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Research Progress on the Relationship Between the Regulation of SLC6A4 Gene and Anxiety Disorders

Hanchang Zheng

Shanghai University, Shanghai, China

zhc2683@shu.edu.cn

Abstract. Anxiety disorder is one of the most common mental disorders. Numerous studies have demonstrated the critical role played by genetic variables in the etiology of anxiety disorders. SLC6A4, which encodes serotonin transporter, is considered to be an important gene associated with anxiety susceptibility. The SLC6A4 gene's upstream promoter has a polymorphism region that has an impact on the transcriptional activity of the gene. Research has shown that this promoter polymorphism has a certain relationship with the occurrence of anxiety disorders and drug treatment. Anxiety disorders are also linked to SLC6A4 gene methylation and intron 2 (Stin2) polymorphism. Stin2 point and SLC6A4 gene methylation are all related to gene expression. This review summarizes the current research on the relationship between SLC6A4 gene promoter polymorphism, Stin2 polymorphism, and SLC6A4 gene methylation in the pathogenesis and drug treatment of anxiety disorder, to understand the current research progress of SLC6A4 gene expression in anxiety disorder.

Keywords: anxiety, SLC6A4, 5-HTTLPR, Stin2

1. Introduction

Anxiety disorders are common psychiatric disorders, the global incidence is about 7.3%, and every 14 people has one was diagnosed with anxiety during their lifespan [1]. Anxiety disorder is an overreaction to fear and anxiety. Although the reaction of fear can help people get alert about potential danger and get prepared immediately, anxiety disorder makes people feel tension and anxiety for a long time. This characteristic helps distinguish fear and anxiety. Anxiety disorders can cause negative emotion which not only influences working, but also affect the ability to live. What's more, anxiety disorders always cause vasoconstriction, poor sleeping, and heart rate and blood pressure increase. When anxiety disorder is severe, it may induce depression.

Many risk factors can lead to anxiety disorders. Childhood treatment, physical punishment, intense social pressure, or other traumatic event has the chance of developing anxiety disorders. Anxiety is also compared with other mental health issues, like depression. Genetic epidemiological studies show that anxiety disorders are related to genetic factors, with heritability estimates vary from 30 to 50% [2]. Many genes have been proved to be related to anxiety behaviors, such as SLC6A4, BNDF, and GABRA6 [3].

In humans, the SLC6A4 locates on chromosome 17q11.2 and encoding the serotonin (5-HT) transporter (5-HTT). 5-HT is a neurotransmitter that controls how neurons grow and differentiate as well as keeps them functioning normally. 5-HT also modulates reward, mood, memory, and many other physiological processes. 5-HTT locates on the presynaptic membrane, which reuptake 5-HT to the

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presynaptic membrane from the synaptic cleft. The balance of 5-HT in the synaptic cleft is significantly maintained by 5-HTT. The expression of 5-HTT is directly related to 5-HT function. Selective Serotonin Reuptake Inhibitor (SSRI) is the most commonly used antidepressant and anti-anxiety drug, which can inhibit the function of 5-HTT. Therefore, the abnormal 5-HT reuptake may be associated with disease occurrence and differences in drug treatment. In its promoter region, SLC6A4 has serotonin transporter-linked polymorphic region (5-HTTLPR). The 5-HTTLPR polymorphism region at 1400bp upstream of the SLC6A4 gene transcription start site is composed of variable number tandem repeat (VNTR), with each repeat unit consisting of 20-24bp nucleotides [4]. Variations in the number of repeat units found so far range from 11 to 24. Additionally, the 5-HTTLPR region contains a single nucleotide polymorphism (SNP) polymorphism at RS25531. Studies have shown that both 5-HTTLPR and RS25531 are closely related to SLC6A4 transcription level and mental disease.

The serotonin transporter gene's intron 2 contains a 17-bp variable number tandem repeat called the SLC6A4 intron 2 (Stin2). Multiple alleles have been identified. And Stin2 has been linked to anxiety disorders, bipolar disorder, and depression in many studies. DNA methylation is a covalent alteration that takes place at the level of DNA dinucleotides that are rich in cytosine and guanine (CpG sites) by attaching a methyl group to the cytosine ring. At present, some studies have indicated that SLC6A4 gene methylation is an important mechanism in the pathogenesis of anxiety and depression. This review will discuss the relationship between the regulation of SLC6A4 gene and anxiety disorders.

