

Review Article

Natural antisense transcripts: Biology, mechanisms, and therapeutic potential: An update

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Abstract

Endogenous RNA molecules called natural antisense transcripts (NATs) are produced from the complementary DNA strand of either non-coding or protein-coding genes. NATs are not byproducts of random transcription but rather important controllers of gene expression, according to mounting evidence. Antisense transcription has been demonstrated to occur extensively in both prokaryotic and eukaryotic genomes with the development of high-throughput sequencing technology, highlighting its biological significance and evolutionary conservation. Numerous processes, such as transcriptional inhibition, chromatin remodeling, epigenetic changes, RNA editing, alternative splicing, regulation of mRNA stability, and translational control, are used by NATs to control gene expression. As a result, they play essential roles in numerous physiological processes, such as embryonic development, cell differentiation, adaptation to stress, and the maintenance of normal cellular homeostasis. Dysregulation of NAT expression has been linked to a variety of illnesses, including cancer, neurological disorders, cardiovascular diseases, metabolic disorders, and autoimmune problems. NATs play important roles in plant development and stress biology. This review highlights current knowledge on NAT biogenesis, classification, and structural organization in the initial chapter by providing a brief introduction to transcription mechanisms and players involved. The following sections cover the molecular mechanisms, biological roles of NATs. The role of NATs in human diseases and plant biology forms the later chapter. The emerging therapeutic applications of NATs are discussed in the last chapter. With the availability of the genomes of several genomes and parallel developments in bioinformatics, antisense biology stands at an exciting junction to address several basic questions and applications.

Keywords: Natural antisense transcripts, Long non-coding RNA, Gene regulation, Antisense oligonucleotides, RNA therapeutics, Epigenetics and transcriptional regulation

Introduction

Advances in genome sequencing and transcriptomic technologies have significantly expanded our understanding of gene regulation by revealing that a large proportion of the eukaryotic genome is transcribed into non-protein-coding RNAs. Although only a small fraction of the genome encodes proteins, pervasive transcription generates numerous regulatory RNA molecules that play essential roles in controlling gene expression (Cao & Kapranov, 2022). Among these, natural antisense transcripts (NATs) have emerged as an important class of endogenous regulatory RNAs. Natural antisense transcripts are RNA molecules transcribed from the DNA strand opposite to protein-coding or non-coding genes. Based on their genomic origin, NATs are classified as cis-NATs, which originate from the same genomic locus as their corresponding sense transcript, and trans-NATs, which arise from different genomic loci but exhibit sequence complementarity to target transcripts (Santini *et al.*, 2022). Studies have shown that antisense transcription is evolutionarily conserved and occurs in organisms ranging from bacteria and archaea to plants and mammals (Layer & Weil, 2009). Approximately 4-9% of human genes, 22% of *Drosophila melanogaster* genes, and 10-20% of *Arabidopsis thaliana* genes are associated with cis-NATs, while nearly 70% of mammalian genes are estimated to

possess antisense partners. Table 1 summarises the present status of NATs across species.

Natural antisense transcripts regulate gene expression by a variety of mechanisms, including chromatin remodeling, transcriptional interference, alternative splicing, RNA stability, RNA editing, and translational regulation (Werner *et al.*, 2024). NATs are interesting targets for RNA-based therapeutics because of their involvement in a variety of biological processes and relationship with diseases such as cancer, neurological disorders, and cardiovascular disease (Huang *et al.*, 2021; Krappinger *et al.*, 2021). As a result, understanding the biology and regulatory activities of antisense transcripts has become a key emphasis in current molecular genetics and functional genomics. We searched PubMed and theses to collate the literature and also consulted selected published reviews and primary research papers. No specific inclusion criteria were applied to the PubMed search. Our main motivation was to update the knowledge with reference the unique mechanisms of NAT, biological roles and their role in human and plant biology.

Basics of transcription

Gene expression is the fundamental biological process through which genetic information encoded in DNA is

Table 1: Distribution of overlapping natural antisense transcripts across different species

Mechanisms	Antisense transcript	Sense gene/NAT localization relative to a sense gene	Disease	Reference
Histone modification	ANRIL	CDKN2B/full overlap	Hepatocellular carcinoma	Huang <i>et al.</i> , 2015
Methylation	TUG1	MORC2/5' end overlap	Small Cell Lung cancer	Ou & Li, 2017
Genomic imprinting	Aberrant LUC7L	HBA2/3' end overlap	Alpha-thalassemia	Guéant <i>et al.</i> , 2022
Modulation of alternative splicing	UBE3A-AS	UBE3A/3' end overlap	Angelman syndrome	Meng <i>et al.</i> , 2013
	ZEB2-AS1	ZEB2/5' end overlap	Hepatocellular carcinoma	Wu <i>et al.</i> , 2022
	17A	GABBR2 full overlap	Alzheimer's disease	Massone <i>et al.</i> , 2011
	AC021224.1–201	retro_hsap_1933	HIV	Szczesniak & Makalowska, 2016
miRNA sponges	ZFAS1	ZNFX1/5' end overlap	Hepatocellular carcinoma	Zhu & Liu, 2025
	TUG1	MORC2/5' end overlap	Endometrial cancer	Liu <i>et al.</i> , 2017
Masking miRNA binding sites	BACE1-AS	BACE1/full overlap	Alzheimer's disease	Li <i>et al.</i> , 2019

converted into functional RNA and protein molecules. The first step of gene expression is transcription, during which DNA-dependent RNA polymerase synthesizes an RNA molecule using one strand of DNA as a template (Chavali *et al.*, 2020). Unlike DNA, RNA contains ribose sugar with a hydroxyl group at the 2' carbon and uracil in place of thymine, enabling RNA molecules to perform diverse structural, catalytic, and regulatory functions (Zhang, 2024). In eukaryotic cells, transcription is carried out by three specialized RNA polymerases. RNA polymerase I synthesizes the precursor ribosomal RNA (45S pre-rRNA), which is processed into 18S, 5.8S, and 28S rRNAs. RNA polymerase II transcribes messenger RNAs (mRNAs) and the majority of regulatory non-coding RNAs, including long non-coding RNAs and natural antisense transcripts. RNA polymerase III synthesizes transfer RNAs (tRNAs), 5S rRNA, and several small RNAs involved in RNA processing and translation (Alberts *et al.*, 2022).

