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Review

Intersection of autism and mental health in SLC6A4: Genetic and neurobiological balances with SSRIs

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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are a class of effective antidepressant drugs that target the serotonin transporter protein and are encoded by the solute carrier family 6 member 4 *(SLC6A4)* gene. Genetic variations in the *SLC6A4* gene, particularly the 5-HTTLPR polymorphism, directly influence the synaptic reuptake of serotonin, thereby significantly shaping individuals' responses to SSRI treatment. Various studies have demonstrated that individuals carrying the long allele exhibit more favorable clinical outcomes compared to those carrying the short allele. Autism spectrum disorder (ASD) is a complex disorder where genetic predispositions play a strong role and affect neurodevelopmental processes. Mutations in the *SLC6A4* gene have been reported to be associated with anxiety, which is frequently observed in individuals with ASD. Anxiety accompanying ASD severely impairs individuals' daily living skills and functionality, making this condition a significant mental health problem that needs to be managed. Selective serotonin reuptake inhibitors are pharmacologic agents commonly used and scientifically proven to be effective in managing symptoms such as anxiety and depression in individuals with autism. This review comprehensively addresses the key role of the *SLC6A4* gene in serotonin regulation, the effects of genetic variations associated with this gene, and the potential benefits of SSRIs in treating anxiety in individuals with ASD. The findings further highlight the necessity of personalized medicine approaches based on individual genetic profiles in the treatment of comorbid psychiatric conditions in autism.

Keywords: Anxiety, autism, genetic variations, neuroplasticity, SSRIs, 5-HTTLPR polymorphism.

Autism spectrum disorder (ASD) is a neurodevelopmental condition that arises from the interaction of both genetic and environmental factors. Autism is characterized by difficulties in social interaction, communication problems, and repetitive, restrictive behaviors.[1] Numerous studies have reported a significant increase in autism prevalence, leading to claims of an autism epidemic.[2,3] Adult individuals with ASD, particularly those without intellectual disability, experience a higher prevalence of mental health problems compared to the general population.[4,5] Furthermore, suicide rates are significantly elevated in these individuals.[6] However, there is a deficiency in interventions and sufficient studies on this subject.[7] Anxiety is prevalent in autistic adults, and anxiety-related stress and avoidance behaviors can severely impede daily functioning. The prevalence of anxiety disorders and related conditions in adults diagnosed with autism typically ranges from 28 to 77%. This wide range arises due to varying study populations. A recent meta-analysis reported this rate as 42%.[4] Social phobia, generalized anxiety disorder, and obsessive-compulsive disorder are common diagnoses, but anxiety in autistic individuals often does not fully align with the strict diagnostic criteria of these disorders.[8] It is believed that the increased prevalence of anxiety in individuals with ASD is due to a combination of biological, psychosocial, and environmental factors.[9] Anxiety in autistic individuals can be managed by ensuring consistency in the environment, avoiding sensory overload, and

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minimizing sudden changes. Additionally, there is some evidence that cognitive behavioral therapies may be effective in this regard.[10] However, it is also quite common for individuals with ASD to seek medication options for anxiety management.

Studies indicate a strong link between autism and genetic factors. In approximately 20% of individuals with ASD, genetic causes can be clearly identified. Animal studies have investigated how alterations in autism-related genes affect brain function. Neurexin genes play a crucial role in the synapses (connection points) of nerve cells, and certain mutations in these genes can lead to autism. Specifically, mutations in the NRXN1 gene can disrupt synapses between nerve cells. Additionally, the CNTNAP2 gene ensures the proper movement and placement of nerve cells; disruption of this gene can result in nerve cells being misplaced in the brain, potentially leading to autism.[11] Neuroligin genes play a role in strengthening connections between nerve cells. Alterations in these genes can affect information flow between nerve cells. For example, mice carrying mutations in the NLGN3 gene have been observed to have reduced brain volume and disruptions in connections between nerve cells.[12]

ANXIETY

Although a large majority of people experience some temporary distress, some individuals experience these distresses as persistent and debilitating anxieties. Illness anxiety disorder, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), has replaced the diagnosis of hypochondriasis from DSM-IV.[1] Anxiety is characterized by the fear of having or contracting a serious illness, such as cancer or heart disease. Individuals with this disorder experience obsessive thoughts or images related to the illness and engage in excessive seeking of medical reassurance, as well as constantly checking their bodies for signs of illness.[13] The prevalence of anxiety in the adult population varies widely in the literature, ranging from 2.1 to 13.1%.[14,15]

