# Long non-coding RNAs in Schizophrenia


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**Introduction**

Schizophrenia is a clinical syndrome characterized by a collection of symptoms that make it difficult to perceive, think, feel, act, and otherwise function normally. Schizophrenia is among the top 10 disabilities worldwide, affecting approximately 1% of the population. High-throughput mapping and scanning of the human genome have enabled rapid identification of disease-specific gene variants. Several studies have established a strong genetic basis for schizophrenia. For example, pedigree analysis has suggested that the rates of schizophrenia are higher among the biological relatives of schizophrenic adoptees than among those of the biological relatives of the controls, supporting the genetic hypothesis. In addition, there was no increase in the risk of schizophrenia among couples who adopted psychotic adoptees, indicating that environmental factors alone did not play a significant role. Despite this, the diagnosis of schizophrenia is still primarily based on clinical presentations, due to the lack of a single gene or set of genes that can be utilized as a definitive diagnostic marker. This is because of the considerable heterogeneity and complexity in heritability and genetic mechanisms associated with the disease

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Recent advances in genetic analyses have enabled high-throughput analysis of genes and proteins involved in the pathophysiology of schizophrenia. Particularly, differential gene expression analysis has identified certain important 'risk' genes associated with schizophrenia.

**Long non-coding RNAs**

Among them, noncoding RNAs (ncRNAs) have received considerable focus globally, with microRNA, a class of ncRNAs, being fully explored in a wide range of neuropsychiatric disorders, including schizophrenia. Among the ncRNAs, long non-coding RNAs (lncRNAs) – a type of ncRNA with transcripts longer than 200 nucleotides, have been recognized as essential gene expression regulators. lncRNAs are transcribed mostly by RNA polymerase II (Pol II), but other RNA polymerases are also involved in their transcription. lncRNAs are transcribed from intergenic regions (lincR-

NAs) as well as sense or antisense transcripts that overlap with other genes (Figure 1). lncRNAs are frequently capped with 7-methyl guanosine (m7G) at their 5 ends, polyadenylated at their 3 ends and spliced similarly to mRNAs.