Transcription is initiated when RNA polymerase II and general transcription factors assemble at promoter regions located upstream of genes. Core promoter elements, including the TATA box, CAAT box, and GC box, recruit transcription factors such as TATA-binding protein (TBP), SP1, and CAAT-binding proteins, facilitating the formation of the transcription initiation complex (Alberts *et al.*, 2022). General transcription factors including TFIIA, TFIIB, TFIID, TFIIIE, TFIIF, and TFIIF sequentially assemble with RNA polymerase II to form the pre-initiation complex. The helicase and kinase activities of TFIIF unwind promoter DNA and phosphorylate the C-terminal domain (CTD) of RNA polymerase II, allowing transcription initiation and promoter clearance (Alberts *et al.*, 2022). Following initiation, RNA polymerase II enters the elongation phase, during which complementary ribonucleotides are incorporated into the growing RNA strand in the 5' to 3' direction. Elongation factors maintain CTD phosphorylation and coordinate transcription with RNA processing events. Transcription termination occurs after recognition of polyadenylation signals, recruitment of cleavage and polyadenylation specificity factors (CPSF), cleavage of the nascent transcript, and degradation of downstream RNA by the 5'–3' exonuclease XRN2, leading to dissociation of RNA polymerase II from DNA (Alberts *et al.*, 2022).

Eukaryotic primary transcripts undergo extensive post-transcriptional modifications before becoming mature RNA molecules. Messenger RNAs receive a 7-methylguanosine cap at the 5' end, undergo pre-mRNA splicing to remove introns, and acquire a poly(A) tail at the 3' end. These modifications increase transcript stability, facilitate nuclear export, and enhance translational efficiency (Alberts *et al.*, 2022). Similarly, precursor ribosomal RNAs and transfer RNAs undergo cleavage, nucleotide modification, and maturation before becoming functionally active. Genome-wide transcriptomic analyses have demonstrated that transcription is not restricted to protein-coding genes. Bidirectional transcription by RNA polymerase II frequently generates overlapping sense and antisense transcripts from opposite DNA strands. This pervasive transcription forms the molecular basis for the production of natural antisense transcripts, which contribute significantly to the regulation of gene expression in eukaryotic cells.

Basic organization and structure of natural antisense transcripts

Natural antisense transcripts (NATs) are endogenous RNA molecules transcribed from the DNA strand opposite to protein-coding or non-coding genes. They exhibit complete or partial sequence complementarity to their corresponding sense transcripts and regulate gene expression through diverse molecular mechanisms. NATs are found in both prokaryotic and eukaryotic organisms, demonstrating that antisense transcription is an evolutionarily conserved feature of genome organization (Pelechano & Steinmetz, 2013; Wight & Werner, 2013). The mammalian transcriptome contains a large number of antisense transcripts, including both protein-coding and non-coding RNAs. Genome-wide studies estimate that approximately 22–40% of genes possess antisense partners, although more recent transcriptomic analyses suggest that this proportion may be even higher depending on the organism and sequencing approach (Katayama *et al.*, 2005; Wright *et al.*, 2022). Based on transcript length, NATs are broadly classified as short non-coding RNAs (<200 nucleotides) and long non-coding RNAs (>200 nucleotides), with long non-coding NATs representing the predominant class in eukaryotic genomes (Wahlestedt, 2013).

The transcription of NATs is initiated from antisense promoters (ASPs), which recruit RNA polymerase II and general transcription factors in a manner similar to conventional promoters. Many antisense promoters are TATA-less and instead contain GC-rich promoter elements and multiple transcription factor-binding sites that regulate tissue-specific and stress-responsive gene expression (Bhaumik, 2011; Yang, 2022). Similar to messenger RNAs, most NATs are transcribed by RNA polymerase II and undergo 5' capping, intron splicing, and 3' polyadenylation before being transported to the nucleus or cytoplasm, where they perform regulatory functions (Krappinger *et al.*, 2021).

The genomic organization of NATs is highly diverse. Antisense transcripts may overlap the entire sense gene, overlap only exonic or intronic regions or originate from adjacent bidirectional promoters. Their orientation relative to the sense transcript determines the type of interaction and regulatory mechanism involved. Depending on the genomic arrangement, NATs may regulate transcription by transcriptional interference, chromatin remodeling, RNA duplex formation, RNA masking, or modulation of mRNA processing and stability (Pelechano & Steinmetz, 2013).

Natural antisense transcripts (NATs) exhibit diverse genomic organizations based on their orientation and overlap with corresponding sense transcripts. Their structural arrangement plays a crucial role in determining the mechanism by which they regulate gene expression. NATs are commonly classified according to the position and extent of overlap between the sense and antisense transcripts into head-to-head (divergent), tail-to-tail (convergent), embedded, fully overlapping, intronic, cis-natural antisense transcripts (cis-NATs), and trans-natural antisense transcripts (trans-NATs) (Pelechano & Steinmetz, 2013; Wright *et al.*, 2022). Head-to-head (divergent) NATs originate from adjacent promoters located on opposite DNA strands, with their 5' ends positioned close to each other or partially overlapping. Transcription proceeds in opposite directions from a shared or bidirectional promoter. This arrangement enables coordinated regulation of sense and antisense gene expression. A well-studied example is the urokinase plasminogen activator receptor (uPAR) antisense transcript, which regulates mRNA stability and contributes to breast cancer progression (Hamada *et al.*, 2024). Tail-to-tail (convergent) NATs are transcribed toward one another, resulting in overlap of their 3' ends. This genomic organization can promote transcriptional interference and facilitate the formation of RNA–RNA duplexes that influence transcript stability and degradation. In mammals, tail-to-tail overlaps are generally shorter than 800 base pairs, whereas studies in zebrafish have demonstrated that the extent of overlap contributes to regulatory function (Wright *et al.*, 2022). The P5CDH antisense transcript involved in plant responses to biotic and abiotic stress represents a typical example of this configuration (Rizzi *et al.*, 2015).

