Taq1A polymorphism in the dopamine D2 receptor gene as a predictor of clinical response to aripiprazole

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Abstract

We investigated whether the clinical response to aripiprazole differed according to the Taq1A polymorphism in the dopamine D2 receptor (DRD2) gene. In this 26-week, prospective, open-label, double-blind, parallel-group study, 90 patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder were recruited and divided into two groups according to their DRD2 genotype (A1A1, n = 14; A1A2+A2A2, n = 76). The efficacy assessment included Positive and Negative Syndrome Scale (PANSS) scores and Clinical Global Impression (CGI) scores. Extrapyramidal symptoms were assessed using the Simpson–Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BAS). Plasma prolactin levels were also measured. Patients with the A1A1 genotype showed a more favorable therapeutic response to aripiprazole when assessed using the PANSS ratio. The changes in the SAS score from baseline to week 4 also differed according to the genotype group. There were no significant differences in the changes in the CGI, AIMS, and BAS scores or plasma prolactin level between the two genotype groups. The results suggest an association between the DRD2 Taq1A polymorphism status and the variation in the clinical response to aripiprazole.
1. Introduction

The variable responses to antipsychotic drugs in the treatment of schizophrenia still present obstacles to tailored medicine. Early efforts to identify the predictors of antipsychotic drug response focused on clinical variables and showed only limited success (Baker et al., 2002; Moeller et al., 1995; Rosenheck et al., 1998; Salin-Pascual et al., 2004; Yoshimura et al., 2003). Recent advances in molecular genetics have provided a novel method for identifying genetic variables influencing clinical responses to antipsychotic drugs and have led to intensive pharmacogenetic research.

The response to clozapine, for example, was associated with the serotonin 5-HT2A T102C polymorphism (Arranz et al., 1995). The Taq1A polymorphism in the dopamine D2 receptor (DRD2) gene has also been found to influence the clinical response to antipsychotic drugs. Specifically, patients with the minor allele, the A1 allele, exhibited more favorable therapeutic responses to haloperidol and nemonapride (Schafer et al., 2001; Suzuki et al., 2000). In addition to therapeutic responses, the adverse effects induced by antipsychotic drugs also appear to be associated with the DRD2 Taq1A polymorphism (Mihara et al., 2000, 2001; Suzuki et al., 2001; Young et al., 2004).

Aripiprazole is a novel antipsychotic drug that is distinguished from other antipsychotic drugs by its unique receptor profile as a dopamine partial agonist. Although it has been demonstrated to be safe and effective in the treatment of schizophrenia, some patients treated with aripiprazole could not be examined, because patients with symptoms that could be misperceived as psychotic symptoms or adverse effects induced by antipsychotic drugs; a clinically significant laboratory abnormality; the administration of long-acting antipsychotic medication, including carbamazepine, valproic acid, or any drug known to inhibit the activity of cytochrome P450 2D6 or 3A4 enzymes; the administration of long-acting antipsychotic drugs prior to study registration; any medical condition that could disturb the absorption of the study drug; the presence of somatic symptoms that could be misperceived as psychotic symptoms or adverse effects induced by an antipsychotic drug; a clinically significant laboratory abnormality; the administration of an investigational drug within 4 weeks prior to the start of the study; a history of participation in any clinical trial on an investigational drug within 4 weeks prior to the start of the study; or any other acute or unstable medical condition.

2.2. Determination of DRD2 Taq1A polymorphism

Genomic DNA was isolated from peripheral blood leukocytes using a commercially available kit (Qiagen Inc., Hilden, Germany). Polymerase chain reaction (PCR) and single base extension in SNAPSHOT analysis were employed in the allelic discrimination (A1 and A2). The primers for PCR amplification were 5′-gctgagcagatgtcataaat-′3′ (forward) and 5′-tggagcctggactgact-′3′ (reverse). After the PCR amplification, the products were purified using exonuclease I and shrimp alkaline phosphatase (USB, Cleveland, OH, USA).

For the SNAPSHOT analysis, the purified products were blended with AmpliTaq DNA polymerase, four fluorescently labeled deoxyribonucleotides, the primer for single base extension, and the reaction buffer from an ABI PRISM® SNAPSHOT™ Multiplex kit (Applied Biosystems, Foster City, California, USA). Single base extension was performed over 25 cycles of 96 °C for 10 s, 50 °C for 5 s, and 60 °C for 30 s, using the primer 5′-cacagccatcctcaagaagctgtt-′3′ for the Taq1A polymorphism.