2. The serotonin transporter linked polymorphic region(5-HTTLPR)

2.1. 5-HTTLPR and rs25531

In 1996, Heils [4] et al. conducted DNA analysis on 52 healthy subjects and found that the upstream regulatory region of SLC6A4 gene was 44bp long, GC-rich, and involved in 6-8 repeat unit insertion/deletion variants, named 5-HTTLPR. The deletion was the S (short) allele and the insertion was the L(long) allele. Subsequently, it was found that the S allele was composed of 14 repeats, while the L allele was composed of 16 repeats. Michaelovsky [5] et al. found an allele L with 18 repeat sequences in Jews from Libya and Tunisia, among which 9-10 repeat units were copies of 7-8 repeat units. In addition, 18, 19, and 20 duplicated alleles have been reported. To achieve a more complete allele analysis of SLC6A4 promoter, Nakamura [6] et al. used PCR-restriction fragment length (RFLP) analysis and single-stranded conformational Polymorphism (SSCP) analysis of 131 Japanese and 76 Caucasian subjects to identify a polymorphism of 5-HTTLPR alleles. Polymorphism of 5-HTTLPR alleles was identified in at least four forms of S allele, and at least six forms of L allele. Ten of them are newly identified alleles. There are 14,15,16,19,20,22 duplicate units, and these alleles have significant ethnic differences. In addition, extra short(XS) repeats (11-13 repeats) and extra long (XL) repeats (24,28 repeats) were also found. Ethnic differences in rare alleles of 5-HTTLPR are important for studying the high prevalence of genetic diseases and ethnic development history in specific races.

The two most prevalent 5-HTTLPR alleles are L and S, although VNTRs with other repeat counts are quite uncommon. In 2005, A functional variant RS25531 was found in the promoter region of SLC6A4 [7]. This variant is located in the 43pb of the sixth repeat unit of 5-HTTLPR, which is A base A>G substitution and mostly occurs in L allele carriers. It produces two alleles, LA and LG. Moreover, RS25531 formed a binding sequence consistent with Activator protein 2 (AP-2), which enhanced the binding of RS25531 to AP-2. Therefore, many researchers refer to 5-HTTLPR and rs25531 as triple alleles.

2.2. Effects of 5-HTTLPR and rs25531 on gene transcriptional activity

Studies have shown that different alleles of 5-HTTLPR affect the transcriptional activity of SLC6A4 gene. When 5-HTTLPR was discovered, because the expression of human placental choriocarcinoma cell line (JAR) was similar to that of 5-HTT in midbrain neurons, Heils [4] et al. conducted in vitro functional research on JAR. It was discovered that the L allele had nearly three times the transcriptional activity of the S allele. Most studies have shown that SLC6A4 gene transcriptional activity of S allele

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is lower than that of L allele [8], so S allele can reduce 5-HTT expression, thereby inhibiting 5-HT reuptake. According to several research, there is no discernible variation in transcription levels between the S allele and the L allele [9], which may imply that other factors may be involved in the effect of different 5-HTTLPR alleles on the transcription activity of SLC6A4 gene. Vijayendran [10] et al. analyzed the 5-HTTLPR genotypes in 480 female subjects and found that the frequencies of S, L, and XL genotypes were 26%, 70%, and 4%. The analysis of transcription efficiency of the three alleles confirmed the linear relationship between promoter activity and repeat sequence length. The effect of LA allele on transcriptional activity was 1.8 times higher than that of LG allele. Ehli et al. also confirmed in their subsequent studies and found three rare alleles XS11, XL17 and XL18. The expression level of XS11 allele was similar to that of S allele, and the transcript level of XL17 was significantly decreased compared with that of LA allele. Activator protein (AP) -2 plays an important role in neuronal development. In RS25531, LG has a binding sequence consistent with AP-2, which can inhibit the binding of the promoter and AP-2, thereby affecting the transcription of SLC6A4 gene [11]. The decreased expression of XL17 is most likely due to differential transcription factor binding leading to attenuation of activity. Interestingly, compared with the S allele, the XS11 allele had a significant reduction in repeat sequence but did not change its expression level.

In A recent study, Ikegame [12] et al. identified the extremely long repeat sequence XL28-A by analyzing DNA samples from Japanese patients with major psychosis and older adults. Interestingly, XL28-A did not show enhanced transcriptional activity. XL28-A showed no promoter activity in the tested population and was not significantly related to psychiatric disorders. It is speculated that promoter activity is not only related to repeat sequence length but also related to other regulatory polymorphisms, such as RS25531 SNP. Considering that the AP-2 binding site is located in the XL28-A repeat, the accumulation of this repeat may result in the inhibition of SLC6A4 promoter activity. Therefore, the real reasons for the difference in SLC6A4 gene transcriptional activity caused by different 5-HTTLPR genotypes still need to be studied in the future.

3. 5-HTTLPR in anxiety disorder and drug efficacy

3.1. 5-HTTLPR in anxiety disorder

SLC6A4 gene is generally considered to be related to the susceptibility of mental diseases. Related studies on SLC6A4 and various mental diseases, such as anxiety disorder, depression, schizophrenia, autism, have been continuing. Since Heils [6] et al. found the correlation between 5-HTTLPR and anxiety disorders in 1996, research on the pathophysiology of anxiety disorders has centered on 5-HTTLPR. However, the function of 5-HTTLPR in anxiety disorders is still debatable.

