Interacting Roles of \textit{COMT} and \textit{GAD1} Genes in Patients with Treatment-Resistant Schizophrenia: a Genetic Association Study of Schizophrenia Patients and Healthy Controls

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Received: 26 April 2021 / Accepted: 3 June 2021 / Published online: 14 June 2021
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Abstract
The projection from dopaminergic neurons to gamma-aminobutyric acid (GABA) interneurons in the prefrontal cortex is involved in the etiology of schizophrenia. The impact of interacting effects between dopamine signals and the expression of GABA on the clinical phenotypes of schizophrenia has not been studied. Since these interactions could be closely involved in prefrontal cortex functions, patients with specific alleles of these relevant molecules (which lead to lower or vulnerable genetic functions) may develop treatment-refractory symptoms. We conducted a genetic association study focusing on \textit{COMT} and \textit{GAD1} genes for a treatment-resistant schizophrenia (TRS) group \((n=171)\), a non-TRS group \((n=592)\), and healthy controls (HC: \(n=447)\), and we examined allelic combinations specific to TRS. The results revealed that the percentage of subjects with Met allele of rs4680 on the \textit{COMT} gene and C/C homozygote of rs3470934 on the \textit{GAD1} gene was significantly higher in the TRS group than the other two groups. There was no significant difference between the non-TRS group and HC groups. Considering the direction of functions of these single-nucleotide polymorphisms revealed by previous studies, we speculate that subjects with the Met/CC allelic combination could have a higher dopamine level and a lower expression of GABA in the prefrontal cortex. Our results suggest that an interaction between the dopaminergic signal and GABA signal intensities could differ between TRS patients and patients with other types of schizophrenia and healthy subjects.

Keywords Clozapine · Dopamine · GABA · Single-nucleotide polymorphism · Treatment-resistant

Introduction
It has been considered that in brains of patients with schizophrenia in the acute phase, the synthesis and release of dopamine are increased in the mesolimbic dopamine system, and it has been suggested that all antipsychotics exhibit preferable actions by blocking post-synaptic dopamine D2 receptors (DRD2) (Howes and Kapur 2009). However, approximately 30% of patients with schizophrenia do not respond well to the standard antipsychotic medications despite sufficient usage in terms of both dose and duration, and these patients are considered to have treatment-resistant schizophrenia (TRS) (Elkis 2007; Kane et al. 1988). Patients with TRS generally continue to present with severe psychopathologies and experience an unstable clinical course for a long time period, leading to very poor outcomes. The clarification of the etiology of TRS and the development of a highly effective treatment for TRS thus remain important challenges in the field of psychiatry.

Schizophrenia patients have serious symptom domains that include negative symptoms and cognitive dysfunctions (Buchanan 2007; Schafer et al. 2013). It is estimated that the neural networks involving these negative domains could differ from the networks underlying positive symptoms: that is, glutamatergic and γ-aminobutyric acid (GABA) systems in the cortical area could be more directly involved in the origins of negative symptoms and cognitive dysfunctions (Schwartz...
et al. 2012; McCutcheon et al. 2020). Several studies indicated that patients with TRS show more profound cognitive impairment compared to general (non-TRS) patients with schizophrenia (Joob er et al. 2002; de Bartolomeis et al. 2018; Frydecka et al. 2016; Nakata et al. 2020). Abnormalities in parvalbumin-positive GABA interneurons and lowered expressions of mRNA/protein of glutamic acid decarboxylase1 (GAD1) in the brains of individuals with schizophrenia have been consistently reported from multiple postmortem studies, and these findings are suggested to be related to the lower expression of γ-oscillation and cognitive dysfunctions in living patients with schizophrenia (Tallon-Baudry et al. 1998; Fries et al. 2001; Lewis et al. 2008; Buzsáki et al. 2004). Clozapine is the only agent for which effectiveness against TRS has been established, and it is strongly suspected that GABA and glutamatergic neural systems are involved in the highly efficacious action of clozapine (O’Connor and O’Shea 2015; Goldstein et al. 2015; Iwata et al. 2019).