The end-point fluorescence intensity was measured using an ABI PRISM® 3700 Automated Sequencer (Applied Biosystems, Foster City, California, USA), and allelic discrimination was performed. DNA sequences proximal to the polymorphic sites were verified via direct sequencing.

2.1. Patients

We fully explained the pharmacogenetic study of APLUS to patients, and they volunteered to consent to participation in the present study.

Men and nonpregnant, nonlactating women aged 18 to 65 years who met DSM-IV criteria for schizophrenia, schizoaffective disorder, or schizoaffective disorder with an acute episode (duration of the present episode ≤ 4 weeks) were eligible for enrollment in the present study.

For inclusion, patients had to have a total score of at least 60 on Positive and Negative Syndrome Scale (PANSS), with a minimum score of 4 (moderate) on at least two of the four PANSS items (hallucinatory behavior, delusions, conceptual disorganization, and suspiciousness).

The exclusion criteria included any psychiatric disorder other than schizophrenia, schizoaffective disorder, or schizoaffective disorder requiring pharmacotherapy; any violent behavior; a recent history of a suicide attempt or serious suicidal ideation; a neurological abnormality other than tardive dyskinesia or extrapyramidal symptoms induced by antipsychotic drugs; a current diagnosis of psychoactive substance dependence or history of substance or alcohol abuse (DSM-IV) within 1 month of the start of the study; any medication, including carbamazepine, valproic acid, or any drug known to inhibit the activity of cytochrome P450 2D6 or 3A4 enzymes; the administration of long-acting antipsychotic drugs prior to study registration; any medical condition that could disturb the absorption of the study drug; the presence of somatic symptoms that could be misperceived as psychotic symptoms or adverse effects induced by an antipsychotic drug; a clinically significant laboratory abnormality; the administration of an investigational drug within 4 weeks prior to the start of the study; a history of participation in any clinical trial on aripiprazole; or any other acute or unstable medical condition.

2. Experimental procedures

This study was conducted as part of the Acute Psychosis treatment in the Long-term Unitary group Study (APLUS) (Kwon et al., submitted for publication). Approval was granted by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea.
2.3. Study design

This was a prospective, open-label, double-blind, parallel-group study carried out at 30 medical centers in Korea. Patients who met all of the inclusion criteria and none of the exclusion criteria underwent a 5-day washout period. The patients who successfully completed the washout period were re-evaluated for their eligibility for the treatment phase. Patients received 15 mg/d of aripiprazole for the first 2 weeks, after which the aripiprazole dosage was adjusted to between 10 mg/d to 30 mg/d according to the patient’s clinical response and tolerability. After adjustment, the dosage was not changed for at least 1 week. Aripiprazole was administered orally once a day, after breakfast.

Patients were followed for a maximum of 26 weeks, or until early discontinuation.

2.4. Assessments

All assessments were performed by trained medical personnel. For each patient, the same personnel rated the assessments throughout the study and was blinded to the patient's genotype.

Treatment efficacy was assessed using the PANSS and Clinical Global Impression (CGI) Scale. Efficacy evaluations were performed at screening and at weeks 1, 2, 3, 4, 6, 8, 12, 16, and 26.

The primary efficacy parameter was the ratio of the PANSS total score compared to the PANSS total score at baseline (30 items). The secondary efficacy parameters included the ratio of the PANSS subscale scores compared to the baseline scores and the scores of the CGI-I and CGI-S.

Extrapyramidal symptoms (EPS) were evaluated employing the Simpson–Angus Scale (SAS), the Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Rating Scale (BAS). EPS evaluations were conducted at the end of the washout period and at weeks 1, 2, 3, 4, 6, 8, 12, 16, and 26.

Determinations of plasma prolactin levels were performed at screening and at weeks 8 and 26. Plasma prolactin levels were measured with electrochemiluminescent immunoassays with commercial kits for measuring prolactin (Elecsys 2010, Boehringer Mannheim, Indianapolis).

2.5. Concomitant medications

The use of psychotropic drugs inducing drug interactions with aripiprazole and disturbing the evaluation of the antipsychotic effect of aripiprazole was prohibited for the first 8 weeks in the treatment phase; concomitant medications were not changed for at least 1 week. Aripiprazole was administered orally once a day, after breakfast.