Basic neuroscience provides guidance in the treatment of individuals with anxiety disorders and the accurate analysis of their responses to treatment. In comparison to other mental illnesses, neuroscience research on anxiety is considered more clinically significant. This is due to the fact that the responses of mammals to threats and the brain circuits that govern these responses show considerable similarity across different species. Studies suggest that the impaired responses to threat perception in anxiety disorders arise from dysfunctions in brain circuits that manage psychological processes such as attention, emotion regulation, learning, and memory. These findings offer valuable insights into understanding how anxiety disorders are related to core brain circuits.[16] The effectiveness of current anxiety treatments varies depending on the severity of the disorder, and appropriately sequencing and combining treatments presents a significant challenge. While further research is needed for treatment-resistant anxiety, the lack of new compounds in the drug development process is notable. However, new target molecules beyond serotonin (5-hydroxytryptamine; 5-HT; C10H12N2O) and gamma-aminobutyric acid have emerged. Small-scale studies, particularly those involving glutamatergic compounds and ketamine, have shown promising results. In the future, the development of new treatments targeting pathological defense mechanisms is expected.[17-19]

SELECTIVE SEROTONIN REUPTAKE INHIBITOR

Selective serotonin reuptake inhibitors (SSRIs) work by inhibiting the reuptake of the serotonin neurotransmitter, as the name suggests, thereby showing therapeutic effects on mood. Today, SSRIs are one of the most commonly used drug classes in the treatment of depression and are typically preferred as first-line treatment. Patients who cannot tolerate the side effects of an SSRI may achieve positive results by switching to a different SSRI. Selective serotonin reuptake inhibitors are considered safer compared to monoamine oxidase inhibitors and tricyclic antidepressants, and they are thought to carry a lower risk of death in cases of overdose. Additionally, they are commonly used in the management of post-traumatic stress disorder, anxiety disorders,

and obsessive-compulsive disorder. Medications in this class selectively target neurotransmitters associated with depression, such as serotonin, norepinephrine, and dopamine. Examples of SSRIs include citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac, Sarafem), fluvoxamine (Luvox), paroxetine (Paxil and others), and sertraline (Zoloft). Common side effects of SSRIs include irritability, agitation, drowsiness, fatigue, headaches, insomnia, gastrointestinal disturbances (nausea and diarrhea), weight changes, and, rarely, serotonin syndrome. Key considerations in the use of these medications include ensuring they are not confused with other antidepressants, not abruptly discontinuing treatment, and gradually reducing the dose. Additionally, if antibiotics, lithium, or other medications are being used, patients should be carefully evaluated for potential drug interactions.[20]

Serotonin is a monoamine and neurotransmitter that plays a role in conditions such as depression and anxiety. It is crucial for regulating sleep, consciousness, aggression, and mood.[21] Serotonin is a highly conserved molecule throughout the evolution of life and is synthesized from an amino acid called L-tryptophan by the enzyme tryptophan hydroxylase (TPH). Serotonin plays an important role in this process and is present in almost all living organisms. In serotonin synthesis, L-tryptophan is processed by the enzyme TPH. This molecule can be converted into a hormone called melatonin by the enzyme serotonin N-acetyltransferase in the pineal gland. Melatonin is associated with the regulation of sleep. There are two main tryptophan hydroxylase enzymes involved in serotonin synthesis: TPH1 and TPH2. While TPH2 is found exclusively in the brain, TPH1 is primarily located in peripheral tissues. The TPH1 enables the synthesis of serotonin in peripheral organs, in contrast to the brain. Serotonin functions as a neurotransmitter in the brain and as a neurohormone in other tissues. Pharmacologically, there are seven main families of serotonin receptors, classified from 5-HT1 to 5-HT7. Within these families, there are more than 15 receptor subgroups. These G protein-coupled receptors activate adenylate cyclase, increasing cyclic adenosine monophosphate production, which in turn activates several important intracellular signaling molecules, such as Rap-1, CREB, and Src.[22]

Selective serotonin reuptake inhibitors, commonly used as antidepressants, are also preferred as first-line medications in the treatment of all anxiety disorders.[23] The antidepressant effect of SSRIs typically begins within one week, with a difference from placebo becoming apparent within 2-4 weeks; however, the effects on anxiety may take longer to manifest.[24] A recent randomized controlled trial conducted in the United Kingdom observed a significant reduction in anxiety symptoms after six weeks of using the SSRI sertraline.[25] However, it has been noted that individuals with anxiety may be more susceptible to side effects, particularly increased restlessness and worsening of initial symptoms.[24] Therefore, prescribing guidelines typically recommend starting at half of the normal initial dose and gradually increasing to the maximum dose as tolerance develops. The response is usually observed within six weeks and continues to improve over time.[26] The optimal duration of SSRI treatment has not been definitively established, but it is recommended that treatment continue for at least six to 12 months after a successful therapeutic response.[27] Patients using SSRIs should be closely monitored, particularly for increased restlessness, anxiety, and suicidal thoughts.[28]