In synapses in which dopaminergic neurons from the ventral tegmental area (VTA) innervate GABAergic interneurons in the prefrontal cortex (PFC), catechol-o-methyltransferase (COMT) plays an important role in the regulation of the dopamine signaling to GABAergic interneurons (Lewis et al. 2005; Lewis and Gonzalez-Burgos 2006) because there are fewer dopamine transporters (another regulator of dopamine signal transduction) in the PFC region (Lewis et al. 2001; Kaenmaki et al. 2010). Val158Met polymorphism (rs4680) on the COMT gene affects the activity of the COMT enzyme: Met homozygote shows 40% lower enzyme activity than Val homozygote, leading to an increase in the dopamine level in the PFC and anterior cingulate cortex (ACC) (Chen et al. 2004; Lachman et al. 1996). Several studies reported that schizophrenia patients with Val/Val homozygote (presumable lower dopamine level) had lower densities of gray matter regions in the ACC, hippocampus, amygdala, and middle temporal cortex, and that these patients had severe negative symptoms and cognitive dysfunctions (Barnett et al. 2007; Tsuchimine et al. 2013; Apud and Weinberger 2007). In addition, numerous studies have indicated that the Val158Met polymorphism could be significantly related to cognitive functions in healthy subjects or patients with psychiatric disorders other than schizophrenia (Nogueira et al. 2019; Pigioni et al. 2019).

Here, to examine the neural substrates specific to TRS (which could be different from those of other types of schizophrenia), we conducted a genetic association analysis focusing on dopamine-GABA interaction. Toward this goal, we selected rs4680 on the COMT gene and rs3749034 on the GADI gene, which were strongly suggested to affect the transcription of GAD1 protein (Straub et al. 2007; Tao et al. 2018). Although there have been several analyses of interacting effects of COMT and GADI (Straub et al. 2007; Kirenskaya et al. 2018), their findings were not consistent. In the study by Straub et al. (2007), none of the single-nucleotide polymorphisms (SNPs) on the GADI gene were related to schizophrenia, but several SNPs created by combining COMT Val/Val homozygotes showed a significant relationship with vulnerability to schizophrenia. In a study by Kirenskaya et al. (2018), subjects with the Val/Val homozygote of COMT rs4680 showed a longer response latency and poorer response rate in a saccade movement task. Patients with C/C homozygote of GADI rs3749034 exhibited a delayed response time, and the T-allele-carrier patients showed a higher error rate on the task. Collectively, these findings suggest that SNPs on the COMT and GADI genes could affect the disease vulnerability and cognitive impairments to some degree, but analyses of combined effects of the two genes have been insufficient. The present study is the first to analyze the interaction between COMT and GADI genes focusing on TRS patients. We hypothesize that TRS patients may have a more clearly allelic combination with a pair of alleles which are more vulnerable to schizophrenia.

Subjects and Methods

We analyzed the cases of a total of 763 patients, all of whom met the criteria of schizophrenia or schizoaffective disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) or the DSM-5, which were diagnosed by experienced psychiatrists. Patients with any other psychiatric disorder as a comorbidity (other than nicotine dependence) were excluded. A total of 447 healthy subjects were also recruited as individuals in the healthy control (HC) group; they were confirmed to have no past history or family member with any psychiatric or neurological disorder. All of the patients and controls were Japanese. The data of rs4680 on COMT gene partly overlapped with two previous studies from our team (Oishi et al. 2018, 2020).

