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**Review**

# Gene-environment Interactions in Psychiatric Disorders: Focus on DNA Methylation of the Serotonin Transporter Gene as an Epigenetic Factor

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Epigenetic regulation by DNA methylation might be a mechanism of gene-environment (G x E) interactions in the pathophysiology of psychiatric disorders. *SLC6A4* (solute carrier family 6, member 4) gene, which encodes a serotonin transporter (5-hydroxytryptamine transporter; 5-HTT), has a functional polymorphism in the promoter region, known as the 5-HTT-linked polymorphic region (5-HTTLPR). Both the 5-HTTLPR genotype and the *SLC6A4* methylation level may control its mRNA expression by interacting with each other, and environmental factors may also affect the methylation status of *SLC6A4*. DNA methylation of *SLC6A4* could be an important clue to the mechanism underlying G x E interactions in psychiatric disorders. Further studies are warranted to elucidate G x E interactions at the molecular level and to develop biologic markers for psychiatric disorders.

**Key Words**: gene-environmental interaction, epigenetics, serotonin transporter gene (*SLC6A4*), DNA methylation

## Introduction

Psychiatric disorders, such as schizophrenia and bipolar disorder, are a severe social burden and thus elucidation of the pathophysiology of these disorders is urgently needed. Epidemiologic studies indicate high heritability of schizophrenia and bipolar disorder, but the results of a large number of genetic studies are inconsistent and no candidate gene with a large genetic effect (odds ratio $>$ 2) has been identified in recent genome-wide association studies. Gene-environmental (G x E) interactions might explain the inconsistent results of genetic studies, and epigenetic mechanisms might be involved in the development of psychiatric disorders.

DNA methylation, a molecular basis of epigenetics, commonly occurs at the fifth position of the cytosine residue in dinucleotide CpG sequences in mammals. While the cytosine residues in dinucleotides are generally methylated, CpG-rich regions, called "CpG islands", that are located within and around the regulatory promoter regions are less methylated. The extent of methylation at the promoter CpG islands usually inversely correlates with the extent of gene expression. DNA methylation is altered by environmental factors[1)2)], and contributes to the long-term regulation of gene expression[3)]. Epigenetic regulation by DNA methylation might underlie G x E interactions in the pathophysiology of psychiatric disorders.

A serotonin transporter (5-hydroxytryptamine transporter; 5-HTT) encoded by *SLC6A4* (solute carrier family 6, member 4) gene transports synaptic serotonin into the presynaptic terminals. 5-HTT is the target molecule of antidepressants, and inhibition of 5-HTT increases the synaptic serotonin concentration, which has antidepressant efficacy. One of the most studied genetic variations in psychiatric disorders is the 5-HTT-linked polymorphic region (5-HTTLPR), which is located at the promoter region of *SLC6A4* and includes a functional polymor-

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phism in which the short (S) allele has lower promoter activity than the long (L) allele[4)~6)]. 5-HTTLPR moderates the influence of stressful life events on depression[7)8)], suggesting the contribution of G x E interactions involving *SLC6A4* to psychiatric disorders.

In this review, we discuss G x E interactions in psychiatric disorders based on recent articles, focusing on DNA methylation of *SLC6A4* as an epigenetic factor (Table 1).