SLC6A4 GENE ACTIVITY

The solute carrier family 6 member 4 *(SLC6A4)* gene produces a protein responsible for the reuptake of serotonin, a neurotransmitter involved in crucial functions such as mood regulation and sleep. This gene is located on chromosome 17 and spans approximately 40,000 base pairs in length.[29] The structure of the gene contains 14 exons, each contributing to the formation of the protein. The serotonin transporter protein produced by the *SLC6A4* gene forms a structure that crosses the cell membrane 12 times, facilitating the reuptake of neurotransmitters like serotonin into the cell. This acts as a "gate" in the cell membrane, playing a critical role in regulating serotonin

levels.[30,31] Additionally, the use of different parts of the gene can lead to the production of various alternative gene products. This process allows the gene to function differently in various tissues or at different times, enabling a single gene to perform multiple functions. These variations have been observed not only in humans but also in other animal species, and they can alter how the gene operates and its effects on the body. Some rare coding single nucleotide polymorphism (SNP) variants of the *SLC6A4* gene have been associated with behavioral disorders, such as obsessive-compulsive disorder and autism. These variants may cause changes in the functioning of the gene and increase the risk of developing related behavioral phenotypes in individuals. Various studies have explored the effects of these genetic alterations, particularly on neuropsychiatric conditions.[32]

Pharmacogenomic studies of *SLC6A4* variants examine the effects of antidepressants and anti-anxiety medications (SSRIs, such as fluoxetine and citalopram) on the serotonin transporter (SERT) protein. These medications bind to SERT, inhibiting serotonin reuptake, thereby regulating serotonin levels in nerve cells. The efficacy of SSRIs is related to how effectively they bind to SERT.[33]

If variants in the *SLC6A4* gene lead to increased production of the SERT protein in an individual, that person is expected to respond better to SSRIs. This means that when administered at an adequate dose, genetic variants that enhance SERT production may increase the effectiveness of SSRIs. This hypothesis has been tested in numerous large studies examining the efficacy of SSRIs in the treatment of depression.[34] Additionally, meta-analyses and systematic reviews have been conducted on this topic. Studies conducted on smaller patient groups, particularly in the context of obsessive-compulsive disorder and other anxiety disorders, have assessed the efficacy of SSRIs. As a result, *SLC6A4* gene variants can influence how an individual responds to antidepressants or anti-anxiety medications.[35]

The 5-HTTLPR is a polymorphism in the *SLC6A4* gene, and this change affects the gene's serotonin transport capacity. In humans, there are two main allele types: long (L) and short (S). Individuals with the L allele typically produce more serotonin transporters, which may help them respond better to antidepressant treatment and experience fewer side effects. Specifically, SSRIs may show more effective results in individuals carrying the L allele. On the other hand, individuals with the S allele may benefit less from these medications and may be more sensitive to side effects. Individuals with the L allele tend to achieve better results when using SSRIs such as citalopram, escitalopram, and sertraline, or tricyclic antidepressants like fluoxetine and clomipramine. On the other hand, individuals with the S allele may respond less to these medications and may experience more side effects. The 5-HTTLPR polymorphism in the *SLC6A4* gene plays a significant role in antidepressant treatments and can influence treatment outcomes based on an individual's genetic makeup.[36]

In contrast to other studies, one article collected blood samples from a large group of 352 families, and deoxyribonucleic acid (DNA) was isolated. The isolated DNA was subjected to detailed genetic analyses to investigate the potential relationship between *SLC6A4* and autism.[37] In the study, the genetic polymorphism 5-HTTLPR and nine other SNPs of the *SLC6A4* gene were examined. Genotyping procedures were carried out using the Illumina BeadArray technology, which offers high accuracy. Additionally, replication tests were conducted in some samples to ensure the reliability of the results, and Mendelian inconsistencies were corrected to minimize errors in genetic analyses.[38]

The genetic data used in the study were analyzed with software such as TRANSMIT, PDTPhase, and TDTPhase. During the analyses, both parametric and non-parametric methods were applied to test the association of genetic variations with ASD. Specifically, for the 5-HTTLPR polymorphism, no evidence was found indicating that the S and L alleles were transmitted at different rates in individuals with ASD. Additionally, when evaluating the association of the nine SNPs with autism, no significant connection was observed. Analyses focusing on subgroups of autism, such as obsessive-compulsive behaviors or

rigid-compulsive traits, also yielded negative results. The findings of this extensive and methodologically rigorous study do not support the conflicting results of previous studies regarding the effect of the serotonin transporter gene on autism. The researchers suggested that genetic heterogeneity and the limited sample sizes of previous studies may have led to misleading results.[39] The findings of the study emphasize the need for larger-scale research that focuses on subgroups in order to better understand the genetic structure of autism. However, it also reminds us that in complex disorders like ASD, environmental factors should be considered alongside genetic influences.[40]