Embedded NATs are completely contained within the genomic boundaries of a larger sense transcript but are transcribed from the opposite strand. They usually overlap only a portion of the sense gene and regulate

alternative splicing or transcript processing. In contrast, fully overlapping NATs extend across the entire length of the corresponding sense transcript and often regulate RNA processing, transcript stability, and translation through RNA duplex formation. An example is FCER1A-AS, which positively regulates expression of the FCER1A gene in human immune cells (Tang *et al.*, 2023).

Intronic NATs originate from the opposite DNA strand within intronic regions of protein-coding genes without overlapping exons. These transcripts participate in epigenetic regulation, modulation of host gene expression, and alternative splicing. For example, antisense transcripts arising from the TRIM43 locus contribute to epigenetic silencing of neighbouring promoters (Ruiz *et al.*, 2026).

Based on their genomic origin, NATs are further classified into cis-NATs and trans-NATs. Cis-NATs are transcribed from the same genomic locus as their corresponding sense transcript but from the opposite DNA strand, resulting in complete or near-complete sequence complementarity (Oono *et al.*, 2017). In contrast, trans-NATs originate from different genomic loci and exhibit only partial sequence complementarity with their target transcripts. Although trans-NATs have been studied less extensively than cis-NATs, increasing evidence suggests that partial RNA–RNA duplex formation enables them to regulate gene expression through mechanisms similar to those of cis-NATs (Shao *et al.*, 2017). Genome-wide analyses have identified thousands of potential trans-NAT interactions highlighting their emerging importance in post-transcriptional regulation (Szczeniuk & Makalowska, 2016). Natural antisense transcripts are transcribed from specialized antisense promoters located within bidirectional promoters, intragenic regions, intergenic regions, untranslated regions (UTRs), or introns. Many antisense promoters lack canonical TATA boxes and instead contain GC-rich regulatory elements that recruit RNA polymerase II and transcription factors. Following transcription, NATs undergo post-transcriptional processing, including 5' capping, splicing, and polyadenylation, before functioning in the nucleus or cytoplasm (Bhaumik, 2011; Yang, 2022). The diverse structural organization of NATs underlies their ability to regulate gene expression through transcriptional interference, chromatin remodeling, RNA masking, RNA editing, alternative splicing, and modulation of mRNA stability and translation. Owing to these diverse regulatory functions, NATs have emerged as promising therapeutic targets for cancer, neurological disorders, cardiovascular diseases, respiratory diseases, and viral infections. Antisense oligonucleotide-based therapies targeting NATs are currently being investigated in both preclinical and clinical studies (Rinaldi & Wood, 2018; Crooke *et al.*, 2021).

Accumulating evidence indicates that dysregulation of NATs contributes to the development of numerous human diseases, including cancer, neurological disorders, cardiovascular diseases, autoimmune disorders, and viral infections. Consequently, antisense transcripts have attracted considerable interest as potential therapeutic

targets, particularly for RNA-based gene regulation strategies and antisense oligonucleotide therapies (Rinaldi & Wood, 2018; Crooke *et al.*, 2021). Figure 1 summarizes the various forms and organization of NAT.

Regulation and cellular roles of natural antisense transcripts

Natural antisense transcripts (NATs) have emerged as important regulators of gene expression in both physiological and pathological processes. Genome-wide transcriptomic studies indicate that antisense transcription occurs at a substantial proportion of genomic loci, with nearly 70% of mammalian genes estimated to possess antisense partners. These transcripts often overlap protein-coding genes, promoter regions, or other regulatory elements and exhibit distinct expression patterns that are frequently tissue-specific, developmental-stage-specific, or stimulus-responsive (Wight & Werner, 2013). Compared with their corresponding sense transcripts, NATs are generally expressed at lower levels but exert significant regulatory effects through both cis-acting mechanisms, which influence neighboring genes, and trans-acting mechanisms, which regulate distant targets through sequence complementarity (Xu *et al.*, 2017a).

Epigenetic regulation

One of the best-characterized functions of NATs is the regulation of chromatin architecture and epigenetic modifications. Many NATs recruit chromatin-remodeling complexes, including Polycomb Repressive Complex 1 (PRC1) and Polycomb Repressive Complex 2 (PRC2), to specific genomic loci, leading to histone modifications such as H3K27 trimethylation (H3K27me3) and H2AK119 ubiquitination. NATs also participate in DNA methylation by recruiting DNA methyltransferases to promoter CpG islands, thereby reducing chromatin accessibility and suppressing transcription. The α -globin antisense transcript generated from the LUC7L locus represents one example in which antisense transcription contributes to abnormal methylation and altered α -globin expression in α -thalassemia (Khorkova *et al.*, 2022).

Regulation of genomic imprinting and X-chromosome inactivation

Natural antisense transcripts play essential roles in genomic imprinting and X-chromosome inactivation (XCI), two major epigenetic processes responsible for monoallelic gene expression. During XCI, the long non-coding RNA XIST coats one X chromosome and recruits chromatin-modifying proteins that establish transcriptionally inactive heterochromatin. In contrast, its antisense transcript TSIX suppresses XIST expression, thereby maintaining the active X chromosome.