In the investigation and analysis of 147 pairs of twin children, Zhao [13] et al. 1 found that the scores of anxiety factors of children with LS and SS genotypes were higher than those with LL genotypes. Children with the S allele tend to have higher anxiety symptoms. In addition, the study found that the young with the S allele whose parents had overprotective and punishing behaviors were more likely to have anxiety problems. One study found that in healthy people, those with the S and LG alleles had a harder time recovering from happy, sad, or fearful stimuli than those with the LL genotype. In their study, Minelli [14] et al. found that Caucasian subjects with SS genotype showed a higher correlation with anxiety. In a study on the relationship between Agoraphobia and triallelic, L allele carriers had a higher correlation of anxiety characteristics than SS genotype carriers. Mismatch negativity (MMN) consists of two stimuli, the standard one being a repeated stimulus with a good probability, and the deviated one being a random stimulus with a small probability. There is a positive correlation between MMN amplitude and anxiety symptoms [15], which can reflect the hyperalert behavior of patients with anxiety disorder. Chen [16] et al. found that S allele carriers had lower MMN, suggesting that S allele had lower anxiety susceptibility. In their analysis of 225 adolescents with genotypes and anxiety diagnoses, Bortoluzzi [17] et al. failed to discover a relationship between 5-HTTLPR and anxiety-related traits. Similarly, Munaf [18] et al. conducted a meta-analysis of a large number of Finnish adults and found no genetic relationship between 5-HTTLPR and anxiety disorders.

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The hypothalamic pituitary adrenal (HPA) axis has a significant role in the genesis of anxiety. The activity of the HPA axis is modulated by negative feedback from its hormones and neurotransmitters such as 5-HT and oxytocin. Serotonin is released by 5-HT neurons and travels up through the Raphe nucleus in the midbrain to the Paraventricular nucleus in the hypothalamus to stimulate HPA axis activity. HPA axis activity and 5-HTTLPR expression were related. Fogelman [19] et al., observed that carriers of the S allele in older adults showed higher baseline cortisol levels and scored higher on potential assessments of anxiety disorders. In the study of maltreated infants in rhesus monkeys [20], it was found that the HPA axis of maltreated infants with SL genotype was more sensitive to early life stress, and the S allele is believed to be involved in regulating neuroendocrine mechanisms under anxiety and stress. In conclusion, the genetic contribution of 5-HTTLPR to anxiety disorders remains controversial. The effect of 5-HTTLPR on anxiety may be just one factor. Environmental factors, including as childhood trauma, social stress, and familial circumstances, as well as genetic factors, have a significant impact in the development of anxiety disorders. Although the causes of anxiety disorders are not clear at present, these research results have important reference significance for further research of anxiety disorders in the future.

3.2. The relationship between 5-HTTLPR heterogeneity and drug efficacy

In the investigation of the effectiveness of 5-HTTLPR in anxiety, SSRI medications are crucial. SSRI drugs can inhibit 5-HTT function and thus exert therapeutic effects. SSRI drugs are anti-anxiety and antidepressant drugs, which have good effects on patients with anxiety and depression. Numerous studies have shown that 5-HTTLPR is directly related to the effectiveness of SSRI medications. Studies in Caucasian populations have found that patients with LS and LL genotypes respond better to SSRI drugs than patients with SS genotypes [21]. However, when 115 depressed patients in South Korea were treated with Escitalopram [22], those with the S allele showed better results after eight weeks of treatment. In a Japanese study, patients with LL and LS genotypes responded better to paroxetine than patients with SS genotypes [23]. It is simple to observe variances between Asians and Caucasians in the association between 5-HTTLPR and SSRI medications. Heterogeneity between the S and L alleles may account for this difference, with studies showing that the S allele is present in 79% of Asians and 41% of Caucasians [24]. There is no conclusive evidence for this conjecture. However, there were no genotypic differences in 5-HTTLPR responses to escitalopram in the Korean and Indian studies [25].