**1. Interaction of genotype and DNA methylation on *SLC6A4* gene expression**

5-HTTLPR is a functional polymorphism of *SLC6A4*, and the S allele, which has lower promoter activity compared with the L allele, is associated with decreased mRNA expression[4)~6)]. In 2007, Philbert et al examined the relationship between DNA methylation at the promoter CpG islands and the *SLC6A4* gene expression level in lymphoblast cell lines (LCLs). Although total DNA methylation was not significantly associated with the mRNA levels, DNA methylation was associated with decreased mRNA levels under control of the 5-HTTLPR genotype[9)]. These findings were not confirmed in a subsequent study[10)], and another group also reported that the changes in the *SLC6A4* mRNA expression associated with the 5-HTTLPR genotype are unlikely to be mediated by DNA methylation within CpG islands, based on studies of the peripheral blood of healthy subjects[11)]. Based on studies of the peripheral blood of infant rhesus macaques, however, carriers of the S allele, which exhibit higher methylation of the CpG islands, have lower *SLC6A4* gene expression[12)]. Moreover, DNA methylation of the CpG island shore region of *SLC6A4* is significantly inversely correlated with mRNA level in individuals with the S/S genotype, based on studies in LCLs[13)]. Methylation within the CpG island shore region of *SLC6A4* influenced by the 5-HTTLPR genotype predicts mRNA expression[14)], and the S allele is associated with both reduced *SLC6A4* mRNA expression and increased DNA methylation of CpG islands in the peripheral blood of healthy subjects[15)]. These findings suggest that both the 5-HTTLPR genotype and the methylation level of CpG islands and/or CpG island shore regions of *SLC6A4* control its mRNA expression by interacting with each other. The interaction of 5-HTTLPR genotype and DNA methylation of *SLC6A4* on cortisol response to stress[15)16)], threat-related amygdala reactivity[17)] and gray matter volume[18)] were also reported, and further studies are needed to elucidate the molecular mechanism underlying this interaction.

**2. Effects of environmental factors on DNA methylation of *SLC6A4***

In 2004, Weaver et al reported that hippocampal hypermethylation of the glucocorticoid receptor induced by poor maternal care may cause stress vulnerability in rats, suggesting that DNA methylation plays a role as an epigenetic mark of G x E interactions[19)]. In the case of *SLC6A4*, a high DNA methylation level is associated with high stress reactivity in adult rhesus macaques that experienced early life stress[12)20)]. In humans, maternal depressed mood alters the promoter methylation level in both the maternal peripheral blood and neonatal cord blood[21)]. Beach et al[22)] reported that sex abuse was associated with overall hypermethylation of the *SLC6A4* promoter region, and this result has been replicated in women[23)]. Furthermore, DNA methylation within both the CpG islands and CpG island shore region of *SLC6A4* is influenced by sex abuse history[14)], and the cumulative socio-economic status in childhood significantly affects DNA methylation within the CpG islands of *SLC6A4*[24)]. Other groups have also reported an association between hypermethylation of *SLC6A4* and stressful life events[25)] and childhood adversities[26)], and increased *SLC6A4* methylation was associated with bullying victimization in a longitudinal study of discordant monozygotic twins[27)]. On the other hand, two groups reported no significant main effect of early life stress on *SLC6A4* methylation[11)15)], although there is a significant interaction between 5-HTTLPR and early life stress on *SLC6A4* methylation when the 5-HTTLPR genotype is taken into account[15)].

Therefore, environmental factors may affect the methylation status of *SLC6A4*, and thus it is important to consider the genetic effects.

**Table 1** Articles relevant to *SLC6A4* methylation

| Article | Subjects | N | Source | Examination | | |
|---|---|---|---|---|---|---|
| | | | | Environmental factors | Biologic factors | Methods |
| Duman, 2015[15] | males | 105 (75: blood and saliva) | blood | early life stress, chronic stress | methylation | mass spectroscopy |
| | | | | | 5-HTTLPR/rs25531 | PCR |
| | | | | | expression | RT-PCR |
| | | | saliva | | cortisol response to stress | immunoassay |
| van der Knaap, 2015[25] | adolescence | 939 | blood | perinatal adversity, stressful life events | methylation | mass spectroscopy |
| | | | | | 5-HTTLPR/rs25531 | PCR |
| Alexander, 2014[16] | healthy subjects | 200 | blood | – | methylation | bisulfite sequencing |
| | | | | | 5-HTTLPR/rs25531 | PCR |
| | | | saliva | | cortisol response to stress | Immunoassay |
| Wankerl, 2014[11] | young adults | 133 | blood | prenatal, early and recent life stress/ trauma | methylation | bisulfite sequencing |
| | | | | | 5-HTTLPR/rs25531 | PCR |
| | | | | | expression | RT-PCR |
| Nikolva, 2014[17] | Discovery cohort: young adults | 80 | saliva | – | methylation | bisulfite sequencing |
| | | | | | 5-HTTLPR/rs25531 | PCR |
| | | | | | threat-related amygdala reactivity | fMRI |
| | Replication cohort: adolescents | 96 | blood | – | methylation | bisulfite sequencing |
| | | | | | 5-HTTLPR/rs25531 | PCR |
| | | | | | threat-related amygdala reactivity | fMRI |
| | third cohort: postmortem brains | 34 | brain | – | methylation | bisulfite sequencing |
| | | | | | expression | RT-PCR |
| Dannlowaki, 2014[18] | healthy subjects | 194 | blood | – | methylation | bisulfite sequencing |
| | | | | | 5-HTTLPR/rs25531 | PCR |
| | | | | | gray matter volume | MRI |
| Domschke, 2014[33] | MD | 94 | blood | – | methylation | bisulfite sequencing |
| | | | | | 5-HTTLPR/rs25531 | PCR |
| | | | | | antidepressant treatment response | HAMD |
| Okada, 2014[34] | MD and CT | MD = 50, CT = 50 | blood | – | methylation | mass spectroscopy |
| | | | | | 5-HTTLPR | PCR |
| | | | | | antidepressant treatment response | HAMD |
| Beach, 2014[24] | young adults | 388 | blood | socio-economic status | methylation | beadchip |
| | | | | | 5-HTTLPR | PCR |
| Kim, 2013[35] | poststroke patients | 286 | blood | – | methylation | bisulfite sequencing |
| | | | | | 5-HTTLPR | PCR |
| | | | | | depression | HAMD |
| Kang, 2013[26] | MD | 108 | blood | childhood adversity | methylation | bisulfite sequencing |
| | | | | | antidepressant treatment response | HAMD |