When a patient exhibited EPS to the extent that he or she needed anti-EPS agents, the agents were administered after the SAS and BAS evaluations were performed.

All concomitant medications used during the study were recorded.

2.6. Statistical procedures

To investigate the effect of the DRD2 Taq1A polymorphism on the clinical response to aripiprazole, we compared the data from patients who were homogenous for the minor allele (A1A1) with the data from patients having the other genotypes (A1A2, A2A2). The minor allele was reported to be associated with low density of dopamine receptor in the brain (Jonsson et al., 1999; Noble et al., 1991; Pohjalainen et al., 1998; Thompson et al., 1997). Because we assumed that the patients with the A1A1 genotype might have the lowest density of dopamine receptor in the brain compared to patients with the other genotypes and the difference in the density might affect the clinical response to aripiprazole, we compared the two genotype groups in the present study.

To investigate the effect of the previous clinical course on the clinical response, we also compared the data from patients who had the first episode with the data from patients who had recurrent episodes.

Independent t-tests were employed to evaluate group differences in continuous data (e.g., age). Categorical data (e.g., sex) were analyzed using chi-square tests.

The primary and secondary efficacy parameters and plasma prolactin level were tested by mixed effects models. The mixed effects models were fit with fixed effects for the group (modeled as a dummy variable: the genotype group, 1 = A1A1, 2 = A1A2 + A2A2; the episode group, 1 = first, 2 = recurrent) and the weeks after starting the treatment phase and with random effects for patients.

The risk of drop-out according to the genotype group was analyzed with the Cox proportional hazard regression model.

3. Results

3.1. Patients

A total of 300 patients were enrolled in the APLUS, and 90 patients consented to participation in the pharmacogenetic study. Among them, 14 patients were homozygous for the variant-type allele (A1A1), 51 patients were heterozygous (A1A2), and 25 patients were homozygous for wild-type allele (A2A2). The allele distribution was in Hardy–Weinberg equilibrium ($\chi^2 = 2.04, df = 1, p = 0.16$). There were no significant differences in the demographic characteristics between the two genotype groups (Table 1).

In all, 64 patients (A1A1: n = 13, A1A2 + A2A2: n = 51) completed the 26-week study period, and the risk of drop-out was not different according to the genotype group (A1A1 vs A1A2 + A2A2; OR = 0.604; 95% CI = 0.39 – 1.22; $p = 0.16$).

Eighty one patients took concomitant medications during the study, but the percentage of patients with concomitant medications was not different between the two genotype groups (Table 2).

3.2. Efficacy data

The mean dose (SD) of aripiprazole was 22.1 ± 7.3 mg/d (A1A1: 20.6 ± 7.1 mg/d, A1A2 + A2A2: 22.4 ± 7.4 mg/d) and
was not different between the two genotype groups ($t=0.811$, $df=88$, $p=0.420$).

The PANSS total score ($\pm SD$) at baseline was $100.7 \pm 22.7$ (A1A1: $102.8 \pm 19.4$; A1A2+A2A2: $100.3 \pm 23.3$), and there was no significant difference in the PANSS total score at baseline between the two genotype groups ($t=-0.371$, $df=88$, $p=0.712$).

When assessed with the PANSS, there were no patients whose psychotic symptoms worsened during the treatment with aripiprazole. The ratio of the PANSS total score decreased as the treatment with aripiprazole progressed, and the change in the ratio was significantly different according to the genotype group (week: $F=3.323$, $df=4,289$, $p=0.011$) (Fig. 1).

The change in the raw PANSS score also differed according to the genotype group (week: $F=84.453$, $df=4,277$, $p<0.001$; genotype: $F=3.294$, $df=1,93$, $p=0.073$; week×genotype: $F=2.825$, $df=4,277$, $p=0.025$) (Fig. 2).

As in the case of the total score, the ratios of the PANSS positive (week: $F=65.469$, $df=4,283$, $p<0.001$; genotype: $F=5.599$, $df=1,112$, $p=0.020$; week×genotype: $F=3.142$, $df=4,283$, $p=0.266$) and negative (week: $F=57.569$, $df=4,288$, $p<0.001$; genotype: $F=9.699$, $df=1,110$, $p=0.002$; week×genotype: $F=3.434$, $df=4,288$, $p=0.009$) symptom subscale score differed significantly according to the genotype group. However, the result for the PANSS general psychopathology subscale was not significantly different between the two genotype groups (week: $F=17.625$, $df=4,288$, $p<0.001$; genotype: $F=0.274$, $df=1,119$, $p=0.601$; week×genotype: $F=0.119$, $df=4,288$, $p=0.922$) (Fig. 1).

