博士論文（要約）

精神疾患患者におけるセロトニントランスポーター遺伝子のエピゲノム変化と低活性遺伝子型の関連解析

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論文の内容の要旨

論文題目

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Abstract

The pathophysiology of psychiatric disorders may involve emotional dysregulation associated with epigenetic changes in the serotonin transporter-encoding gene, *SLC6A4*. Although altered DNA methylation (DNAm) in bipolar disorder (BD) at the CpG island (CGI) shore of *SLC6A4* has been reported, *in vivo* and *in vitro* pathophysiological consequences remain unclear.

I examined the DNAm levels of two CpG sites in *SLC6A4* CGI shore and performed detailed genotyping of serotonin transporter-linked polymorphic region (5-HTTLPR) in patients with BD and schizophrenia (SZ) as well as age-matched controls (CTs). The possible effect of antipsychotic on DNAm was tested using the common marmosets treated with chronic risperidone. The functional and pathophysiological role of DNAm was assessed by a luciferase reporter assay with a site-specific methylated construct and *in vivo* brain imaging analysis on the selected subjects, respectively.

I found significant hypermethylation of single CpG site within the CGI shore of *SLC6A4* in patients with BD or SZ. Hypermethylation was dominantly detected in male patients harboring the

low-activity 5-HTTLPR alleles. Animal model experiment ruled out the effect of antipsychotic medication on DNAm. I revealed that DNAm at the single CpG site diminished *SLC6A4*'s promoter activity. I also found that significant negative correlation between DNA methylation levels and left amygdala volumes in patients with low-activity 5-HTTLPR alleles.

Taken together, my results suggest that CpG hypermethylation within CGI shore of *SLC6A4* has functional role on transcription regulation, and pathophysiological consequence of reduced amygdala volume in the male patients with low-activity 5-HTTLPR alleles.