

COMT Val 108/158 Met polymorphism and treatment response to aripiprazole in patients with acute schizophrenia

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Introduction: The *COMT* Val 108/158 Met polymorphism (rs4680) may affect treatment response to antipsychotics, as well as metabolism and dynamics of neurotransmitters during the treatment of schizophrenia. We investigated the effects of the *COMT* Val 108/158 Met polymorphism on treatment response to aripiprazole and plasma monoamine metabolite levels in patients with acute schizophrenia.

Materials and methods: Forty patients with schizophrenia were treated with aripiprazole for 6 weeks. We measured Positive and Negative Syndrome Scale (PANSS) and plasma levels of homovanillic acid (HVA) and plasma MHPG (3-methoxy-4-hydroxyphenylethylene glycol) at baseline and endpoint. The *COMT* Val 108/158 Met polymorphism was genotyped with the polymerase chain reaction and restriction fragment length polymorphism.

Results: There were significant genotype–time interactions on PANSS total and general psychopathology scores, with Met/Met genotype showing greater improvement. The response rate to aripiprazole did not differ between *COMT* Val 108/158 Met genotype groups. We found a significant time effect on plasma MHPG levels, but no time effect on plasma HVA levels or time–genotype interactions in the plasma levels of HVA and MHPG. Although the responder rate did not differ among the 3 genotype groups.

Conclusion: Our results suggest that individuals with the Met/Met genotype had greater improvement in PANSS score after the treatment with aripiprazole. On the other hand, the Val 108/158 Met polymorphism may not induce changes in plasma levels of monoamine metabolites during aripiprazole treatment. Because of the small sample size, further studies are needed to confirm and to extend our results.

Keywords: schizophrenia, *COMT*, Val 108/158 Met polymorphism (rs4680), aripiprazole, pharmacogenetics

Introduction

Although antipsychotics play a critical role in the treatment of schizophrenia, there are considerable interindividual differences in the treatment response to antipsychotics. Pharmacogenetic studies have focused on various genes to identify meaningful predictors for treatment response to antipsychotics. Previous meta-analyses showed significant associations between the treatment response to antipsychotics and the -141C Ins/del (rs1799732) polymorphism in *DRD2*,¹ the T102C (rs6313) polymorphism in *5HT2A*,² the C1019G (rs6295) polymorphism in *5HT1A*,³ and Val 108/158 Met (rs4680) polymorphism in *COMT*.⁴

COMT methylates neurotransmitters, such as dopamine and noradrenaline, and drugs such as L-dopa. *COMT* is positioned in the q11.21 on chromosome 22 and has various

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single-nucleotide polymorphisms (SNPs). One base of the 108/158th codon replaces G with A, which changes valine to methionine.⁵ The activity of the Val allele enzyme is 3- to 4-fold higher than that of the Met allele enzyme,⁶ and this SNP may affect the dynamics of neurotransmitters and the antipsychotic response. A recent meta-analysis showed that individuals with Met/Met genotype were associated with favorable response to atypical antipsychotics.⁴ This meta-analysis included both positive⁷⁻¹⁰ and negative¹¹⁻¹⁴ studies regarding the association between the Val 108/158 Met genotype and treatment response to antipsychotics. However, the meta-analysis did not include studies with aripiprazole, which has a unique pharmacological profile as a partial agonist for dopamine D2 receptors. Furthermore, the underlying biological basis of the association between the Val 108/158 Met genotype and treatment response to antipsychotics remains unclear.

Homovanillic acid (HVA) and plasma MHPG (3-methoxy-4-hydroxyphenylethylglycol) are the main metabolites of dopamine and noradrenaline, respectively. Plasma levels of HVA and MHPG reflect 30%–50% of HVA¹⁵ and one-third of MHPG¹⁶ in the central nervous system, respectively. Although it is difficult to regard plasma monoamine metabolites as direct reflections of central nervous system activity, plasma HVA levels are considered a possible indicator of the clinical response to antipsychotic drugs.¹⁷ Furthermore, plasma HVA levels parallel improvement in positive symptoms during treatment of schizophrenia.¹⁸

Because no studies have examined the association between the *COMT* Val 108/158 Met polymorphism and treatment response to aripiprazole and because the genotype effects on monoaminergic neurotransmission during antipsychotic treatment remains unknown, we investigated the effects of the *COMT* Val 108/158 Met polymorphism on treatment response to aripiprazole and on plasma monoamine metabolite levels in patients with acute schizophrenia.