Post-transcriptional regulation

NATs regulate gene expression at the post-transcriptional level by directly interacting with

complementary sense RNAs. Formation of RNA–RNA duplexes influences mRNA stability, nuclear export, RNA editing, translation, and degradation (Ali *et al.*, 2024). RNA duplexes generated by NATs can serve as substrates for adenosine deaminases acting on RNA (ADARs), promoting A-to-I RNA editing that alters transcript function or stability (Keegan *et al.*, 2023). NATs can also mask microRNA-binding sites within target mRNAs, thereby preventing microRNA-mediated degradation, or recruit transcripts into the Staufen-mediated mRNA decay pathway, resulting in selective transcript degradation (Ortega *et al.*, 2024). Several NATs also function as competing endogenous RNAs (ceRNAs) by acting as molecular sponges for microRNAs (Shahpari *et al.*, 2024).

Regulation of alternative splicing and transcription

Natural antisense transcripts influence pre-mRNA processing by masking splice sites or modulating the activity of spliceosomal proteins, thereby altering alternative splicing patterns. For example, UXT-AS1 regulates alternative splicing of the UXT gene and contributes to colorectal cancer progression by promoting production of oncogenic transcript isoforms (Yin *et al.*, 2017). Other NATs indirectly regulate splicing through interactions with RNA-binding proteins such as CELF1 and MBNL1 (Guo *et al.*, 2024). NATs also regulate gene expression through transcriptional interference, a cis-acting mechanism in which simultaneous transcription from overlapping loci reduces transcriptional efficiency.

Regulation of protein function and translation

In addition to regulating RNA metabolism, some NATs directly influence protein stability and localization. Recent studies have further demonstrated that certain NATs contain short open reading frames capable of encoding biologically active micropeptides (Zhang & Liu, 2024).

Collectively, NATs regulate gene expression at multiple levels, these multilayered regulatory activities enable NATs to participate in embryonic development, cellular differentiation, stress responses, and maintenance of tissue homeostasis. Dysregulation of NAT expression has been implicated in numerous diseases, including cancer, neurological disorders, cardiovascular diseases, autoimmune disorders, and metabolic diseases, making them attractive targets for antisense oligonucleotide-based therapeutics and other RNA-directed treatment strategies (Crooke *et al.*, 2021). Table 2 lists selected NATs, their target genes, and their functions. Figure 2 summarizes various cellular functions of NAT.

Antisense transcripts in human diseases

Although scientists are only beginning to investigate the biological significance and regulatory mechanisms of natural antisense transcripts (NATs), they are already recognized as a crucial component of the human transcriptome. NATs are important for the normal metabolism of healthy cells and are also implicated in numerous human diseases, making

have further shown that APOA1-AS modulates histone methylation patterns associated with active and repressed gene expression (Halley *et al.*, 2014).

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that functions as a growth factor essential for neuronal development, maintenance, and differentiation (Colucci-D'Amato *et al.*, 2020). Its antisense transcript, BDNF-AS (also known as BDNFOS), negatively regulates BDNF expression by forming double-stranded RNA duplexes and altering chromatin structure. Elevated BDNF-AS expression reduces endogenous BDNF levels, thereby inhibiting neuronal growth and promoting neuronal apoptosis (Bach *et al.*, 2025). Conversely, suppression of BDNF-AS increases BDNF mRNA and protein expression. Examples of concordant regulation include BACE1 and its antisense transcript BACE1-AS, in which the NAT stabilizes BACE1 mRNA by masking microRNA-binding sites (Santos *et al.*, 2020). Increased expression of both BACE1 and BACE1-AS has been reported in patients with Alzheimer's disease (Hempel *et al.*, 2021). Since BACE1 is the rate-limiting enzyme in β -amyloid production, its dysregulation contributes significantly to Alzheimer's disease pathogenesis.

Several NATs are involved in regulating circadian rhythms by influencing mRNA expression. Circadian clock components coordinate numerous cellular functions with the organism's approximately 24-hour biological rhythm, and disruption of these processes has been associated with multiple diseases (Korf & von Gall *et al.*, 2024). NATs such as PER2AS and CRY1AS, transcribed from the PER2 and CRY1 loci, respectively, exhibit rhythmic expression patterns synchronized with their corresponding protein-coding genes (Mosig *et al.*, 2021). These NATs enhance the stability of their corresponding mRNAs by blocking microRNA-binding sites, thereby influencing the dynamics of core circadian clock genes.

Numerous NATs have also emerged as important regulators in human cancers. ANRIL (Antisense Noncoding RNA in the INK4 Locus) was first identified in melanoma patients and is overexpressed in several malignancies, including lung, breast, gastric, liver, prostate cancers, and melanoma (Sanchez *et al.*, 2023). ANRIL interacts with Chromobox 7 (CBX7) and Suppressor of Zeste 12 (SUZ12), essential components of Polycomb Repressive Complexes 1 and 2 (PRC1 and PRC2), respectively. These interactions promote chromatin remodeling and repression of the tumor suppressor locus INK4b-ARF-INK4a (Meseure *et al.*, 2016). In hepatocellular carcinoma (HCC), ANRIL interacts with Enhancer of Zeste Homolog 2 (EZH2) at the promoter region of KLF2, leading to epigenetic silencing of this tumor suppressor gene (Zhang *et al.*, 2024). The overexpression of FAM83A (Family with Sequence Similarity 83 Member A) is frequently observed in lung adenocarcinoma (LUAD), where it promotes tumor growth and is associated with poor patient survival. As an oncogene, FAM83A enhances cancer cell proliferation, migration, and invasion (Liu *et al.*, 2022). HNF4A-AS1L regulates the expression of its sense gene HNF4A, a well-established cancer-associated gene, through

a promoter-specific mechanism. It selectively activates the tumor-suppressive HNF4A P1 promoter via HNF1A while having no effect on the oncogenic P2 promoter, thereby increasing the expression of tumour-suppressive P1-derived isoforms. Analysis of RNA sequencing data from 23 tissue and cancer types identified approximately 100 ncNATs whose expression correlated specifically with the activity of one promoter of their corresponding sense genes. Silencing two of these ncNATs, ENSG00000259357 and ENSG00000255031, altered promoter usage of CERS2 and CHKA, respectively (Molias *et al.*, 2021).

