraspeckles. *NEAT1* recruits proteins, including CARM1, PSPC1 and P54NRB and thus regulates processes such as cell differentiation and embryonic development [55].

4.3. Decoy

LncRNAs can function as decoys by binding to proteins or other RNAs, preventing them from interacting with their target sites and inhibiting their normal functions. For example, the lncRNA *DINO* interacts with the p53 protein and thereby influences p53-mediated phenotypes [56].

4.4. Guide

LncRNAs act as guides that direct transcriptional complexes to specific genomic locations and allow precise control of chromatin modifications that influence the expression of target genes. These guide lncRNAs often recruit chromatin-modifying complexes such as PRC2, to regulate gene expression. For example, the lncRNA *FENDRR* recruits PRC2 to promoters of genes involved in mesoderm development [57].

4.5. Architect

LncRNAs act as architectural components and contribute to the maintenance of the spatial organization of the genome. They enable crucial three-dimensional interactions within the nucleus, such as enhancer-promoter loops, which are essential for effective transcriptional regulation. For example, the lncRNA *FIRRE*, which is transcribed from the X chromosome, binds to hnRNP-U and serves as a platform for interactions between different chromosomes [58].

4.6. miRNA sponge; ceRNA

LncRNAs can function as sponges for miRNAs, short RNA fragments (18–25 nt) that play an important role in gene expression without encoding proteins. MiRNAs bind to mRNAs, leading to their degradation or inhibition of translation [59]. By binding to miRNAs and preventing their interaction with target mRNA, lncRNAs capture miRNAs and thus protect mRNAs from miRNA-mediated degradation or translational repression. Through this mechanism, lncRNAs function as competing endogenous RNAs (ceRNAs) and influence protein production [60].

Three ceRNA genes are currently listed in the HGNC database: *CERNA1* (competing endogenous lncRNA 1 for miR-4707-5p and miR-4767), *CERNA2* (competing endogenous lncRNA 2 for microRNA let-7b) and *CERNA3* (competing endogenous lncRNA 3 for miR-645).

5. Biological functions and associations with diseases

LncRNAs regulate diverse biological processes and are implicated in various diseases. They influence gene expression and cellular functions through mechanisms such as cell differentiation, DNA repair and inhibiting tumor growth. In immune cells, they facilitate processes like V(D)J recombination and antibody class switching, essential for antibody diversity and adaptive immunity. LncRNAs also regulate genes, involved in inflammation, cytokine expression and glucose metabolism. These diverse functions emphasize their significance in genetic regulation and maintaining cellular and organismal homeostasis [61–63].

5.1. Regulation of cell differentiation

Cell differentiation establishes cellular identity and function and is influenced by lncRNAs. LncRNAs such as *HOTAIR* influence cell differentiation by altering chromatin state and gene expression patterns. *HOTAIR* interacts with PRC2 to induce histone modifications, leading to transcriptional silencing of target genes. This mechanism is particularly significant in cancer, as abnormal *HOTAIR* expression suppresses normal differentiation pathways and promotes malignant transformation, contributing to tumor growth and metastasis. In addition, lncRNAs play diverse roles in stem cell biology, supporting lineage-specific differentiation or maintaining pluripotency during development [64].

5.2. p53-mediated response to DNA damage

LncRNAs are involved in p53-mediated response to DNA damage, support DNA repair and inhibiting malignancy growth. *PANDAR*, for example, regulates of genes involved in cell cycle arrest and apoptosis through interactions with the p53 protein and other regulatory factors. Upon DNA damage, p53 activates *PANDAR* transcription, which then influences cell fate decisions. This regulatory axis ensures that cells either repair DNA damage or undergo programmed cell death, thereby preventing the propagation of damaged DNA [65].

5.3. V(D)J recombination and class switch recombination in immune cells

Class switch recombination (CSR) and V(D)J recombination are essential for generating antibody diversity and supporting adaptive immunity. LncRNAs regulate these processes by modulating the accessibility and rearrangement of immunoglobulin gene regions, which are critical for proper immune function. Through interactions with chromatin modifiers and transcription factors, lncRNAs coordinate the precise genomic rearrangements required for antibody production and diversity [66].

5.4. Glucose metabolism

LncRNAs modulate signaling pathways related to energy balance and insulin response. They influence GLUT-mediated glucose transport and metabolic processes including PPP, oxidative phosphorylation and glycolysis. The lncRNA *H19* has been associated with glucose metabolism and insulin sensitivity and contributes to the maintenance of metabolic balance. In addition, lncRNA *H19* has been shown to enhance muscle insulin sensitivity, in part by stimulating the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway, which promotes glucose uptake, mitochondrial biogenesis, and muscle insulin sensitivity [67].