Materials and methods

The subjects were Japanese patients who were diagnosed with schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV). Subjects included both drug-naïve and drug-free recurrent patients who had received no antipsychotic drugs (neither oral nor long-acting injection) for at least 2 weeks before entry into this study. For inclusion in this study, patients had to have a Positive and Negative Syndrome Scale (PANSS) total score of at least 80 and minimum score of 4 on at least 2 psychotic item subscales (hallucination, delusion, conceptual disorganization, and suspiciousness). Patients who

abused alcohol/drugs and/or those who had organic brain disorders were excluded. Patients received 18 mg/d aripiprazole on day 1. From day 2 to the endpoint, physicians regulated the doses of aripiprazole carefully based on the clinical symptoms. Benzodiazepines and anticholinergics were permitted as additional medications to manage insomnia, restlessness, and extrapyramidal symptoms. The efficacy of the treatment was evaluated using PANSS, the Clinical Global Impression (CGI)-S (Severity), and CGI-I (Improvement) Scale. Patients with a CGI-I score of 1 or 2 or a $\geq 30\%$ decrease from baseline in the PANSS total score were defined as responders.

Blood samples were obtained before breakfast at 0 and 6 weeks after aripiprazole administration. Concentrations of plasma monoamine metabolites were analyzed with high-performance liquid chromatography with electrochemical detection. Plasma levels of HVA and MHPG were analyzed using the methods of Watanabe et al.¹⁹ The intra-assay coefficients of variation for plasma HVA and MHPG in our laboratory were 3.2% and 3.1%, respectively. The interassay coefficients of variation for plasma HVA and MHPG were 8.6% and 7.6%, respectively. Genomic DNA was extracted from white blood cells from patients, and the Val 108/158 Met genotype in *COMT* was determined with the polymerase chain reaction and restriction fragment length polymorphism method as previously described.²⁰ The amplification program included initial denaturation at 95°C for 3 minutes, followed by 30 cycles of 58°C for 30 seconds, 72°C for 1 minutes, and 95°C for 30 seconds, followed by a final extension at 72°C for 10 minutes. *Nla* III was added to the polymerase chain reaction products (217 bp), and samples were incubated at 37°C for 60 minutes. Samples were then electrophoresed on 4% agarose gels (Wako Agarose Xp, Wako Pure Chemical Industries Ltd, Osaka, Japan) and visualized with UV. Following amplification and *Nla* III digestion, the Val/Val genotype yielded bands of 136 and 81 bp, Val/Met yielded bands of 136, 96, 81, and 40 bp, and Met/Met yielded bands of 96, 81, and 40 bp. This study was approved by the ethics committee of Fukushima Medical University, and the patients provided written informed consent after having been informed of the purpose of the study.

We investigated the genotype effects on treatment response (responder rate and changes in PANSS scores) and on plasma levels of monoamine metabolites. Furthermore, we performed responder versus nonresponder comparison. One-way analysis of variance (ANOVA) was used to compare the patient's demographics (age, duration of illness, etc.), each PANSS score, and the plasma levels of HVA and MHPG among genotypes. The χ^2 test was used to compare the sex

ratio. The last observation carried forward method was used when a dropout occurred. Repeated-measures ANOVA was used to compare the genotypes, treatment period, changes in the PANSS score, and plasma monoamine metabolite levels. The significance level was defined as $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics 23 (IBM Corporation, Armonk, NY, USA).