The mean CGI-S score ($\pm SD$) at baseline was $5.4 \pm 1.2$ (A1A1: $5.4 \pm 1.1$; A1A2+A2A2: $5.4 \pm 1.2$), and there was no significant difference in the CGI-S score at baseline between the two genotype groups ($t=0.030$, $df=87$, $p=0.976$). The change in the CGI-S score was not significantly different according to the genotype group (week: $F=46.144$, $df=4,287$, $p<0.001$; genotype: $F=1.277$, $df=1,106$, $p=0.261$; week×genotype: $F=0.369$, $df=4,287$, $p=0.830$). The results for the change in the CGI-I score were similar to those in the CGI-S score (week: $F=14.151$, $df=4,284$, $p<0.001$; genotype: $F=2.239$, $df=1,104$, $p=0.138$; week×genotype: $F=0.462$, $df=4,284$, $p=0.763$).

We also analyzed the clinical response according to the previous clinical course. There were 33 patients with the first episode and 57 patients with recurrent episodes. The PANSS total scores ($\pm SD$) at baseline were $101.2 \pm 22.2$ in the first episode and $100.4 \pm 23.1$ in the recurrent episode group, respectively. There was no significant difference in the PANSS

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### Table 1. Demographic characteristics at baseline

<table>
<thead>
<tr>
<th>Genotype</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1A1</td>
<td>A1A2+A2A2</td>
</tr>
<tr>
<td>Subject (n)</td>
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<tr>
<td>Sex (%)</td>
<td>p=0.885a</td>
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<tr>
<td>Male</td>
<td>42.9</td>
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<tr>
<td>Female</td>
<td>57.1</td>
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<tr>
<td>Age±SD (years)</td>
<td>38.6±11.0</td>
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<tr>
<td>Diagnosis (%)</td>
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<td>Schizophrenia</td>
<td>85.8</td>
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<tr>
<td>Schizoaffective</td>
<td>7.1</td>
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<tr>
<td>Episode (%)</td>
<td>p=0.260a</td>
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<tr>
<td>First</td>
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</tr>
<tr>
<td>Recurrent</td>
<td>50.0</td>
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<tr>
<td>Previous medication (%)</td>
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<td>Typical AP</td>
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<tr>
<td>Olanzapine</td>
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<tr>
<td>Quetiapine</td>
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</tr>
<tr>
<td>Amisulpride</td>
<td>14.3</td>
</tr>
<tr>
<td>Others</td>
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<td>Illness duration±SD (month)</td>
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<tr>
<td>116.9±131.5</td>
<td>97.0±94.4</td>
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<tr>
<td>Number of admission±SD</td>
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<td>3.3±3.2</td>
<td>2.9±2.7</td>
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<tr>
<td>Symptom rating score±SD</td>
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<tr>
<td>PANSSc</td>
<td>102.8±19.4</td>
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<tr>
<td>CGI-Sd</td>
<td>5.4±1.1</td>
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<tr>
<td>SASd</td>
<td>13.9±6.7</td>
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<tr>
<td>AIMSf</td>
<td>0.4±1.6</td>
</tr>
<tr>
<td>BASf</td>
<td>0.9±1.6</td>
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<tr>
<td>Plasma prolactin level±SD (ng/ml)</td>
<td></td>
</tr>
<tr>
<td>23.8±27.4</td>
<td>24.6±29.1</td>
</tr>
</tbody>
</table>

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### Table 2. Number of patients who took concomitant medication at least once during the study

<table>
<thead>
<tr>
<th>Genotype</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1A1</td>
<td>A1A2+A2A2</td>
</tr>
<tr>
<td>(n=14)</td>
<td>(n=76)</td>
</tr>
<tr>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Antipsychoticsb</td>
<td>2</td>
</tr>
<tr>
<td>Antidepressantc</td>
<td>0</td>
</tr>
<tr>
<td>Benzodiazepined</td>
<td>11</td>
</tr>
<tr>
<td>Anti-EPS agentd</td>
<td>9</td>
</tr>
<tr>
<td>Mood stabilizerf</td>
<td>2</td>
</tr>
<tr>
<td>Zolpidem, trazodone</td>
<td>7</td>
</tr>
</tbody>
</table>