5.5. Cytokine expression and inflammation

LncRNAs regulate inflammation-related genes through chromatin modification, mRNA stability, miRNA sponging and signaling pathways. They influence cytokine synthesis [27]. By modulating inflammasome activity and signaling pathways such as NF-κB, lncRNAs play a significant role in the regulation of inflammatory responses. The lncRNA *THRIL* regulates the synthesis of proinflammatory cytokines, such as TNF-α by interacting with hnRNPL to modulate TNF-α transcription. This precise regulation is important in autoimmune diseases, where controlling cytokine expression prevents excessive inflammation. *THRIL* and other lncRNAs can influence the progression of inflammatory diseases by regulating cytokine networks, making them promising therapeutic targets [68].

5.6. Association with diseases

LncRNAs are implicated in various diseases, including neoplasms, gliomas and neurodegenerative disorders. Several databases, including LncRNADisease v3.0, provide information on associations between lncRNAs and diseases [11]. For example, *NEAT1* has been associated with prostate neoplasms, gliomas and Alzheimer's disease. More than 335 lncRNAs, including *H19* and *PVT1*, are associated with gliomas.

In the cardiovascular system, numerous lncRNAs such as *H19*, *MEG3* and *HOTAIR*, have been shown to influence cardiovascular development and pathology [6]. In addition, several lncRNAs have been identified as essential molecules involved in the pathophysiology of renal injury, with potential applications as biomarkers for the early diagnosis and prognosis of kidney disease. For example, *DANCR* regulates cell death and the production of inflammatory cytokines [12]. Certain lncRNAs have multiple disease associations or are the subject of more intensive research, highlighting their potential for biomarker discovery and therapeutic development [11].

6. Gene Ontology

Gene ontology (GO) terms associated with lncRNAs provide insights into their roles in biological processes, molecular functions and localization in cellular components. Although current knowledge is limited, lncRNAs have been identified in various cellular components, including the nucleus and nucleolus, where they play a role in RNA processing and gene regulation. They also play an important role in various biological processes, including gene silencing and inhibition of cell proliferation. Molecular functions of lncRNAs include protein binding and interactions with miRNAs that influence gene expression and chromatin remodeling. Notably, many lncRNAs host miRNA genes, highlighting their role in regulatory systems.

Future studies will likely expand our understanding of lncRNAs by improving their annotation and characterization, which will lead to deeper insights into their regulatory roles. GO terms for lncRNAs, categorized into cellular component, biological process and molecular function, are shown in Supplementary Table S1 and summarized in Table 2 [8].

7. Role lncRNA in pharmacology and drug development

The impact of lncRNAs extends to pharmacology and drug development, where they influence resistance mechanisms and drug metabolism. Their potential as biomarkers for drug response and disease progression opens up new possibilities for personalized medicine. LncRNAs are associated with chemoresistance in cancer treatment as they modulate the expression of proteins for drug uptake and efflux, thus reducing the efficacy of chemotherapy [69]. For example, *NEAT1* increases treatment sensitivity and drug accumulation in non-small cell lung cancer by regulating the copper transporter CTR1. Another example is *MALAT1* (Metastasis-associated lung adenocarcinoma transcript 1), which is associated with tumor progression. Another example is MALAT1 (metastasis-associated lung adenocarcinoma transcript 1),

Table 2
Functional annotation and Gene Ontology (GO) classification of lncRNA genes.

Gene	GO: Cellular component	GO: Biological process	GO: Molecular function
DANCR	Nucleolus	RNA processing	–
MEG3	RISC complex	MiRNA-mediated gene silencing Negative regulation of cell growth	–
NEAT1	RISC complex Paraspeckles	LncRNA-mediated post-transcriptional gene silencing MiRNA-mediated gene silencing Nuclear body organization Positive regulation of inflammatory response Positive regulation of miRNA catabolic process Positive regulation of synoviocyte proliferation Regulation of mRNA export from nucleus	MiRNA binding MiRNA inhibitor activity via base-pairing Molecular condensate scaffold activity Protein binding RISC complex binding
MIR17HG	RISC complex	MiRNA-mediated gene silencing	–
SNHG5	Nucleolus	RNA processing	–
SNHG1	Nucleolus	RNA processing	–
ZFAS1	Nucleus Nucleolus Cytoplasm	RNA processing	–
SNHG3	Nucleolus	RNA processing	–
SNHG14	Nucleolus	RNA processing	–
LINC00461 (MIR9-2HG)	RISC complex	MiRNA-mediated gene silencing	–
LINC00657 (NORAD)	–	Regulation of mRNA stability	Protein sequestering activity
DLX6-AS1	–	Forebrain development Positive regulation of DNA-templated transcription	–
XIST	–	Constitutive heterochromatin formation Dosage compensation by inactivation of X chromosome Establishment of chromosome localization Random inactivation of X chromosome	Chromatin-protein adaptor activity
HOTAIR	–	Heterochromatin formation	Protein binding
FIRRE	–	Chromatin organization	DNA-DNA tethering activity
MALAT	–	Positive regulation of cell motility	–

which is associated with tumor progression and influences metastasis and treatment outcomes [70].