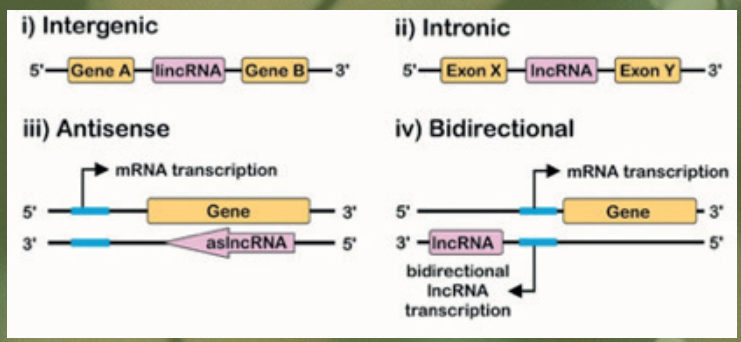
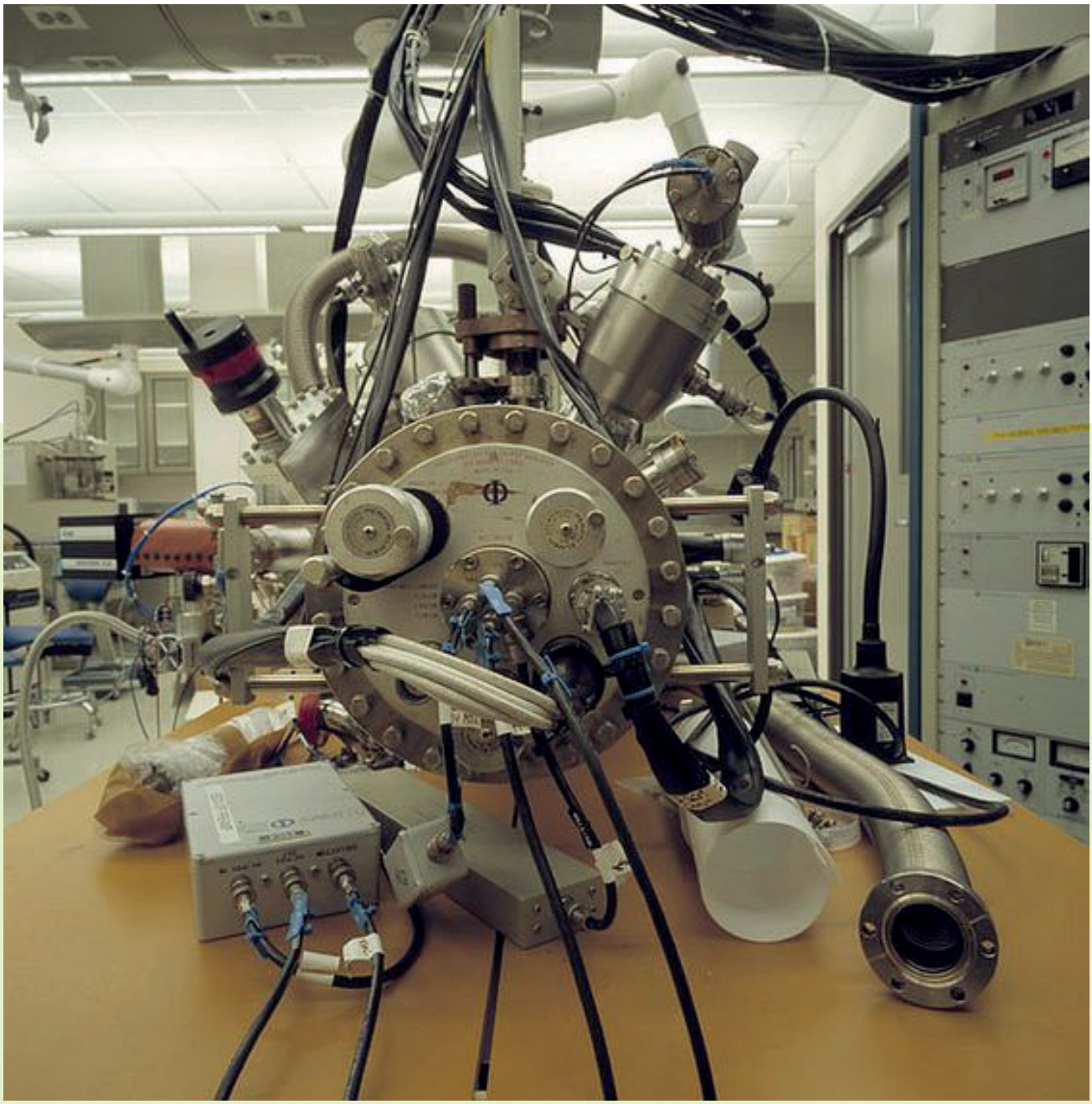


Figure 1: Types of lncRNA: lncRNAs are classified as i) intergenic RNAs (lincRNAs) that are located between two protein-coding genes, ii) intronic lncRNAs that are located within an intronic region of a protein-coding gene, iii) antisense lncRNAs (aslncRNAs) that are transcribed from complementary strands, and iv) bidirectional lncRNAs that originate from the bidirectional transcription of protein-coding genes. Adapted from Fernandes, Acuña, Aoki, Floeter-Winter, & Muxel, 2019.

The lncRNAs were commonly regarded as 'noise' in transcriptional data. Several studies now suggest that lncRNAs have crucial roles in a variety of biological processes, such as gene expression regulation, cell proliferation and differentiation, and disease (Table 1).