(Continued)

**Table 1** Articles relevant to *SLC6A4* methylation (Continued)

| Article | Subjects | N | Source | Examination | | |
|---|---|---|---|---|---|---|
| | | | | Environmental factors | Biologic factors | Methods |
| Ouellet-Morin, 2013[27] | MZ twin discordant for bullying victimization | 28 pairs | buccal cells | bullying | methylation | mass spectroscopy |
| | | | saliva | | cortisol response to stress | immunoassay |
| Vijayendran, 2012[14] | females | 158 | LCLs | child abuse | methylation | bisulfite sequencing |
| | | | | | 5-HTTLPR | PCR |
| | | | | | expression | RT-PCR |
| Sugawara, 2011[36] | MZ twins discordant for BD | 2 pairs | LCLs | – | methylation | tiling array, bisulfite sequencing, pyrosequencing |
| | BD and CT | BD = 20, CT = 20 | LCLs | – | methylation | pyrosequencing |
| | | | | | 5-HTTLPR | PCR |
| | | | | | expression | RT-PCR |
| | BD and CT | BD = 35, CT = 35 | brain | – | methylation | pyrosequencing |
| Park BY, 2011[29] | AD and CT | AD = 27, CT = 15 | blood | – | methylation | pyrosequencing |
| Koenen, 2011[31] | PTSD | 100 | blood | traumatic events | methylation | beadchip, pyrosequencing |
| | | | | | 5-HTTLPR | PCR |
| Kinnally, 2011[20] | female bonnet macaques | 20 | blood | early life stress | methylation | pyrosequencing |
| Beach, 2011[23] | adoptee | 192 | LCLs | child abuse | methylation | mass spectroscopy |
| Devlin, 2010[21] | pregnant woman and infant | 82 | maternal blood, umbilical cord blood | – | methylation | pyrosequencing |
| van Ijzendoorn, 2010[30] | adoptee | 143 | LCLs | unresolved loss or trauma | methylation | mass spectroscopy |
| | | | | | 5-HTTLPR | PCR |
| Wong, 2010[38] | MZ and DZ twins | MZ twin-pairs = 46, DZ twin pairs = 45 | buccal cells | – | methylation | mass spectroscopy |
| Kinnally, 2010[12] | infant rhesus macaques | 87 | blood | early life stress | methylation | pyrosequencing |
| | | | | | 5-HTTLPR | PCR |
| | | | | | expression | RT-PCR |
| Olsson, 2010[32] | MD and CT | MD = 25, CT = 125 | buccal cells | – | methylation | mass spectroscopy |
| | | | | | 5-HTTLPR | PCR |
| Beach, 2010[22] | adoptee | 155 | LCLs | child abuse | methylation | mass spectroscopy |
| | | | | | 5-HTTLPR | PCR |
| Philibert, 2008[10] | adoptee | 192 | LCLs | – | methylation | mass spectroscopy |
| | | | | | 5-HTTLPR | PCR |
| | | | | | expression | RT-PCR |
| Philibert, 2007[9] | human | 49 | LCLs | – | methylation | mass spectroscopy |
| | | | | | 5-HTTLPR | PCR |
| | | | | | expression | RT-PCR |