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*aChi-square test.*

*bAmisulpride, chlorpromazine, clozapine, haloperidol, nemonapride, quetiapine, risperidone, sulpiride.*

*cAmirtriptiline, bupropion, citalopram, venlafaxine, fluvoxamine, mirtazapine.*

*dAlprazolam, clonazepam, diazepam, flurazepam, lorazepam, triazolam.*

*eBenztropine, trihexyphenidyl.*

*fLithium, topiramate.*
The changes in the ratios of PANSS scores according to the genotype after the treatment with aripiprazole. Ratio of PANSS score ($t$) = PANSS score at week $t$ / PANSS score at baseline. A: week: $F = 106.219$, $df = 4,289$, $p < 0.001$; genotype: $F = 10.544$, $df = 1,115$, $p = 0.002$; week $\times$ genotype: $F = 3.323$, $df = 4,289$, $p = 0.011$. B: week: $F = 65.469$, $df = 4,283$, $p < 0.001$; genotype: $F = 5.595$, $df = 1,112$, $p = 0.020$; week $\times$ genotype: $F = 1.312$, $df = 4,283$, $p = 0.266$. C: week: $F = 57.569$, $df = 4,288$, $p < 0.001$; genotype: $F = 9.699$, $df = 1,110$, $p = 0.002$; week $\times$ genotype: $F = 3.434$, $df = 4,288$, $p = 0.009$. D: week: $F = 17.625$, $df = 4,288$, $p < 0.001$; genotype: $F = 0.274$, $df = 1,119$, $p = 0.601$; week $\times$ genotype: $F = 0.229$, $df = 4,288$, $p = 0.922$.

Among the secondary efficacy parameters, the changes in the ratio of the negative symptom subscale score and CGI-S (week: $F = 6.682$, $df = 1,117$, $p = 0.011$; week $\times$ episode: $F = 2.245$, $df = 4,292$, $p = 0.064$) (Fig. 3).

Among the secondary efficacy parameters, the changes in the ratio of the positive symptom (week: $F = 2.526$, $df = 4,287$, $p = 0.041$) and the general psychopathology (week: $F = 34.326$, $df = 4,290$, $p < 0.001$; episode: $F = 7.568$, $df = 1,121$, $p = 0.007$; week $\times$ episode: $F = 2.212$, $df = 4,290$, $p = 0.068$) sub-scale scores, and CGI-I (week: $F = 88.316$, $df = 4,289$, $p < 0.001$; episode: $F = 5.202$, $df = 1,107$, $p = 0.025$; week $\times$ episode: $F = 1.111$, $df = 4,289$, $p = 0.352$) and CGI-I (week: $F = 3.380$, $df = 3,163$, $p < 0.001$; episode: $F = 6.268$, $df = 1,80$, $p = 0.014$; week $\times$ episode: $F = 3.018$, $df = 3,163$, $p = 0.032$) were significantly different between the two groups. The CGI-I score at baseline did not differ according to the previous clinical course ($t = 0.149$, $df = 88$, $p = 0.611$). The change in the ratio of the negative symptom subscale score was not different between the first episode group and the recurrent episode group ($t = 0.149$, $df = 88$, $p = 0.882$).

We compared the data from the patients having the A1A1 genotype and recurrent episodes with those from the other patients (Fig. 4). The change in the ratio of the PANSS total score was significantly different between the two groups (week: $F = 167.734$, $df = 4,292$, $p < 0.001$; genotype $\times$ episode: $F = 17.357$, $df = 1,117$, $p < 0.001$; week $\times$ genotype $\times$ episode: $F = 4.952$, $df = 4,292$, $p = 0.001$).