Cryptic antisense polyadenylated transcripts (CAPTs) are abundant in tumor tissues (Zhao *et al.*, 2023b). LRRK1-CAPT, an oncogenic transcript derived from the antisense strand of the LRRK1 gene, is highly expressed in squamous cell lung carcinoma and promotes tumor growth and proliferation. Its expression is associated with epigenetic alterations, including DNA methyltransferase activation). Experimental suppression of LRRK1-CAPT significantly inhibits tumor cell proliferation.

NATs also play important roles in several neuropsychiatric disorders. A Dicer-dependent regulatory mechanism has been proposed for the HTT gene, which contains expanded CAG trinucleotide repeats in Huntington's disease (Arning & Nguyen, 2022). The Huntingtin natural antisense transcript (HTTAS) has emerged as an important regulator of HTT expression. In human embryonic kidney cells, increased expression of the HTTAS_v1 isoform was associated with reduced HTT expression in wild-type mouse embryonic cells. However, in Dicer-null cell lines, HTTAS_v1 failed to suppress HTT expression, demonstrating that Dicer is essential for this regulatory mechanism (Mills *et al.*, 2016).

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are devastating neurodegenerative disorders that share clinical, genetic, and neuropathological features (Grigore & Goebel, 2025). Expansion of a GGGGCC hexanucleotide repeat in a non-coding region of C9ORF72 is the primary genetic cause of both disorders. The expanded repeat forms nuclear RNA foci and undergoes repeat-associated non-AUG (RAN) translation, generating aggregation-prone proteins that contribute to neurotoxicity. Interestingly, RNA foci and poly (GP) inclusions rarely occur within the same cell, suggesting distinct pathogenic mechanisms (Gendron *et al.*, 2013).

Schizophrenia (SCZ) has been associated with dysfunction of the serotonin signaling pathway (Jiménez-Trejo *et al.*, 2024). HTR5A-AS1, a long non-coding RNA antisense to the serotonin receptor gene HTR5A, has shown strong transcriptome-wide association study (TWAS) signals in the hippocampus and dorsolateral prefrontal cortex (dlPFC). HTR5A-AS1 is strongly co-expressed with HTR5A, and functional analyses suggest roles in synaptic signaling and GABAergic neurotransmission, consistent with cortico-hippocampal dysfunction in schizophrenia (Ruttenberg, 2026).

NATs have also been implicated in diabetes, cardiovascular diseases, and muscle disorders. Qiu *et al.* (2016) identified the antisense lncRNA MEG3 (Maternally Expressed Gene 3) as an important regulator of microvascular dysfunction in diabetic complications. MEG3 expression is significantly reduced in the retinas of streptozotocin-induced diabetic mice and in endothelial cells exposed to high glucose. Knockdown of MEG3 increases retinal vascular abnormalities by promoting endothelial cell proliferation, migration, and tube formation.

The antisense transcript H19 has been linked to cardiovascular diseases such as coronary artery disease (CAD). As a precursor of miR-675, H19 suppresses cardiac hypertrophy by targeting CaMKII δ , a serine/threonine protein kinase (Su *et al.*, 2021). Knockdown of H19 induces cardiomyocyte hypertrophy, demonstrating its protective role in cardiac homeostasis.

Another antisense lncRNA, SIRT1-AS, regulates myogenesis. Knockdown of SIRT1-AS promotes differentiation of C2C12 myoblasts and human skeletal muscle cells (Lou *et al.*, 2021). In contrast, overexpression of SIRT1-AS increases SIRT1 expression by forming RNA duplexes that enhance SIRT1 translation while competing with miR-34a for SIRT1 binding. Consequently, dysregulation of SIRT1-AS may impair normal muscle development and contribute to muscle disorders.

Antisense transcripts in plants

Natural antisense transcripts (NATs) have emerged as a major class of regulatory RNAs that contribute to the complexity of gene expression in plants. NATs are now known as functional regulatory molecules involved in transcriptional regulation, chromatin remodeling, RNA processing, translation and environmental adaptation (Santini *et al.*, 2022). Originally thought to be transcriptional noise because they come from the DNA strand opposite to protein-coding genes. The extensive use of long-read transcriptomics, high-resolution genomic analyses and strand-specific RNA sequencing has shown that antisense transcription is ubiquitous in plant genomes, indicating that it is a conserved regulatory mechanism rather than an exception to canonical gene expression (Santini *et al.*, 2022).

In plants, NATs are classified into cis-natural antisense transcripts (cis-NATs) and trans-natural antisense transcripts (trans-NATs) according to their genetic origin. Plant cis-NATs have various chromosomal layouts, which influence their regulatory features. The direction and overlap of sense and antisense genes determine whether they are convergent (tail-to-tail), divergent (head-to-head), entirely overlapping, nearby tail-to-tail, or nearby head-to-head (Osato *et al.*, 2003). These genomic organizations determine the extent of RNA complementarity and influence the molecular mechanisms through which NATs regulate gene expression. Fully overlapping transcripts frequently generate extensive RNA duplexes that influence RNA stability, whereas head-to-head and tail-to-tail arrangements predominantly

affect transcription initiation or termination through transcriptional interference (Nakatake *et al.*, 2026).