MD: major depression, CT: control, MZ: monozygotic, BD: bipolar disorder, AD: alcohol dependence, PTSD: posttraumatic stress disorder, DZ: dizygotic, LCLs: lymphoblastoid cell lines, HTTLPR: serotonin transporter-linked promoter region, PCR: polymerase chain reaction, RT-PCR: reverse transcription-PCR, HAMD: Hamiliton Depression Rating Scale.

### 3. DNA methylation of *SLC6A4* in psychiatric disorders

A large number of genetic studies of *SLC6A4* have been conducted in patients with various psychiatric disorders. A meta-analysis revealed a significant association between the 5-HTTLPR genotype in patients with alcohol dependence[28], however, no difference in the methylation status of the *SLC6A4* promoter region was found in the peripheral blood between patients with alcohol dependence and control subjects[29]. Furthermore, Philbert et al reported a higher methylation level of the *SLC6A4* promoter region in LCLs in patients with a life history of major depression, but not in those with alcohol dependence[10].

A number of traumatic events are associated with a diagnosis of posttraumatic stress disorder (PTSD), and the association might be modified by the *SLC6A4* methylation level. van Ijzendoorn et al reported that higher *SLC6A4* methylation levels predict more unresolved loss or trauma in subjects with the L/L allele, but a higher level of methylation is associated with less traumatic experience in subjects with the S/S allele, suggesting that the different effects of *SLC6A4* methylation on PTSD depend on the 5-HTTLPR genotype[30]. Another group reported that subjects with a lower *SLC6A4* methylation level and more traumatic events are at increased risk for PTSD, while those with higher methylation levels are considered to be protected from PTSD[31]. Therefore, complex interactions between the *SLC6A4* methylation status and both genetic and environmental factors may in part cause psychiatric disorders.

In depression, G x E interactions may occur at *SLC6A4*[7,8]. Olsson et al examined the methylation status of the *SLC6A4* promoter region in major depressive patients using buccal cells, and found no association between depressive symptoms and the methylation level or 5-HTTLPR genotype, but depressive symptoms were more common among those with elevated methylation levels who carried the S allele[32]. Kang et al, in studies of the peripheral blood, investigated the association between the methylation status of the *SLC6A4* promoter region, childhood adversity, and treatment outcomes in major depressive patients. They found that the *SLC6A4* promoter methylation status is significantly associated with childhood adversity, but not treatment outcomes[26]. On the other hand, Domschke et al, reported that hypomethylation of *SLC6A4* was associated with impaired antidepressant treatment response[33]. Okada et al examined the utility of *SLC6A4* methylation as a diagnostic biomarker for major depression using peripheral blood. They could not distinguish between healthy control and major depressive patients, but the methylation rates for several CpGs differed significantly after treatment[34]. Kim et al, also using peripheral blood, investigated the association between the *SLC6A4* promoter methylation status and poststroke depression, and found that higher *SLC6A4* promoter methylation status was significantly associated with poststroke depression only in subjects with the 5-HTTLPR S/S genotype[35]. These findings suggest that both epigenetic and genetic factors of *SLC6A4* might be related to depressive symptoms, and further studies are needed to evaluate the utility of *SLC6A4* methylation as a diagnostic or treatment response biomarker.

To investigate the possibility that epigenetic changes in the specific genes are associated with bipolar disorder, we performed an unbiased screen of promoter methylation patterns from LCLs of monozygotic twins discordant for bipolar disorder and detected *SLC6A4* hypermethylation in the bipolar twin[36]. Differences in the methylation patterns between monozygotic twins may depend on age and differences in the nurturing environment[37]. In another monozygotic twin study, the variation of DNA methylation in *SLC6A4* was attributable to unique environmental factors rather than heritable factors[38]. We confirmed the hypermethylation of *SLC6A4* in bipolar disorder using an independent cohort. The *SLC6A4* methylation level is inversely correlated with gene expression in a genotype-specific manner. Importantly, hypermethylation of *SLC6A4* is also detected in the postmortem prefrontal cortices of patients with bipolar disorder[36]. Moreover, we examined the effect of mood stabiliz-

ers and quetiapine, which is used for treatment of bipolar depression, on *SLC6A4* methylation using human neuroblastoid cells, and found that both mood stabilizers and quetiapine decreased the *SLC6A4* methylation level[39)40)]. Taken together, these findings suggest that G x E interactions increase the risk of bipolar disorder via an epigenetic modification of *SLC6A4*.