Blood drawing from each subject was performed after acquiring his/her written informed consent after a detailed explanation of the study. In the informed consent process, two psychiatrists judged the patient’s ability to consent. If the patient was judged to be unable to understand the contents of the research due to his/her disease condition, the researchers sought and obtained informed consent from the patient’s family member(s). This study was approved by the Ethics Committee of the Chiba University Graduate School of Medicine and was conducted following the Helsinki Declaration.
The Diagnosis of Treatment-Resistant Schizophrenia

The diagnosis of having TRS was made based on both the assessment by the patient’s physician(s) and all available medical records. The criteria of TRS were based on the Clozapine Patients Monitoring Service (CPMS) criteria, and the present study included only the non-responder type of schizophrenia patient: this type was defined as never having shown a sufficient response (i.e., <40 points on Global Assessment of Functioning over the past 12 months) to at least two types of antipsychotics with each chlorpromazine-equivalent dose of >600 mg for >4 weeks. Patients who were judged as belonging to the intolerance type were excluded from this study.

Genotyping SNPs

The genome was derived from each subject’s blood sample with the QIAamp DNA Blood Mini Kit (250) (Qiagen, Valencia, CA). We examined two SNPs: rs4680 (Val158Met>G>A) in exon3 of COMT gene and rs3749034(C>T) in the 5′-UTR of GAD1 gene. The genotypes of these SNPs were determined by a TaqMan probe assay (Applied Biosystems, Foster City, CA) with an ABI PRISM 7300 real-time polymerase chain reaction (PCR) system (Applied Biosystems). All procedures followed the manufacturer’s manual: one cycle of 95°C for 10 min followed by 40 cycles of 92°C for 15 s and 60°C for 60 s.

Statistical Analyses

All statistical procedures were performed with SPSS version 19.0 software (IBM, NY). For the subjects’ demographic information, we performed Student’s t-test or an analysis of variance (ANOVA) for the continuous variable (age) and used the χ²-test for categorical variable (sex or SNP distribution). As a post-hoc test, Bonferroni correction was then conducted for the ANOVA and a residual analysis was conducted for the χ²-test.

Previous investigations of Japanese subjects conducted by other teams indicated that the allelic distributions of both rs4680 and rs3749034 were not significantly different between subjects with schizophrenia and healthy subjects. When we calculated the necessary sample sizes to reach statistical significance in the present comparison of the schizophrenia groups and healthy controls in reference to the two prior studies with the largest Japanese sample sizes to date (Ikeda et al. 2007; Okochi et al. 2009), the value for rs4680 was n=121,410 per group and that for rs3749034 was n=23,908 per group under the condition of α=0.05, β=0.20, and power=0.80. The present study’s sample size was much smaller than these estimations, and we therefore set the statistical significance level at p<0.10 in the three-group comparisons (2×3 χ²-test) in order to avoid a possible type II error. For the identification of the cell(s) with a significant increase or decrease, we performed the residual analysis with the statistical significance set at p<0.05.

Results

As shown in Table 1, female subjects were significantly dominant in the schizophrenia group. The age at blood sample-drawing was significantly higher in the schizophrenia group compared to the HC group. In the comparisons separating the TRS and non-TRS groups, the dominant gender was opposite between the non-TRS and HC groups, and the gender distribution in the TRS group was approximately

| Variables          | SCH group   | HC group  | Statistics          |
|--------------------|-------------|-----------|---------------------|
|                    | n=763       | n=447     |                     |
| Sex: male/female, n| 366/396*    | 253/189*  | χ²=9.496, p=0.002   |
| Age, yearsb         | 46.09 (14.97)* | 36.36 (15.06)* | t=10.747, p<0.001   |
|                    | n=171       | n=592     |                     |
|                    | 86/85       | 280/311*  | χ²=9.737, p=0.008   |
| Sex: male/female, n| 49.66 (13.045) | 45.03 (15.35)* | F=64.64, p<0.001    |
| Age, yearsb         | 49.66 (13.045) | 45.03 (15.35)* |                     |

*The sex of one subject in the non-TRS group and five in the HC group were unknown
aThe values of 18 subjects in the non-TRS group and 12 in the HC group were unknown
bThese data are mean (SD)
The ages also differed among the three groups: TRS > non-TRS > HC group.