Genome-wide studies have demonstrated that antisense transcription is remarkably widespread in plants. Approximately 10-20% of genes in *Arabidopsis thaliana* are associated with cis-NATs, while thousands of antisense transcripts have been identified in rice, maize, tomato, and other species (Wang *et al.*, 2014). However, despite the abundance of identified NATs, only a relatively small number have been experimentally validated. Santini *et al.* (2022) reported that among more than 1,100 antisense-related gene entries available in public plant databases, fewer than 1% have been functionally confirmed, highlighting a substantial gap between transcript discovery and biological characterization.

The molecular mechanisms underlying NAT-mediated regulation are remarkably diverse. At the transcriptional level, simultaneous transcription of overlapping sense and antisense genes may result in RNA polymerase II collisions, promoter competition, or transcriptional interference, thereby modulating transcript abundance (Pelechano & Steinmetz, 2013). Epigenetic regulation by recruiting chromatin-remodeling complexes enables plants to rapidly adjust gene expression in response to developmental and environmental cues (Swiezewski *et al.*, 2009; Csorba *et al.*, 2014). The discovery of nat-siRNAs represents a major breakthrough in understanding plant antisense biology because it established a direct molecular link between antisense transcription and small RNA-mediated gene regulation. One of the most well-studied examples of NAT-mediated regulation is the SRO5-P5CDH locus in *Arabidopsis thaliana*. Under salt stress, the overlapping transcription of these genes produces double-stranded RNA, which is converted into nat-siRNAs. These nat-siRNAs then modulate oxidative stress responses by influencing proline metabolism and reactive oxygen species buildup, revealing how antisense transcription directly contributes to abiotic stress adaptation (Borsani *et al.*, 2005). This discovery established NATs as active controllers of environmental responses, rather than passive transcriptional byproducts.

Beyond abiotic stress, accumulating evidence demonstrates that NATs contribute to plant immunity. Antisense transcripts have been identified during interactions fungal pathogen *Mycosphaerella eumusae* in banana and several virus–host systems. In rice, herbivore attack induces expression of NATJAZ10, which is positively correlated with its corresponding sense transcript *JAZ10* gene, a key regulator of jasmonate signaling. This observation illustrates that NATs may enhance, rather than repress, defense-associated gene expression, thereby expanding current understanding of antisense-mediated regulation (Santini *et al.*, 2022). Plant NATs also play essential roles during development. One of the best-studied examples is COOLAIR, a long antisense transcript produced from the FLOWERING LOCUS C (*FLC*) locus in *Arabidopsis*. During prolonged cold exposure, the antisense transcript COOLAIR is substantially produced and contributes to the epigenetic silencing of *FLC*, supporting the transition

from vegetative to blooming during vernalization. This regulation is related with coordinated changes in chromatin architecture and histone modification patterns that result in a repressed state at the *FLC* gene (Heo & Sung, 2011).

Additional studies have identified developmentally regulated NATs during flowering in maize, reproductive development in *Paspalum notatum*, circadian regulation in sugarcane, and fruit development in tomato, indicating that antisense transcription is integrated into multiple developmental programs (Krzyszmonik *et al.*, 2017).

Overall, current evidence firmly establishes plant NATs as versatile regulators operating at multiple levels of gene expression. Rather than functioning exclusively as transcriptional repressors, NATs constitute dynamic regulatory molecules that integrate developmental signals, environmental cues, epigenetic modifications, and RNA-based regulatory mechanisms. Their widespread occurrence across diverse plant species and involvement in growth, development, stress tolerance, and pathogen defense underscore their importance in plant biology. Continued functional characterization of NATs will not only advance understanding of plant gene regulatory networks but may also provide novel molecular targets for crop improvement aimed at enhancing resilience, productivity, and climate adaptability.

Antisense transcripts and therapeutic applications

Antisense therapy leverages synthetic oligonucleotides to specifically bind to target RNA sequences, altering gene expression. This is accomplished by preventing translation via steric hindrance or inducing transcript degradation. Key applications include correcting aberrant RNA splicing, suppressing toxic gene products in neurological disorders, and downregulating overactive genes. The following section covers few representative disorders and the applications of NATs.

Angelman syndrome is a severe neurodevelopmental disorder caused by maternal *UBE3A* deficiency. A promising therapeutic strategy for treating Angelman syndrome is to reactivate the intact paternal *UBE3A* allele by suppressing *UBE3A*-ATS. Currently, there is no curative treatment for Angelman syndrome. The disorder is typically caused by a deletion or mutation affecting the maternal *UBE3A* gene, which encodes the E3 ubiquitin protein ligase. Since the paternal allele is genetically imprinted and silenced in cis by its antisense transcript, no functional copy of *UBE3A* is expressed (Kang *et al.*, 2026). Therefore, suppression of *UBE3A*-ATS results in the unsilencing of the paternal *UBE3A* allele, thereby compensating for the loss of maternal gene expression. Lee *et al.* (2023) evaluated EEG power spectra and sleep architecture in mouse models following antisense oligonucleotide treatment. The results suggest ASO rescues disturbed brain rhythms and sleep in juvenile and adult mouse models. Amanat *et al.* (2022) demonstrated that paternal *Ube3a* expression was significantly increased in mice following reduction of *Ube3a*-ATS using two antisense oligonucleotide (ASO) gapmers. ASO treatment

partially rescued cognitive impairments without affecting the expression of neighboring genes, including *Snrpn*, *Snord115*, and *Snord116*. These findings suggest that targeting inhibitory natural antisense transcripts using ASOs may provide an effective therapeutic strategy for haploinsufficiency disorders such as Angelman syndrome.