The *SLC6A4* gene plays a critical role in brain development, influencing essential processes. By coding for the serotonin transporter, it regulates serotonin levels in the synaptic cleft, thus affecting processes such as synaptogenesis, neuron migration, and synaptic plasticity. During synaptogenesis, connections form between neurons, and serotonin acts as a key neuromodulator in regulating this process. Genetic alterations in *SLC6A4* are thought to disrupt serotonin balance, potentially leading to improper formation or weakening of synaptic connections.[41]

Neuron migration is also a critical step in development, ensuring that neurons reach their proper locations. Serotonin plays a crucial role in regulating this process, and it is modulated through the *SLC6A4* gene. Disruptions in the gene's function can lead to improper neuronal migration, which has been associated with certain neurodevelopmental features of autism. Additionally, during synaptic plasticity, serotonin levels influence the strengthening or weakening of synapses, laying the foundation for cognitive functions such as learning and memory.[42]

In autism research, the role of the *SLC6A4* gene is complex. While it has been suggested that this gene is associated with ASD, its effects vary from individual to individual. It has been found that polymorphisms in the *SLC6A4* gene have a significant effect on some individuals with ASD, while they remain ineffective in others. Additionally, the high serotonin levels frequently observed in individuals with ASD provide clues suggesting that *SLC6A4* may contribute to this disorder. However, the underlying mechanisms of this phenomenon are not yet fully understood. In this context, further genetic and neurobiological studies are needed to clarify the precise role of *SLC6A4* in ASD. Pharmacological approaches or genetic interventions targeting the serotonin transporter may have the potential to alleviate autism symptoms. A better understanding of the effects of *SLC6A4* on brain development will contribute to the development of new strategies for treating neurodevelopmental disorders such as autism.[40]

The *SLC6A4* gene plays a critical role in serotonin transport. However, it has been noted that there is no direct association between the 5-HTTLPR polymorphism and autism. Nevertheless, analyses conducted on specific subgroups have shown that this relationship may be statistically significant.[43]

A study conducted in 2024 highlighted that the *SLC6A4* gene plays a critical role in regulating mood-related behaviors, such as anxiety and depression. The study suggests that an individual's genetic makeup may increase their susceptibility to mood disorders. These findings emphasize the importance of considering genetic factors in treatment approaches.[44]

Neuroplasticity, defined as the brain's ability to reorganize and adapt, relies on processes such as synaptic plasticity and neurogenesis as fundamental mechanisms of adaptation. Studies have shown that antidepressant treatments affect neuroplasticity through the mammalian target of rapamycin and Wnt signaling pathways. These pathways play a critical role in the formation and strengthening of synaptic connections. Additionally, genetic variations in the *SLC6A4* have been noted to influence neuroplasticity indirectly. This could contribute to understanding the underlying biological mechanisms behind the varying antidepressant responses in individuals.[45]

Bipolar disorder, as a neuropsychiatric condition, is associated with several biological processes, including mitochondrial dysfunction. It is believed that mitochondrial dysfunction contributes to the progression of the disease

by damaging neuronal functions through oxidative phosphorylation and inflammation. These processes are thought to negatively impact synaptic plasticity and lead to limitations in neuroplasticity. Targeting such biological mechanisms in bipolar disorder could pave the way for the development of new treatment strategies in disease management in the future.[46]

Today, the effects of genetic variations on individual treatment responses are increasingly understood. In particular, variations in the *SLC6A4* gene can influence the function of the serotonin transporter, shaping individuals' responses to treatment. Pharmacogenomic studies show that, in addition to these genetic variations, pharmacokinetic (e.g., CYP2D6 metabolism) and pharmacodynamic (e.g., serotonin and norepinephrine transporters) factors also play a critical role in treatment outcomes. In light of this information, the development of personalized treatment approaches based on individuals' genetic profiles is considered an important step in the management of psychiatric disorders.[47]

Neuroplasticity, mitochondrial dysfunction, and genetic factors clearly play a significant role in the pathophysiology of neuropsychiatric disorders. A better understanding of these processes may enable the development of personalized treatment approaches in the future. Given that genetic variations, such as those in the *SLC6A4* gene, influence individual treatment responses, the increasing integration of pharmacogenomic models into clinical practice has the potential to improve patient outcomes. Therefore, next-generation modeling approaches that combine genetic and biological risk factors offer a great opportunity to support individualized treatment decisions and identify new therapeutic targets.[45]

In conclusion, the management of complex neuropsychiatric disorders such as ASD and anxiety requires the consideration of genetic, neurobiological, and environmental factors together. The role of the *SLC6A4* gene in neuroplasticity and serotonin regulation is critical in shaping treatment strategies for individuals with both ASD and other psychiatric disorders. Future large-scale studies will contribute to a better understanding of these genetic variations and the development of more effective personalized treatment methods based on individual genetic profiles. These approaches hold great potential for improving individuals' quality of life and optimizing mental health management.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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