4. Stin2 polymorphism in anxiety disorder and drug efficacy

The SLC6A4 gene contains the Stin2 polymorphism, a 17 bp variable tandem repeat. The two major alleles Stin2.10 and Stin2.12 have 10 and 12 repeat units. MacKenzie [26] et al. reported that Stin2.. 7 and STIN2.9 are two low-frequency alleles with seven and nine repeats. The Stin2.12 allele plays a role as a transcriptional enhancer [27], so it enhances SLC6A4 gene expression and has a certain effect on the amount of 5-HTT protein. However, Bah [27] et al. found reduced 5-HTT protein availability in Stin2.12/Stin2.12 homozygous carriers, which was inconsistent with the characteristics of Stin2.12 enhancer. In their genetic investigation of anxiety disorders and healthy individuals, Ohara [28] et al. discovered that the frequency of the Stin2.12 allele was substantially greater in patients with anxiety disorders than it was in controls. Anxiety disorders have certain similarities with depression, and SLC6A4 is also a potential pathogenic gene for depression. Therefore, the related research on SLC6A4 in depression has a certain reference significance for anxiety disorders. According to Sarosi [29] et al., in the Stin2 genotype analysis of patients with major depression disorders, patients with depression and those with anxiety both had greater rates of Stin2.12/Stin2.12 homozygotes.

Stin2 polymorphism has a certain influence on the therapeutic effect of SSRI drugs. Popp [30] et al. found that patients homozygous for Stin2.10/Stin2.10 had more significant side effects than patients heterozygous for Stin2.10/Stin2.12 and homozygous for Stin2.12. Ramesh [31] et al., found that patients homozygous for Stin2.12/Stin2.12 had a more significant decrease in depression scores after treatment than patients homozygous for Stin2.10/Stin2.10. In addition, the Stin2.12 allele was found to respond better to fluoxetine and paroxetine in a research of South Korean [32]. In white people, the response to

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paroxetine was worse [35]. These variations could result from racial disparities in allele frequencies.

5. The epigenetic effect of SLC6A4 gene on anxiety disorders

Environmental stresses, such as childhood trauma, social stress, and family stress, all contribute to the development of mental illness, including anxiety and depression. Environmental stress is closely related to anxiety and depression. Although the mechanism of environmental association with psychiatric disorders has not been determined, increasing evidence suggests that epigenetics is a key mechanism triggering the emergence of anxiety and depression. The methylation of SLC6A4 gene has made some progress. When DNA is methylated, methyltransferase primarily adds a methyl group to the cytosine at position 5 in the CpG molecule. In general, DNA methylation will lead to the reduction of gene expression levels or gene silencing. The majority of research has been on the DNA methylation of promoter CpG islands or polymorphism 5-HTTLPR upstream repeats.

Alaasari [34] et al. found that nurses working in high-pressure environments had reduced methylation of five sites in the SLC6A4 gene promoter. However, CpG hypermethylation has been found in patients with major depression in many studies. Maternal symptoms of anxiety and depression have an impact on DNA methylation in offspring. Mendonca [35] et al. found that SLC6A4 gene methylation was reduced in mothers and children with depression after a study on mothers who experienced depression during pregnancy. Of course, the study has major limitations when considering other environmental factors or medication use. Lam [36] et al. discovered that in people with the 5-HTTLPR and 5-HTTLPR/rs25531 genotypes SS and SS', depression was substantially linked with CpG 21 and CpG 25.26 hypomethylation. CpG 21 hypermethylation was linked to depression in people with the 5-HTTLPR and 5-HTTLPR/rs25531 genotypes LL and LL', respectively. The specific mechanism behind the relationship between DNA methylation and neurological diseases is yet unknown and needs further study.

6. Conclusion

At present, a variety of 5-HTTLPR genotypes have been found, and studies on the effect of different alleles of 5-HTTLPR on the transcriptional activity of SLC6A4 gene have been ongoing. Most studies believe that the increase of repetitive sequences is beneficial to the improvement of transcriptional activity. The L allele is more active during transcription than the S allele, which means that the S allele can reduce 5-HTT expression. Many studies of 5-HTTLPR in anxiety disorders have also confirmed that carriers of the S allele are more likely to develop anxiety disorders. Stin2.12 allele is associated with anxiety disorder. Stin2.12 can enhance SLC6A4 gene expression, and Stin2.12 was found to be more frequent in anxiety disorder patients. Currently, a large number of research have also shown a connection between SLC6A4 methylation and anxiety and depression.

However, there are still many research findings that raise doubts. For example, the XL28-A ultra-long repeats did not show enhanced transcriptional activity. In some studies, people with the L allele have been found to have more pronounced anxiety traits. The reason may be that the effect on SLC6A4 gene transcriptional activity may be influenced by other transcription factors or environmental factors. At present, the mechanism of 5-HTTLPR on anxiety disorders is not clear. Stin2.12 and anxiety disorders are rarely studied, and more studies are needed to prove their association with anxiety disorders. Although methylation is associated with anxiety disorders, the mechanisms underlying the relationship between methylation and neurological disorders are unclear. In conclusion, although numerous studies have demonstrated the tight connection between the SLC6A4 gene and anxiety in a variety of aspects, the specific mechanism of SLC6A4 gene causing anxiety disorders needs to be further studied.

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