Dravet syndrome is a severe developmental and epileptic encephalopathy that manifests during early infancy. In addition to drug-resistant seizures, patients commonly experience developmental delay, crouch gait, sleep disturbances, and an increased risk of premature mortality. In more than 90% of patients, the disorder is caused by pathogenic variants in *SCN1A* gene, which encodes the voltage-gated sodium channel subunit NaV1.1 (Myers, 2023). Current treatments for Dravet syndrome are primarily symptomatic and focus on reducing seizure frequency, with little or no effect on associated comorbidities. One of the most promising therapeutic strategies is to increase functional NaV1.1 expression using antisense oligonucleotides (ASOs) or viral vector-mediated gene therapy. This approach has the potential not only to reduce seizure frequency but also to improve the neurological comorbidities associated with the disorder. However, further clinical trials are required to establish the safety of these therapies and determine the extent to which they can alter the natural history of Dravet syndrome (Yuan *et al.*, 2024). Precision medicine has introduced additional therapeutic approaches by activating NaV1.1 or increasing functional *SCN1A* expression. These strategies include ASO that target the inhibitory natural antisense transcript (*SCN1ANAT*) and the nonproductive *SCN1A* transcript containing poison exon 20N (Lee *et al.*, 2023). Originally discovered in prokaryotes, CRISPR-Cas9 genome-editing technology has revolutionized molecular biology. CRISPR-Cas9 provides powerful precision gene-editing strategies for the treatment of genetic disorders, including neurodevelopmental diseases, and also has become an invaluable tool for generating animal models. Preclinical studies have demonstrated promising results using CRISPR/dCas-mediated activation of *SCN1A* and adeno-associated virus (AAV)-based gene therapy employing the transcriptional activator ETX101. Although these approaches show considerable promise as disease-modifying therapies for Dravet syndrome, additional clinical studies are required to confirm their safety and therapeutic efficacy (Lersch *et al.*, 2023). *SCN1A* also represents an example of discordant regulation by natural antisense transcripts. Expression of this protein-coding gene is increased when its antisense transcript (*SCN1ANAT*, also known as AC010127.3) is depleted or when its interaction with epigenetic regulatory proteins is disrupted using antisense oligonucleotides (Wanowska *et al.*, 2018). Furthermore, in a mouse model of Dravet syndrome, ASO treatment was shown to partially rescue the disease phenotype (Isom & Knupp, 2021).

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors that plays a critical role in neuronal development, differentiation, survival, and synaptic plasticity (Modarresi *et al.*, 2012). Altered expression of neurotrophins has been reported

in several neurodegenerative and psychiatric disorders (Wanowska *et al.*, 2018). Therefore, restoring or enhancing BDNF expression is considered a promising therapeutic strategy for these conditions. Similar to the examples discussed previously, the NATs BDNF-AS (also known as BDNF-OS) negatively regulates BDNF expression both in vitro and in vivo. BDNF-AS is a naturally occurring antisense transcript that regulates BDNF gene expression. Although modulation of BDNF expression is considered the principal mechanism by which BDNF-AS contributes to neurological disorders, accumulating evidence suggests that BDNF-AS also participates in tumorigenesis through both BDNF-dependent and BDNF-independent pathways. Locus-specific upregulation of BDNF has been achieved by ASOs that inhibit BDNF-AS, thereby increasing endogenous BDNF expression (Bazzari & Bazzari, 2012). Studies conducted in several cancer types indicate that BDNF-AS generally functions as a tumor suppressor. Primary studies in both animal models and patients suggest that administration of exogenous BDNF or enhancement of endogenous BDNF production may provide therapeutic benefits in neurodegenerative diseases. However, successful BDNF-based therapy requires careful optimization of dosage, timing, delivery, and tissue-specific targeting to ensure efficacy and safety. Furthermore, interventions such as long-term fluoxetine treatment, physical exercise, and environmental enrichment have been shown to increase neurogenesis, improve cognitive function, and elevate serum BDNF levels, highlighting the therapeutic potential of BDNF modulation. Nevertheless, several methodological and safety concerns must be addressed before these approaches can be translated into routine clinical practice. Future research should focus on well-designed clinical trials and further elucidate the multifunctional roles of BDNF in different regions of the brain (Jalaiei *et al.*, 2026).

Alzheimer's disease (AD) is characterized by increased expression of both *BACE1* gene and its natural antisense transcript BACE1-AS. BACE1 protein is an attractive therapeutic target because it is the rate-limiting enzyme responsible for the production of β -amyloid, a neurotoxic peptide that contributes to AD pathogenesis. However, direct inhibition of BACE1 has produced undesirable adverse effects, likely because the enzyme also performs essential physiological functions (Azman & Zakaria, 2022). Faghihi *et al.* (2008) demonstrated that intracerebral administration of small interfering RNAs (siRNAs) targeting BACE1-AS significantly reduced both BACE1-AS and BACE1 mRNA and protein expression in mouse brains. Consequently, β -amyloid accumulation was reduced, and soluble β -amyloid levels decreased in vivo. These findings suggest that targeting BACE1-AS indirectly lowers *BACE1* gene expression while preserving its normal physiological functions, thereby providing a potentially safer therapeutic strategy than direct BACE1 inhibition. Therefore, modulation of BACE1-AS offers an alternative approach for reducing AD-associated β -amyloid pathology, particularly when conventional therapeutic strategies prove ineffective (Dubey *et al.*, 2026). In addition to oligonucleotide-based therapies, genome-

editing technologies such as CRISPR-Cas9 have emerged as promising therapeutic approaches for NAT-associated diseases. Recent studies have demonstrated that CRISPR-Cas9 can correct disease-causing mutations and reverse pathological phenotypes in vivo, as shown in mouse models of Duchenne muscular dystrophy (Raswanthiya *et al.*, 2026). These findings highlight the potential of gene-editing technologies as future therapeutic strategies for disorders associated with dysregulated natural antisense transcripts.

