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Review

Non-Coding RNAs in Brain Function and Disorders

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ABSTRACT

With science advancing daily, psychiatric disorders are more of a concern now than in the past. It is a significant step forward to increase societal awareness of psychiatric disorders since they do not fall under the category of visible and simply identified conditions as physical illnesses. The fact that ribonucleic acids (RNAs), which are responsible for conveying and interpreting the genetic code, have transcripts that do not code for proteins, is one of the key variables contributing to psychiatric disorders, which are known to be influenced by both environmental and genetic factors. An overview of the connection between brain function and non-coding RNA is intended in this review.

Keywords: Genetics, ncRNA, neurology, psychiatric disorders, ribonucleic acid

Psychiatric disorders are a class of uncontrollable conditions that must be observed over time to be diagnosed. In addition to physical and mental issues, they experience daily, such as introversion, mood changes, obsessions, insomnia, difficulty performing routine tasks, getting exposed to negative behaviors like social exclusion, stigmatization, prejudice, distant attitude and categorization by the public leads to exacerbates of patients' condition.[1] Apart from the known environmental factors, non-coding ribonucleic acids (ncRNAs) in the human genome also have a great impact on such disorders.[2]

Despite being functional, these RNAs cannot be translated into proteins, which explains their inability to code.[3] While coding RNAs are absent in particular parts of the human body, ncRNAs are mostly found in the brain and have a significant impact on psychiatric disorders.[4] Numerous studies have shown that ncRNA defects are directly related to psychiatric disorders since these RNAs are linked to neurodegeneration, defense mechanism deficiencies, and dysfunction in the brain.[5]

The ncRNAs are broken down into numerous categories within themselves and are engaged in a wide range of cellular functions, including cellular defense and response, catalyzing reactions, and regulating gene expression. The "Human Genome Project" has greatly advanced our understanding of the genes associated with psychiatric disorders and their variation of coding, and it has also sped up research on psychiatric genetic testing and related areas. To directly comprehend the connection between psychiatric disorders and ncRNAs, it is very valuable to grasp the varied activities of ncRNAs, changes in signaling activity, and other alterations.[6] Understanding this mechanism will also contribute to the diagnosis and treatment of these disorders.

A MODEL APPROACH TO PSYCHIATRIC DISORDERS

Intron and exon regions in deoxyribonucleic acid (DNA), which are responsible for the maintenance of vital functions and the biological development of organisms, are of great importance for coding. Exon regions participate in protein and messenger RNA (mRNA) coding, while introns do not. In cases where genetic information is transmitted by RNA, introns are spliced out, whereas exon regions are preserved and this causes the protein to fail to maintain its pattern

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structure.[7] In particular, protein synthesis in the brain has been the target of research in psychiatric disorders such as stress disorder, sociophobia, obsessive-compulsive disorder, depression, panic disorder, bipolar disorder, attention deficit hyperactivity disorder, dissociative identity disorder, agoraphobia, schizophrenia, autism spectrum disorder, generalized anxiety disorder, nicotine and substance addiction, sleep and eating disorders, post-traumatic disorders, and other specific phobias as shown in Figure 1.

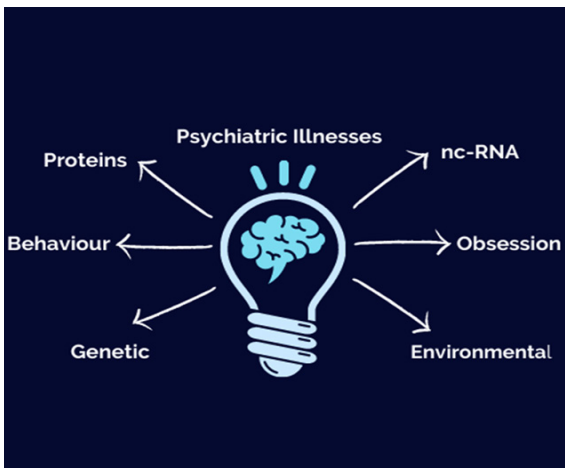

Figure 1. Keywords for the relationship between psychiatric disorders and non-coding RNA.

NON-CODING RNA

Most connections, mental disorders, and biological processes in the brain are mediated by ncRNAs. Despite their incapacity to code, they can alter synaptic signaling, dendrite shape, and neurogenesis.[7,8]