Results

Of the 40 patients, 39 patients completed the study, and 1 patient dropped out at week 4 because of a lack of efficacy based on the physician's clinical decision. Among the 40 patients, 16 (40.0%) were responders (Table S1). At the endpoint, doses of aripiprazole ranged from 9 to 30 mg/d (mean \pm SD = 24.33 \pm 6.33 mg/d). Of the 40 patients, 29 (72.5%) received benzodiazepines (Val/Val: $n=18$ (5–18.3 mg/d), Val/Met: $n=9$ (4.2–22.5 mg/d), Met/Met: $n=2$ (5 mg/d) (doses were converted to diazepam equivalents) and 10 (25%) received biperiden (Val/Val: $n=6$ (2–3 mg/d), Val/Met: $n=4$ (1–4 mg/d), Met/Met: $n=0$). In responders, aripiprazole decreased plasma levels of HVA ($p=0.015$), whereas the drug did not change plasma HVA levels ($p=0.418$) in nonresponders. The plasma levels of MHPG decreased in both responders ($p=0.001$) and nonresponders ($p=0.038$). Of the 40 patients, 23 patients were homozygous for Val, 13 were heterozygous, and 4 were homozygous for Met. The allele distribution was in Hardy–Weinberg equilibrium ($\chi^2=0.98$, $df=1$, $p>0.05$). At baseline, no significant differences in PANSS scores, CGI-S, or plasma levels of monoamine metabolites were found (Table 1).

The responder rate to aripiprazole did not differ among the 3 genotype groups ($p=0.157$) (Table 1). Repeated-measures ANOVA revealed significant time effects on PANSS total ($p < 0.001$) and positive ($p < 0.001$) and negative ($p < 0.001$) scores (Figure 1). There was significant genotype–time interactions on PANSS total ($p=0.009$) and general psychopathology ($p=0.007$) scores, with Met/Met genotype showing greater improvement (Figure 1). We also found a trend level genotype–time interaction in the PANSS negative score ($p=0.065$).

We found a significant time effect on plasma MHPG levels ($p=0.009$), but no time effect was found for plasma HVA levels ($p=0.756$) or time–genotype interactions on plasma levels of HVA ($p=0.21$) or MHPG ($p=0.47$).

Discussion

To the best of our knowledge, this is the first study to investigate the effects of the Val 108/158 Met polymorphism in

Table 1 Comparisons among the 3 genotypes

Genotype	Val/Val group (n=23)	Val/Met group (n=13)	Met/Met group (n=4)	p-value
At baseline				
Age (years)	41.6 \pm 11.9	43.5 \pm 14.2	35.7 \pm 2.1	0.621 ^a
Sex, male/female	13/10	9/4	3/1	0.648 ^b
Duration of illness (years)	10.0 \pm 9.6	13.7 \pm 14.2	8.0 \pm 7.0	0.576 ^a
PANSS total	105.1 \pm 13.2	109.5 \pm 15.1	113.8 \pm 10.6	0.412 ^a
PANSS positive	28.1 \pm 4.9	28.5 \pm 3.5	27.3 \pm 2.5	0.867 ^a
PANSS negative	23.8 \pm 5.6	24.8 \pm 6.4	28.3 \pm 6.5	0.390 ^a
PANSS general	53.2 \pm 7.7	55.9 \pm 9.3	59.5 \pm 7.2	0.305 ^a
CGI-severity	5.5 \pm 0.5	5.5 \pm 0.8	5.5 \pm 0.6	0.983 ^a
Plasma HVA level (ng/mL)	17.0 \pm 7.1	19.1 \pm 7.9	14.1 \pm 5.6	0.455 ^a
Plasma MHPG level (ng/mL)	11.3 \pm 5.3	13.9 \pm 7.6	7.9 \pm 3.3	0.195 ^a
At endpoint				
Dose of aripiprazole (mg/d)	22.0 \pm 7.4	26.8 \pm 4.0	26.0 \pm 3.5	0.097 ^a
Responders/nonresponders	10/13	3/10	3/1	0.157 ^b
PANSS total	83.5 \pm 17.8	92.2 \pm 22.1	67.3 \pm 24.0	0.094 ^a
PANSS positive	20.6 \pm 6.5	23.0 \pm 7.0	14.8 \pm 5.9	0.107 ^a
PANSS negative	20.6 \pm 5.5	22.2 \pm 6.8	20.3 \pm 9.2	0.734 ^a
PANSS general	42.3 \pm 8.1	46.9 \pm 11.8	33.3 \pm 12.3	0.058 ^a
CGI-severity	3.8 \pm 1.4	4.2 \pm 1.4	2.5 \pm 1.7	0.119 ^a
CGI-improvement	2.7 \pm 1.1	3.0 \pm 1.1	1.5 \pm 1.0	0.061 ^a
Plasma HVA level (ng/mL)	16.8 \pm 11.0	15.4 \pm 7.4	19.6 \pm 10.6	0.759 ^a
Plasma MHPG level (ng/mL)	7.9 \pm 3.3	8.6 \pm 3.9	6.5 \pm 1.9	0.552 ^a