The two above-described SNPs did not deviate from Hardy-Weinberg equilibrium in either the schizophrenia group or the HC group. For rs4680, no significant difference was observed among the three groups (p>0.10). For rs3749034, however, there was a significant difference among the three groups: C/C homozygote was significantly dominant in the TRS group, whereas T-allele carriers was the dominant type in the HC group (χ²=4.942, p=0.085; Table 2). However, the residual analysis as a post-hoc test did not show any cell reaching statistical significance (p>0.05): the adjusted residual value was ±1.918 (p=0.055) for the TRS group, ±0.269 (p=0.788) for the non-TRS group, and ±1.663 (p=0.096) for the HC group, indicating that the TRS and HC groups had trends toward significant differences in the SNP distributions.

When these analyses were performed separately for the male and female subjects, there was no significant difference in the SNP distribution of rs3759034 or rs4680 for male or female subjects (p>0.10).

Based on several previous studies, we divided the genotypes of rs4680 into three subgroups (Val/Val, Val/Met, and Met/Met) and divided the genotypes of rs3749034 into two subgroups (C/C and C/T+T/T), taking the number of each genotype into consideration (Table 3). When the combinations of both SNPs were compared among the three diagnosis groups, there was a significant difference (χ²=5.073, p=0.079). The residual analysis showed that the adjusted residual value of the TRS group was ±2.246 (p=0.025), and those of the non-TRS and HC groups were ±0.743 and ±0.852, respectively (p>0.05). This result indicated that the TRS group had a higher percentage of subjects with Met(+)+T(−) compared to the other two groups, whereas the percentage of subjects in the TRS group with other allelic combinations was lower than those in the other two groups.

When this three-group comparison was conducted separately for the male and female subjects, the results for the male subjects revealed a significant difference among the three groups (χ²=6.809, p=0.033). The residual analyses showed that the adjusted residual value of the TRS group was ±2.551 (p=0.011), indicating that the TRS group had a higher percentage of subjects with Met(+)+T(−) compared to the other two groups, whereas the percentage of subjects in the TRS group with other allelic combinations was lower than those in the other two groups. The 2×3 χ²-test for the female subjects did not observe such a significant difference (p>0.10).

We performed additional comparisons for the same allele combinations of the two SNPs between pairs of groups, since two-pair group comparisons are more common in genetic association studies. The results revealed that there were significant differences between the TRS and HC groups (χ²=4.421, p=0.036) and between the TRS and non-TRS group (χ²=4.259, p=0.039), indicating that the percentage of Met(+)+T(−) subjects and the percentage of other allele combinations of the TRS group were significantly higher and lower, respectively, compared to the HC or non-TRS group. There was no difference in the distribution of combined alleles between the non-TRS and HC groups.

### Table 2 Genotype distributions of rs4680 on COMT gene and of rs3749034 on GAD1 gene

| SNP    | TRS group | Non-TRS group | HC group | MAFa | Statistic values |
|--------|-----------|---------------|----------|------|-----------------|
| rs4680 |            |               |          |      |                 |
| Met (−) | 75 (43.9%) | 274 (46.3%)   | 196 (43.8%) | 45.4% | χ²=0.723, p=0.697 |
| Met (+) | 96 (56.1%) | 318 (53.7%)   | 251 (56.2%) | 54.6% |                 |
| rs3749034 |       |               |          |      |                 |
| T (−)  | 95 (55.6%) | 291 (49.2%)   | 204 (45.8%) | 45.2% | χ²=4.942, p=0.085 |
| T (+)  | 76 (44.4%) | 301 (50.8%)   | 243 (54.2%) | 54.8% |                 |

aMAF data were derived from healthy subjects in Okochi et al. (2009) for rs4680 and Ikeda et al. (2007) for rs3749034

### Table 3 Combined analysis of genotypes of rs4680 on COMT gene and rs3749034 on GAD1 gene

| rs4680/rs3749034 | TRS group | Non-TRS group | HC group | Statistic values |
|------------------|-----------|---------------|----------|-----------------|
| Met(+)/T(−)      | 56 (32.7%)| 147 (24.8%)   | 109 (24.4%) | χ²=5.073, p=0.079 |
| Others           | 115 (67.3%)| 445 (75.2%)  | 338 (75.6%) |                 |
Discussion