Table 1: Functions and mechanisms of selected long non-coding RNAs implicated in neurocognitive disorders. Adapted from Statello, Guo, Chen, & Huarte, 2020.

| Function | lncRNAs | Interacting with DNA;proteins | Pathophysiological process |
|---|---|---|---|
| **Regulation of transcription** | ANRIL | PRC1, PRC2; YY1 | Multiple roles in diseases |
| **Regulation of transcription** | UMLILO | WDR5–MLL | Primes transcription of immune genes during trained immunity |
| **Regulation of transcription** | lncPRESS1 | Sirtuin 6 | Regulates ESC differentiation |
| **Regulation of transcription** | XIST | PRC2, YY1, hnRNPK, SHARP and others240 | Multiple roles in the development |
| **Regulation of transcription** | AIRN | PRC2 | Functions in embryonic development |
| **Regulation of transcription** | KCNQ1OT1 | PRC2, DNMT1 | Implicated in congenital growth disorders |
| **Post-transcriptional regulation** | AS-Uchl1 | Uchl1 mRNA | Neuroprotective function under stress through regulating Uchl1 translation |
| **Post-transcriptional regulation** | FAST | β-TrCP | Promotes pluripotency by maintaining the WNT pathway in human ESCs |
| **Structural functions** | sno-lncRNAs | RBFOX2 | Five sno-lncRNAs are missing in individuals with Prader–Willi syndrome |
| **Genome integrity** | PANDA | NF-YA | Reduces apoptosis and cell senescence |
| **Genome integrity** | DINO | p53 | Causes cell cycle arrest and induces DNA damage |



**lncRNA in Schizophrenia**

lncRNAs are frequently expressed in a tissue- or cell-type-dependent manner and can be detected in peripheral blood (circulating lncRNAs), making them minimally invasive, accessible, and efficient biomarkers for neuropsychiatric disorders, including schizophrenia. Unfortunately, only a handful of reports have identified the expression profile of circulating lncRNAs in the peripheral blood of schizophrenia patients and their response to antipsychotic drugs. For example, Zhang et al, identified differential expression (upregulation) of three lncRNA, namely NONHSAT089447, NONHSAT021545, and NONHSAT041499 in the peripheral blood of schizophrenia patients, when compared to healthy patients. Co-expression analysis identified 1773, 638, 1602, and 89 mRNAs to be co-expressed with NONHSAT021545, NONHSAT041499, NONHSAT089447, and three lncRNAs, respectively. Gene ontology analysis of the mRNAs co-expressed with lncRNAs were found to be involved in diverse functions, such as signal transduction, cell cycle, cell proliferation, differentiation, pallium growth, axon guidance, and extension, synaptic transmission, learning, memory, etc. that may be important in the pathophysiology of schizophrenia.

Similarly, a systemic review by Ghafouri-Fard, et al, identified lncRNA Gomafu, PINT, GAS5, TCONS_I2_00021339, IFNG-AS1,

FAS-AS1, PVT1, and TUG1 to be down-regulated while lncRNA MEG3, THRIL, HOXA-AS2, Linc-ROR, SPRY4-IT1, UCA1, and MALAT1 to be up-regulated in patients with schizophrenia. Dysregulation of these lncRNAs has been linked to changes in neuronal structural plasticity and abnormal neurodevelopment. Similarly, Chen et al. reported differential expression of 125 lncRNAs, particularly downregulation of ENST00000394742, TCONS_I2_00025502, ENST00000563823, ENST00000521622, and TCONS_I2_00021339 in schizophrenia patients when compared to healthy controls. These transcripts have a key role in the interferon pathway, suggesting a link between lncRNA dysregulation, inflammation, and the development of schizophrenia.

**Conclusion**

Although the role of lncRNA in schizophrenia has been inadequately explored, the body of published literature suggests that dysregulation of these non-coding transcripts not only plays a significant role in the pathophysiology of schizophrenia but also highlights the value of these non-coding RNAs as diagnostic markers for schizophrenia.

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