Their categorization varies according to their length, shape, and location.[9] Short ncRNAs include microRNA (miRNA), and piwi-interacting RNA (piRNA) linked within animal cells, among others. Small nucleolar (snoRNA) is an example of medium-length ncRNA, and lastly, there are long ncRNAs (lncRNA). Not all of these RNAs have the same functional properties, especially in the case of psychiatric disorders, miRNAs have the major role.[3] For instance, the X chromosome inactivation is regulated by the lncRNAs, which are encoded by polymerase II and have functions in the DNA-chromatin complex as well as contributing to the mature RNA template structure.[10] Add to that, the piRNAs, are directly related to neural regulation, memory, and neural plasticity.[3] And although the functioning and connections of brain-specific snoRNAs are still unclear, it is speculated that they are responsible for memory-related activities too.[11] But primarily, miRNAs lead to gene repression due to their failure to pair with their crosstalk. In the central nervous system, they are stably inserted into the genome, forming a regular link in brain morphogenesis and the process of brain development, translational degradation, and evolution. In addition, microRNA-7 (miR-7), which is abundant in the brain, is known to promote blood vessel occlusion, stroke, and brain damage.[12] Besides playing a key role in various metabolic events, cellular changes, and regulations as well as other activities, miRNAs are directly linked to psychiatric disorders.[13,14]

Since more RNAs than anticipated have been found in ncRNA research, nomenclature issues have also arisen. Their categorization has not been fully completed and resolved since it's unclear how each RNA functions or what significance it holds. There are yet other ncRNAs that are unknown to us, yet certainly, they will be discovered with further research.[15] Figure 2 depicts the visualization of coding and non-coding RNA.

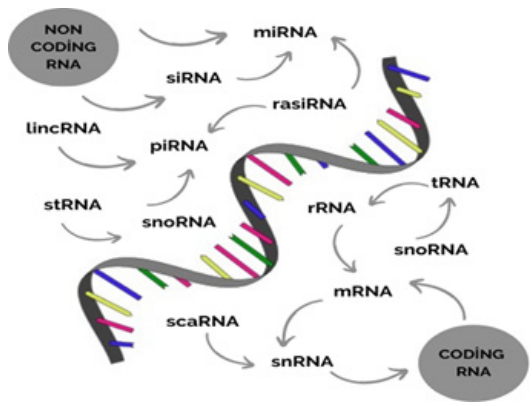

Figure 2. Coding and non-coding RNA visualization.

NON-CODING RNA IN THE BRAIN

The brain has the most complex system in a living organism, and ncRNAs have been involved in its rapid evolution for centuries. The expression of miRNAs in this evolutionary process is particularly crucial since their localization in the brain varies according to their differences. They frequently play a role in the disorder, malfunction, and occurrence of aberrant processes in the regulatory networks in the brain, where they are abundantly produced.[16,17] Examples of ncRNA activities include telomere functioning, protein localization control, the development of organelles and new short RNAs, miRNA binding and interaction

sites, and the basic functions of lncRNAs. They are quite beneficial to the brain in this regard. Furthermore, the neural changes occurring due to lncRNAs elimination through RNA interference imply the formation of new neurons.[18] The most well-known epigenetic modifications in the interaction between ncRNAs and the brain include cognitive and behavioral problems, aberrant neuronal and cellular development, and age-related degenerative and psychiatric disorders lncRNAs can also modify the structure and functioning of chromatin, have an impact on translation, and help regulate organelles as a result of their interactions with DNA and proteins. Generally, these changes may be congenital or acquired.[19,20]

MICRORNA

Despite their relatively short length of 19-25 nucleotides, miRNAs play significant roles in several phases of the cell, such as cell evolution, development, stress, and change.[21] They oversee cell growth, cellular cycle, physiological and psychological disorders, tumors, biosynthesis, DNA methylation, and chromatin modification. More importantly, during the development of psychiatric disorders, miRNA reports abnormal and complex connections in gene expression.[11] While most of the miRNAs in different locations are stable, some of them can constantly change their location in the genome. The example of the *DGCR8* gene, an RNA-binding protein, which is associated with the mutated chromosome of some psychiatric disorders, highlights the importance of these findings. Non-coding RNAs, which have not yet been fully decoded, play a major functional role in mental illness, brain evolution, and development.[22,23] Although in a recent study, it was shown that miRNAs' improper expression during adolescence leads to deterioration in brain development and psychological state, these issues and deficiencies may also occur in the early period, as they may cause long or short-term disruptions during the development of premature babies.[24] Since miRNAs play such a major role in the recovery and diagnostic process for psychiatric disorders, they are used as biomarkers, as is the case with the human-specific ncRNA *LOC389023*.[25,26]

EPIGENETICS

Although methylation, a chemical modification of DNA, comes to mind when we think of epigenetic modifications, nowadays ncRNAs are the focus of most studies. To better understand the onset of complex conditions including psychiatric and neurological disorders, these epigenetic alterations should not be disregarded. Although environmental factors hold great importance, gene expressions are equally significant. Further, ncRNAs are thought to be the root of expression variations from an epigenetic perspective, despite the absence of any variations in DNA sequence.[27] Epigenetic modifications, which are preserved through cell division and passed on to generations, are also affected by environmental factors such as nutrition, chemical exposure, radiation exposure, and various diseases.