Note: ^aOne-way ANOVA, ^bPearson's χ^2 test.

Abbreviations: PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression; HVA, homovanillic acid; ANOVA, analysis of variance.

COMT on treatment response to aripiprazole and plasma monoamine metabolite levels in patients with acute schizophrenia. Although the responder rate did not differ among the 3 genotype groups, we found a significant association between the Val 108/158 Met polymorphism and the improvement in PANSS score after the treatment with aripiprazole. On the other hand, no significant genetic effects were found on plasma levels of monoamine metabolites during treatment.

Our results showing a significant relationship between the Met/Met genotype and greater improvement in PANSS score are consistent with a recent meta-analysis⁴ demonstrating that Met/Met individuals show significantly greater improvements than Val carriers, although the meta-analysis included studies of typical and atypical antipsychotics, but not aripiprazole. Notably, the meta-analysis reported no significant associations between the Val 108/158 Met

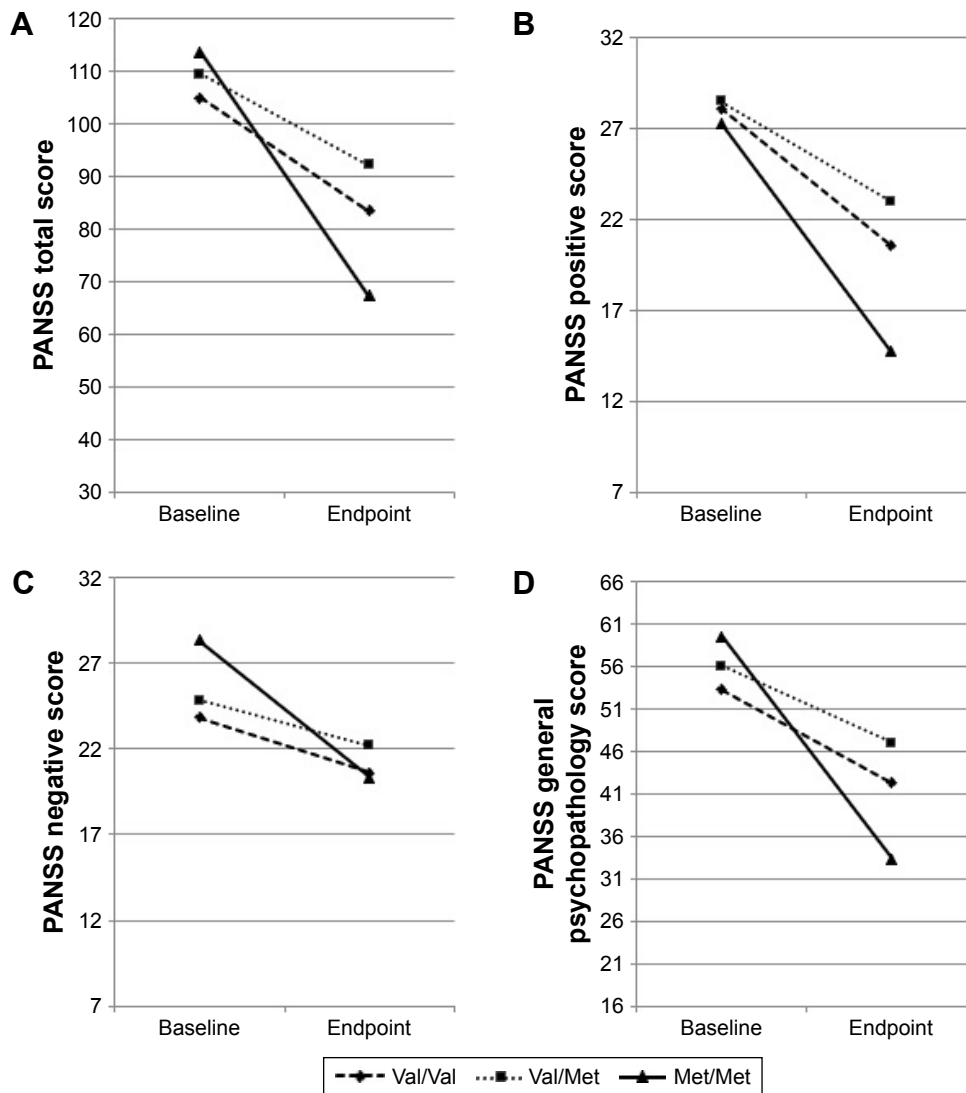


Figure 1 A mean change in PANSS total, positive, negative, and general psychopathology scores at baseline and 6 weeks.

Notes: (A) Genotype \times time interaction on PANSS total score ($F=5.296$; $p=0.009$). (B) Genotype \times time interaction on PANSS positive score ($F=2.493$; $p=0.096$). (C) Genotype \times time interaction on PANSS negative score ($F=2.941$; $p=0.065$). (D) Genotype \times time interaction on PANSS general psychopathology score ($F=5.741$; $p=0.007$).

Abbreviation: PANSS, Positive and Negative Syndrome Scale.