Accumulating evidence from multiple studies suggests that the brains of patients with schizophrenia have impaired GABA functions. GAD1 plays a main role in the synthesis of GABA in the central nervous system (CNS), accounting for approximately 80% of the GABA production in the CNS (the remaining 20% of GABA is produced by GAD2) (Asada et al. 1997; Condie et al. 1997; Mitchell et al. 2015; Varju et al. 2002). The synthesis of GABA is influenced by SNPs on the GADI gene (Straub et al. 2007; Marenco et al. 2010; Tao et al. 2018) and regulated by a dopamine signal (Shukla et al. 2016). In the present study, we examined genetic influences of the functional SNPs (rs4680 and rs3749034) on the severity of schizophrenia, and the results revealed that the TRS group included greater percentages of patients with Met carrier of rs4680 (lower COMT enzyme, leading to higher dopamine in the PFC) and T-allele non-carriers (i.e., C/C homozygote) of rs3749034 compared to the non-TRS patients and the HC group. There was no significant difference in the allelic distribution between the non-TRS and HC groups.

This finding might be somewhat unexpected since Met allele innervates a higher dopamine level in the PFC. We also observed that C-allele, the major allele of rs3749034, was significantly dominant in the TRS group by its single analysis with a less rigorous statistical threshold, and this allele appears to be less related to the vulnerability to schizophrenia.

Regarding COMT gene, several studies have suggested that this gene could be related to treatment-refractoriness or responsiveness to medications, and most of those studies demonstrated that carrying the Met-allele could be linked to treatment-refractoriness (Inada et al. 2003; Sagud et al. 2018; Hajj et al. 2019) with the exception of one report (Terzić et al. 2016) which was in line with our present finding. COMT gene could function differently in the brains of male and female individuals, i.e., with sex-dichotomous effects (Papaleo et al. 2015; Sannino et al. 2020; Wu et al. 2020). However, our present findings do not support this; there was no significant difference in the allele distribution of rs4680 for the male or female subjects. The allelic distribution for rs3749034 on GADI gene, on the other hand, was significantly different among the groups (including both the males and females), whereas no such difference was observed in rs4680. Therefore, rs3794034 seemed to contribute to the overall difference in the combined (rs4680 and rs3749034) SNP distributions in the both sex-combined comparison among the three groups.

Some research groups examining COMT and GAD1 suggested that the interacting effects of both genes could not simply explain the synthesis of GABA and the clinical phenotypes in schizophrenia. For example, in a magnetic resonance spectroscopy (MRS) study of healthy individuals by Marenco et al. (2010), the subjects with the Val/Met heterozygote of COMT rs4680 showed higher GABA concentrations compared to those with other homozygotes (i.e., Val/Val and Met/Met homozygotes). In that study, the subjects with minor alleles of two SNPs (rs1978340 and rs769390, which were not examined in the present study) among three SNPs that significantly affect the GABA concentration showed higher GABA levels compared to the subjects with major alleles of these polymorphisms. A study by Straub et al. (2007) demonstrated that rs3749034 on GADI was the only polymorphism affecting the expression of GAD1 mRNA and that its major allele (i.e., G allele) was related to lower expression. In a total of 19 SNPs on the GADI gene examined in that study, no significant SNP was observed to be significantly related to schizophrenia, but when the interactions between these SNPs and rs4680 Val/Val homozygote were examined, there were some SNPs related to the disease vulnerability: these relevant SNPs were a mixture of major and minor alleles, and it is thus difficult to estimate the impacts of these SNPs on the transcription of GAD1. Recent evidence demonstrated that GABA synthesis could be influenced by the methylation of GADI (Tao et al. 2018), suggesting that such other factors should be taken into consideration concerning the production of GABA.