## Perspectives

Some studies report that *SLC6A4* methylation levels are higher in females than in males[10)22)31)]. The molecular basis of the sex difference is unclear, and further studies are needed to elucidate the sex differences of *SLC6A4* methylation. Careful attention should be paid to the sex effect on *SLC6A4* methylation when designing case-control association studies.

Many of the studies presented here focused on methylation of the CpG islands in the *SLC6A4* promoter region. In contrast, the region identified in several studies, including ours, was located ~300 basepairs downstream of the CpG islands. Such a region, known as the CpG island shore, is reported to have an important role in mRNA regulation[41)]. Further studies are needed to elucidate whether alterations in DNA methylation at a few CpG sites within the CpG island/shore of *SLC6A4* functionally affect its mRNA expression.

Most of the previous studies examined *SLC6A4* methylation using peripheral tissues, and, among them, LCLs are often used for epigenetic studies. Most patients with psychiatric disorders take medication, which may significantly affect the methylation status. Culturing the LCLs in drug-free medium may eliminate the effect of medication. The LCLs were established by transformation of B lymphocytes by Epstein-Barr virus, and this process can also alter the epigenetic status of B lymphocytes[42)]. To exclude the effect of transformation, in our case, we pre-determined and filtered the genomic regions whose methylation statuses were affected by the transformation[13)], and finally detected *SLC6A4* hypermethylation in bipolar disorder[36)]. Moreover, we found that both mood stabilizers and quetiapine decreased the *SLC6A4* methylation level in cultured human neuroblastoid cells, suggesting that *SLC6A4* methylation is associated with the pathophysiology of bipolar disorder and the therapeutic effects of the drugs.

The mechanism of the effects of some environmental factors on DNA methylation of *SLC6A4* has been largely unclear. As an example of how environmental factors cause a locus specific DNA methylation, it has been reported that maternal care increases glucocorticoid receptor expression in the offspring via increased hippocampal serotonergic tone accompanied by increased not only DNA demethylation but also histone acetylation[43)]. Valproate, which is one of mood stabilizers, has been known as a histone deacetylase inhibitor, and chromatin-mediated neuroplasticity has been suggested as a target mechanism for novel treatments of psychiatric disorders[44)]. Further studies are needed to elucidate the epigenetic mechanisms including DNA methylation and histone modification of psychiatric disorders.

## Conclusion

In conclusion, DNA methylation of *SLC6A4* could be an important clue to elucidate the mechanism of G x E interactions in psychiatric disorders. Further studies are warranted to understand G x E interactions at the molecular level, and to develop biologic markers for psychiatric disorders.

The authors indicate no conflicts of interest.

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## 精神疾患における遺伝環境相互作用
## —エピジェネティック要因としてセロトニントランスポーターのDNAメチル化に注目して—

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エピジェネティクスの分子基盤の1つであるDNAメチル化は，精神疾患における遺伝環境相互作用との関与が示唆されている．セロトニントランスポーターをコードする*SLC6A4*遺伝子のプロモーター領域には，5-HTTLPRと呼ばれる機能的な多型が存在し，5-HTTLPR遺伝子多型と*SLC6A4*遺伝子のDNAメチル化の両者は相互作用をもち，mRNAの発現に関与しており，さらに環境要因によって*SLC6A4*遺伝子のDNAメチル化が変化しうる．*SLC6A4*遺伝子のDNAメチル化は，精神疾患における遺伝環境相互作用のメカニズム解明において重要な手がかりとなりうることから，遺伝環境相互作用の分子レベルでの解明ならびに，精神疾患における生物学的指標としての検討について，更なる研究が必要である．