polymorphism and treatment response in patients treated with typical antipsychotics. Although aripiprazole has a different pharmacological profile than other antipsychotics as a partial agonist for DRD2, aripiprazole is classified as an atypical antipsychotic drug, and our results support the results of Huang et al.⁴

The difference in treatment response among the genotypes may be partially explained by the enzyme activity of COMT. The activity of the Val allele enzyme is 3- to 4-fold higher than that of the Met allele enzyme.⁶ If individuals with the Met/Met genotype have lower COMT activity, dopamine will not be metabolized sufficiently, which may lead to hyperdopaminergic neurotransmission. In such a case, antipsychotics may inhibit the hyperdopaminergic state with

antagonism for DRD2 in the mesolimbic system more effectively in the acute phase of schizophrenia, although we found no significant genotype–time interaction on PANSS positive score. Furthermore, the inverted U-curve hypothesis of dopamine function suggests that too much dopamine activity in the prefrontal cortex impairs working memory performance, whereas hypofunction of dopamine leads to cognitive dysfunction in patients with schizophrenia.²¹ Atypical antipsychotics including aripiprazole have inhibitory effects on DRD2 and 5-HT2A receptors, which may be related to appropriate dopamine neurotransmission in the prefrontal cortex. On the other hand, typical antipsychotics inhibit DRD2 but not 5-HT2A receptors, which may induce hypofunction of dopamine. Additionally, aripiprazole is a partial agonist

for DRD2, which may also stabilize dopamine function in the prefrontal cortex. Taken together, favorable response to aripiprazole in patients with the Met/Met genotype may be explained by stabilizing dopamine function in the prefrontal cortex, which leads to improve cognitive function.