In addition, lncRNAs are being investigated as therapeutic targets to overcome drug resistance and improve therapeutic efficacy. By synthesizing multimodal pharmacogenomics data, researchers seek to gain a better understanding of regulatory networks, including lncRNAs, paving the way for new drug development approaches. Despite their potential, targeting lncRNAs for medical purposes represents a major challenge. Due to their different modes of action and context-dependent activities, lncRNAs are difficult to characterize functionally. In addition, the development of lncRNA-based therapies requires cutting-edge delivery mechanisms to ensure stability, specificity and effective cellular uptake. Advances in RNA biology and drug delivery technologies, such as nanoparticle carriers and RNA aptamers, are helping to overcome these obstacles. In summary, lncRNAs are promising frontier in pharmacology and drug development. Due to their unique regulatory capabilities and their involvement in disease-related processes, they are attractive targets for novel therapeutic strategies.

8. Future directions

Future research will further explore the diverse roles of lncRNAs in cellular processes and disease mechanisms. Investigations of lncRNAs in previously understudied areas, such as their role in rare diseases and new biological pathways, are particularly valuable. Expanding and organizing databases such as cbioPortal, TCGA or UALCAN and ensuring their accuracy can simplify the analysis of lncRNA genomic locations and facilitate practical applications [71]. In addition, the development of new approaches and technologies is essential to accurately characterize and manipulate lncRNAs. This includes the refinement of delivery mechanisms for potential medical applications and the development of advanced computational tools for lncRNA analysis. Collaborative efforts across disciplines are expected to fully exploit the potential of lncRNAs as biomarkers and therapeutic targets and lead to methods of personalized medicine that could significantly improve patient outcomes.

9. Conclusion

LncRNAs play an important role in the regulation of various biological processes and have a significant impact on health and disease. In this review, the genome location, mode of action and biological functions of lncRNAs are highlighted. Although analyzing lncRNAs is challenging, ongoing research has begun to reveal their potential as effective diagnostic and therapeutic tools. As our understanding of lncRNA biology grows, it is becoming evident that these molecules have the potential to advance medical research and improve clinical practice. Future research should aim to fill existing knowledge gaps and discover novel applications for lncRNAs in medicine.

CRediT authorship contribution statement

Barbara Chodurska: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Tanja Kunej:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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Abbreviations

ABC: ATP-binding cassette
AML:: Acute myeloid leukemia
AS1: Antisense RNAs
ceRNAs: Competitive endogenous RNAs
circRNAs: Circular RNAs
ciRNA: Circular intronic RNAs
COAD: Colon adenocarcinoma
CSR: Class switch recombination

CVD: Cardiovascular disease
DT: Divergent transcripts
ecircRNA: Exonic circular RNAs
ElciRNA: Exon-intron circular RNAs
EMT: Epithelial-mesenchymal transition
EZH2: Enhancer of zeste homolog 2
FAM [number]: Long non-coding RNAs with FAM root system
HCC: Hepatocellular carcinoma
HG: Host gene
HGNC: The HUGO Gene Nomenclature Committee
HNSCC: Head and neck squamous cell carcinomas
HOTAIR: HOX Transcript Antisense RNA
IGF2: Insulin-like growth factor 2
IL1RL1: Transmembrane receptor interleukin 1 receptor-like 1
IT1: Intronic transcripts
LCDR: Lysosome cell death regulator
LINC: Long intergenic non-protein coding RNAs
lncRNA: Long non-coding RNA
LSCC: Laryngeal squamous cell carcinoma
LUAD: Lung adenocarcinoma
MALAT1: Metastasis-Associated Lung Adenocarcinoma Transcript 1
miRNA: MicroRNA
miscRNA: Miscellaneous RNA
mRNA: Messenger RNA
NCBI: National Center for Biotechnology Information
ncRNA: Non-coding RNA
NEAT1: Nuclear Enriched Abundant Transcript 1
NORAD: Non-Coding RNA Activated by DNA Damage
NSCLC: Non-small cell lung cancer
Nt: Nucleotides
OT: Overlapping transcripts
PPP: Pentose phosphate pathway
PRC2: Polycomb repressor complex 2
RISC: RNA-induced silencing complex
RNPs: RNA-protein complexes
SHP2: Src homology 2 domain-containing phosphatase 2
snoRNA: Small nucleolar RNA
SOX: SRY-related HMG-box
TGF-beta: Transforming growth factor-beta
UTR: Untranslated region