Epigenetic mapping of RNA is becoming more and more valuable in visualizing many biological functions. To date, at least 160 genera of RNA modifications have been discovered.[28] Since environmental influences, especially stress, have a significant impact on the epigenetic mechanisms due to the remodeling of chromatin, these modifications can easily lead to anxiety, addiction, and depression when they impair neural plasticity.[29] Such factors can show such impacts even at the embryonic or fetal stages. For these reasons, epigenetic mapping and intergenerational transitions are of great importance.[30,31]

Although there are not yet as many studies focusing on the significance of epigenetic factors, viruses may be able to guide us in the future. The connections between cells are a subject that needs to be explored in order to recognize and conclude steps such as the expression of gene expression. It has been noted that a completely new mechanism than before is found in gene expression after the interaction of miRNAs and host miRNAs. New task distinctions and a shift in the functions of the inhibitors and activators were observed.[32]

MOLECULAR GENETICS IN PSYCHIATRIC DISORDERS

Molecular genetics is a subfield of genetics that analysis the connections between genes, their structures, and their functions on a molecular level. Encompassing DNA, RNA, and the synthesis of polypeptides. Identifying polymorphisms and mutations in gene expression that result in illness is the overall goal of this field. It operates utilizing genetic and molecular biology methods and scientific classification which are crucial for understanding and analyzing information. Furthermore, the field of molecular genetics, which we combine with psychiatry at the molecular level with the nervous system and brain, is known as molecular psychiatry. It targets the chemistry of brain physiological research

at the molecular level and associated behaviors, motions, and responses. Molecular genetic tests are crucial for making future early diagnoses, forecasting the onset of diseases, identifying the side effects of the pharmaceuticals used, and assisting in the continuation of therapy more beneficially while also improving quality of life.[33,34] More importantly, Investigating the root causes of psychiatric disorders is fundamental for treatment. When molecular mechanisms indications, prognosis, treatment response, whether favorable or unfavorable, and biomarkers are employed in these areas, they aid in better understanding the entire complicated process and, if required, advance drug design.[34,35]

In conclusion, it is extremely challenging to make a diagnosis or to track the progression of the disorders' stages since, with the exception of genotyping methods, there are no laboratory and test facilities related to the physiology of psychiatric disorders. Treatments today rely more on the patient's or the family's recognition of symptoms. Moreover, due to the lack of appropriate biomarkers in psychiatric disorders, the prognosis of psychiatric disorders is usually based on trial and error by the clinician, therefore, the resolution of potential symptoms and diagnosis is further delayed. However, with molecular genetics testing and by determining whether the condition is hereditary and by spotting the involved genes, polymorphisms, and mutations, it will be easier to comprehend the disorder, and prognosis, diagnosis, and treatment options would be easier to identify. Additionally, epigenetics also have a significant impact on disease prognosis. Along with environmental influences, ncRNAs have lately been on the study agenda for psychiatric disorders due to their inability to convert them into proteins. The distinction between coding and ncRNAs is an especially important element in the brain for psychiatric disorders since RNAs are involved in the nervous system as markers and important triggers for psychiatric disorders, neurological development, and brain evolution. To better understand complex diseases, epigenetic mechanisms have been used to explore new methods and treatments with positive results. There are several ncRNAs in addition to coding RNAs, which facilitate signaling cascades and cellular communication via diverse epigenetic processes. The variety of ncRNAs and neurological disorders have contributed significantly to the understanding of molecular genetics, and robust statistical techniques used in genome studies have demonstrated the direct relationship between ncRNAs and the brain. Particularly miRNA, which has also emerged as a novel study issue in terms of gene expression, has been investigated more than other types of RNA and has been linked to psychiatric disorders. For this reason, miRNAs have developed into an effective biomarker. Nevertheless, the mechanisms and pathways of all ncRNAs and the communication between them and the disorders they affect have not been fully explored. When the awareness of psychiatric illnesses, causes of which are not related to a single disorder, is increased, when methods that enable a more comprehensive examination of gene expression and genetic material at the cellular level are developed, and when all the mechanisms of ncRNAs are discovered, along with the development of gene-based treatments, gene regulation, and the previously described biomarkers, this procedure may become simpler. The effect of gene-environmental factors should not be underestimated and identifying not only the influencing factors but also the risk factors, recognizing increased susceptibility to disease, and being a good observer are as important as epigenetic factors for the prognosis of such disorders. From a hereditary perspective, the complete comprehension of ncRNA functions, their growth, and alterations at a cellular level, as well as the new rays of hope that will be born with the resolution of all the riddles, will be highly valuable in terms of diagnosis and treatment. It is expected that ncRNAs would aid in the recovery process in addition to the existing gene therapies, particularly when the therapeutic potential of siRNA is beginning to be employed appropriately. Lastly and most importantly, with the development of science, it may be possible to turn damage and mutations into benefits through chemical modifications as a result of the relationship between psychiatric disorders and RNA.

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