In this study, the Val 108/158 Met polymorphism was not associated with changes in plasma levels of monoamine metabolites. Previous studies had reported that the Val 108/158 Met polymorphism is not associated with monoamine metabolites levels in cerebrospinal fluid^{22–24} or plasma,^{25–27} although no studies examined the association between the polymorphism and changes in levels of monoamine metabolites during treatment with antipsychotics. Our results suggest that the Val 108/158 Met polymorphism may not be related to changes in plasma levels of HVA or MHPG after aripiprazole treatment in schizophrenia. We previously reported associations between variants in *DRD2* and plasma levels of monoamine metabolites,^{17,28} suggesting that Taq1A polymorphism in *DRD2* may have effects on plasma HVA levels.¹⁷ COMT metabolizes dopamine and other monoamines and is not directly affected by antipsychotics. Therefore, the Val 108/158 Met polymorphism may not have effects on plasma levels of HVA or MHPG as do *DRD2* polymorphisms.

Our study has several limitations. First, our sample size was very small, and there were only 4 subjects in Met/Met genotype group. This limitation restricts our preliminary results. Second, this study included both first-episode and recurrent patients. Recurrent patients may be influenced by previous treatment effects such as upregulation of D2 receptors. Third, this study focused on only a *COMT* polymorphism, and we did not examine gene–gene interactions. Finally, we did not examine cognitive functions such as working memory with a neuropsychological test battery. Nevertheless, this is the first study to investigate the effects of the Val 108/158 Met polymorphism in *COMT* on treatment response to aripiprazole, and our results showed that individuals with the Met/Met genotype had greater improvement in PANSS score after the treatment. Further studies should investigate the underlying biological mechanism of the association between the Met/Met genotype and a favorable response to antipsychotics.

Conclusion

We found a significant association between the Val 108/158 Met polymorphism in *COMT* and the improvement in PANSS score after the treatment with aripiprazole. Although the responder rate did not differ among the 3 genotype groups, individuals with the Met/Met genotype had greater

improvement in PANSS score after the treatment. On the other hand, the Val 108/158 Met polymorphism may not affect plasma levels of HVA or MHPG. Caution is needed when interpreting our results because of the small sample size and heterogeneity among patients. Additional studies with a larger sample size are needed to confirm and extend our results.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Comparisons between responders and nonresponders

Response	Responders (n=16)	Nonresponders (n=24)	p-value
At baseline			
Age (years)	40.3±12.0	42.9±12.1	0.644 ^a
Sex, male/female	8/8	17/7	0.182 ^b
Duration of illness (years)	11.8±11.1	10.9±11.2	0.981 ^a
PANSS total	107.1±9.2	107.6±16.1	0.053 ^a
PANSS positive	27.5±3.8	28.6±4.5	0.750 ^a
PANSS negative	24.9±4.2	24.4±6.9	0.080 ^a
PANSS general	54.6±7.3	54.8±9.0	0.359 ^a
CGI-severity	5.6±0.5	5.5±0.7	0.214 ^a
Plasma HVA level (ng/mL)	17.1±6.5	17.6±7.8	0.466 ^a
Plasma MHPG level (ng/mL)	11.5±6.0	12.0±6.3	0.608 ^a
At endpoint			
Dose of aripiprazole (mg/d)	21.3±6.2	26.4±5.7	0.618 ^a
Genotype groups (ValVal/ValMet/MetMet)	10/3/3	13/10/1	0.157 ^b
PANSS total	67.8±10.1	96.0±17.9	0.046 ^a
PANSS positive	15.1±3.2	24.5±5.9	0.009 ^a
PANSS negative	17.8±2.9	23.3±6.9	0.020 ^a
PANSS general	34.9±5.5	48.3±9.2	0.056 ^a
CGI-severity	2.6±0.7	4.7±1.2	0.006 ^a
CGI-improvement	1.5±0.5	3.5±0.5	0.000 ^a
Plasma HVA level (ng/mL)	12.7±3.7	19.3±11.5	0.006 ^a
Plasma MHPG level (ng/mL)	6.3±1.8	9.1±3.8	0.004 ^a

Notes: ^aStudent's t-test (unpaired). ^bPearson's χ^2 test.

Abbreviations: PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression; HVA, homovanillic acid.

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