Discussion

Antisense regulation (mediated by cis-encoded antisense) has been implicated in many aspects of gene regulation, including translational regulation, genomic imprinting, RNA interference, alternative splicing, X chromosome inactivation, RNA editing, and heterochromatic gene silencing (Alberts *et al.*, 2022). NATs play crucial cellular roles within the complex regulatory networks that finely tune gene expression during transcription. This form of regulation significantly impacts subsequent post-transcriptional events by dictating the mRNA's sequence, chemical modifications, as well as its movement, cellular positioning, and proficiency in translation. Most of the natural antisense transcripts are cis-encoded antisense. In the human genome, it was predicted that from 1 to 2% to 8% of the human genes were influenced by antisense transcripts (Miller *et al.*, 2021). Human brain is the most complex organ in the human body, and is much more complex than the brains of other mammals. It was hypothesized that an increase in noncoding regulatory capacity reflects the higher demands of human brain learning, memory, speech, and cognitive capabilities. Studies have performed a comparison of antisense transcription prevalence between human and mouse regarding three different tissue/cell types including brain, liver, and embryonic stem cells.

Despite progress in Antisense biology, few challenges exist. The major challenge to identifying natural SA transcripts from public databases is how to determine the correct orientation of candidate sequences, especially expressed sequence tag (EST) sequences. EST sequences are single-pass and partial sequencing reads generated from either the 5' or 3' end of cDNA clones. As the cDNA libraries are generated from either normal or pathological samples from different tissues and different developmental stages, ESTs provide a tremendous resource for transcript analysis at the genome level. While there is still no conclusive evidence demonstrating a functional role for these long, intronic antisense messages, the far-reaching implications of their existence for the mechanisms regulating gene expression certainly warrant further experimentation (Fachel *et al.*, 2013). Despite considerable advances in transcript identification, functional characterization of plant NATs remains a major challenge. Many currently identified antisense transcripts lack experimental validation, and distinguishing functional regulatory RNAs from transcriptional noise remains difficult. The emergence of long-read sequencing technologies, single-cell transcriptomics, CRISPR/Cas-mediated genome editing, RNA structure mapping, and epitranscriptomic

profiling is expected to substantially accelerate functional investigations of plant antisense transcripts (Shen *et al.*, 2023). Integration of these complementary approaches will provide deeper insights into how NATs interact with chromatin, transcription factors, RNA-binding proteins, and small RNA pathways to coordinate gene expression under both normal and stress conditions.

While it appears intuitively reasonable to suppose that organisms differ in their “complexity,” this apparently simple assertion begs numerous further questions. One issue is definitional, that is, what is complexity, and how might it be measured? What factors underlie the differences in complexity? Following the discovery of the remarkably small number of protein-coding genes in the human genome, it was suggested that complexity might arise from alternative splicing (Zhao *et al.*, 2023a). While no doubt this is true in part, it is remarkable that across a wide span of taxa, there is little difference in the abundance of alternative splicing. What else might underpin the differences in complexity? It has been suggested that the basis of eukaryotic complexity and phenotypic variation may lie primarily in a control architecture composed of a highly parallel system of transacting RNAs that relay state information required for the coordination and modulation of gene expression. Further organismal complexity arises from progressively more elaborate regulation of gene expression (Golomb *et al.*, 2026). Research evidences implicate that humans are in any way unusual among the vertebrates regarding antisense transcription. Why the fly is especially rich in antisense transcription while the nematode is especially poor is far from clear. Genomic compaction seems not to be the primary reason for the enrichment of antisense in fly, because the nematode genome is even more compact than the fly genome. The expression patterns of many antisense transcripts are conserved across species, suggesting selective pressure on these transcripts (Ling *et al.*, 2013). When compared to protein-coding genes, antisense transcripts show a lesser degree of expression conservation. Studies have found a positive correlation between the sense and antisense expression across tissues. From an evolutionary perspective Antisense transcripts can recruit epigenetic machinery (like DNA methyltransferases and Polycomb complexes) to specific loci, essentially turning genes on or off (Fan *et al.*, 2026). This provides a highly flexible mechanism for organisms to adapt their gene expression to changing environments. While overlapping sequences constrain the evolutionary rate (since both strands must maintain functionality), they also provide an organism with a flexible mechanism to rapidly regulate gene networks in response to environmental or developmental changes (Xu *et al.*, 2017b). Their bi-directional nature creates distinct evolutionary disadvantages. These challenges explain why cells heavily regulate and sometimes discard these transcripts. If a protein-coding gene overlaps with an antisense transcript that also encodes a protein, a mutation to optimize the function of one strand will simultaneously alter the amino acid sequence of the complementary strand (Iyengar *et al.*, 2024). This creates a severe evolutionary conflict where neither protein can be independently optimized.

While the therapeutic potential of natural antisense transcripts is vast and has attracted several researchers and clinicians the field faces several limitations. Delivering ASOs across the blood-brain barrier (BBB) or into systemic target tissues without rapid clearance requires complex chemical modifications. Unintended binding to off-target RNA can lead to unintended toxicity or adverse immune responses. Finally, synthetic oligonucleotide sequences must be protected against degradation by cellular endonucleases.

Conclusion

Natural antisense transcripts (NATs) have become significant gene expression regulators that affect a variety of biological processes via transcriptional, post-transcriptional, and epigenetic pathways. Their biological and clinical significance is highlighted by their role in development, cellular homeostasis and the development of diseases like cancer and neurological disorders. Our knowledge of NAT activities has grown as a result of developments in transcriptomics and RNA-based technologies, which have also demonstrated their promise as therapeutic targets and diagnostic biomarkers. Although challenges remain regarding safety, specificity, and delivery, additional research is anticipated to hasten the clinical translation of NAT-based treatments. Overall, NATs are an exciting area of molecular biology that has great promise for improving precision medicine and also an important tool in plant biology.

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