The projection of dopamine signal to the GABAergic neurons in the PFC is modulated by both excitatory dopamine D1 receptors (DRD1s) and inhibitory DRD2s. Pyramidal neurons are also involved in this modulation (Momiyama and Nishijo 2017; Shukla et al. 2016). It has long been believed that higher or lower dopamine signal transduction had negative influences on PFC-modulating cognitive functions, and that this characteristic shows a so-called inverted-U-shape curve (Lidow et al. 1998; Ira et al. 2013). That is, the dopamine network projects onto both GABAergic interneurons and glutamatergic pyramidal neurons, which further project to other pyramidal neurons; these are connected to each other in a very complicated manner, and they determine the excitatory and inhibitory balance in the PFC (Sohal and Rubenstein 2019). According to a postmortem study, healthy individuals with COMT Val/Val homozygote (which may lower the dopamine level) showed higher mRNA of GAD1 compared to individuals with Met/Met homozygote (Shukla et al. 2016), suggesting the maintenance of the homeostasis of signal transmissions to the PFC in healthy individuals. In contrast, subjects with schizophrenia had GAD1 mRNA levels that did not differ between those with Val/Val and those with Met/Met homozygotes, possibly indicating an attenuated ability to maintain homeostasis. These findings suggest the possibility that schizophrenia patients have a weakened capacity to...
adjust to a variety of stimulations from the external world, further leading to the origins of cognitive impairments at the cortical level and impaired dopamine synthesis at the subcortical level.

In the present study, when we divided the schizophrenia patients into the TRS and non-TRS groups, we observed that these groups’ SNP distributions of COMT and GAD1 differed: some of the TRS patients had a combination of the two genes that differed from those of non-TRS patients or healthy subjects, and we suspect that this may provide a clue to the interacting roles of the two molecules in the disease etiology. Earlier studies of TRS patients indicated that the synthesis of dopamine or the dopamine volume in the synaptic clefts could differ in patients with TRS compared to other schizophrenia patients who achieve a good response to antipsychotic medications (Demjaha et al. 2012; Kim et al. 2017). Several studies uniformly observed more severe cognitive impairments in TRS patients (Jooper et al. 2002; de Bartolomeis et al. 2018; Frydecka et al. 2016; Nakata et al. 2020), and another line of evidence suggests that such severe cognitive dysfunctions could be related to an attenuation of GABA signal transduction (Tallon-Baudry et al. 1998; Fries et al. 2001; Lewis et al. 2008; Buzsáki et al. 2004). It was also reported that clozapine could enhance GABA signal transduction (Daskalakis et al. 2008; Liu et al. 2009; Kaster et al. 2015; Miyazawa et al. 2021). Collectively, these findings suggest that TRS patients could have a neural substrate that is distinct from those of other general schizophrenia patients. The present results may indicate that a specific allele combination of COMT and GAD1 genes provides consistently lower GABA systems, leading to treatment-refractory symptoms. It is important to further investigate the relationships among SNPs of COMT/GAD1 and GABA concentrations in the human brain by MRS techniques.

The present study was preliminary, with several weaknesses as follows. The sample sizes of both the patients and controls were too small to reach a firm conclusion. We did not examine the cognitive functions of the subjects. Although most of the prior relevant studies seemed to presume that the interaction of dopamine and GABA in the PFC underlies cognitive impairments in schizophrenia, we did not directly examine cognitive functions of our participants. However, this study has some strengths: the TRS patients were well characterized and selected through a process that was identical to clinical practice when the introduction of clozapine is considered. Another strength is that the two SNPs examined are well characterized in terms of their function and interaction, providing the opportunity to investigate the patients’ brain networks from a genetic perspective.

In conclusion, our findings are preliminary, but by focusing on TRS patients, the data suggest that this group could have one or more different COMT and GAD1 allelic combinations compared to non-TRS patients or healthy controls. Overall, our results suggest that TRS patients are less capable of appropriately tuning the excitatory and inhibitory balance and homeostasis, leading to a difficulty in regulating the subcortical dopamine system and to severe cognitive impairments and negative symptoms.

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