### 3.3. Extrapyramidal symptoms

The change in the SAS score from baseline to week 4 was different between the two genotype groups (week: $F = 6.589$, $df = 1,120$, $p = 0.011$; genotype: $F = 1.289$, $df = 1,120$, $p = 0.258$; week $\times$ genotype: $F = 5.150$, $df = 1,120$, $p = 0.025$) (Fig. 5). A separate analysis based on the previous clinical course revealed that the result for patients with recurrent episodes ($n = 56$) was similar to the result of the pooled analysis (week: $F = 13.038$, $df = 1,64$, $p = 0.001$; genotype: $F = 6.575$, $df = 1,64$, $p = 0.013$; week $\times$ genotype: $F = 8.452$, $df = 1,64$, $p = 0.005$), but the result for patients with the first episode ($n = 33$) was not (week: $F = 0.644$, $df = 1,46$, $p = 0.427$; genotype: $F = 3.352$, $df = 1,46$, $p = 0.074$; week $\times$ genotype: $F = 0.644$, $df = 1,46$, $p = 0.427$) (Fig. 5). Among patients with the A1A1 genotype,
patients with recurrent episodes ($n = 7$) showed higher SAS scores at baseline than patients with the first episode ($n = 7$) ($t = 2.573$, $df = 6$, $p = 0.042$).

The scores of the AIMS (±SD) were 1.5±9.6 at baseline (A1A1: 0.4±1.6, A1A2+A2A2:1.7±10.4) and 1.3±9.6 at week 4 (A1A1: 0.0±0.0, A1A2+A2A2:1.7±10.4). The AIMS scores were not different according to the genotype group (baseline: $t = 0.445$, $df = 88$, $p = 0.658$; week 4: $t = 0.538$, $df = 86$, $p = 0.592$).

In the case of the BAS, the scores (±SD) were 1.0±1.8 at baseline (A1A1: 0.9±1.6, A1A2+A2A2: 1.0±1.8) and 1.2±2.2 at week 4 (A1A1: 1.6±2.8, A1A2+A2A2: 1.1±2.0). The BAS scores were not different between the two genotypes (baseline: $t = 0.210$, $df = 88$, $p = 0.834$; week 4: $t = 0.800$, $df = 86$, $p = 0.426$).

The changes in the AIMS (week: $F = 1.076$, $df = 1,143$, $p = 0.301$; genotype: $F = 0.640$, $df = 1,143$, $p = 0.425$; week × genotype: $F = 0.312$, $df = 1,143$, $p = 0.577$) and BAS (week: $F = 0.773$, $df = 1,164$, $p = 0.381$; genotype: $F = 0.206$, $df = 1,164$, $p = 0.651$; week × genotype: $F = 0.562$, $df = 1,164$, $p = 0.455$) scores from baseline to week 4 did not differ according to the genotype group.

3.4. Plasma prolactin level

The plasma prolactin levels (±SD) were 24.5±28.7 ng/ml at baseline (A1A1: 23.8±27.4 ng/ml, A1A2+A2A2: 24.6±29.1 ng/ml), 5.4±5.5 ng/ml at week 8 (A1A1: 3.1±2.7 ng/ml, A1A2+A2A2: 5.8±5.8 ng/ml), and 17.9±37.6 ng/ml at week 26 (A1A1: 13.1±19.8 ng/ml, A1A2+A2A2: 18.8±40.3 ng/ml).

The plasma prolactin levels were not significantly different according to the genotype group (baseline: $t = 0.090$, $df = 82$, $p = 0.929$; week 8: $t = 1.565$, $df = 69$, $p = 0.122$; week 26: $t = 0.388$, $df = 47$, $p = 0.700$).

The changes in the plasma prolactin level were not different between the two genotype groups (week: $F = 6.387$, $df = 3,127$, $p = 0.002$; genotype: $F = 0.319$, $df = 1,78$, $p = 0.574$; week × genotype: $F = 0.131$, $df = 3,143$, $p = 0.942$).

4. Discussion

We did not find any significant differences in the demographic characteristics between the two genotype groups. In addition, the daily dosage of aripiprazole and the drug compliance, inferred from the risk of drop-out, were not different according to the genotype group. These results suggest that the difference in the clinical response to aripiprazole between the two groups may result from the genotypic difference.

Patients with the A1A1 genotype exhibited a more favorable therapeutic response to aripiprazole when assessed using the PANSS ratio (Fig. 1). The difference in the clinical response

![Figure 2](image-url)
as seen in the present study was anticipated by the previous study, which reported the difference in the frontal metabolic response to aripiprazole according to the DRD2 Taq1A genotype (Kim et al., 2008). Given earlier findings that changes in the frontal activity, expressed in terms of glucose metabolic rate, after the administration of antipsychotic drugs have been associated with the effects of antipsychotic drugs (Bartlett et al., 1998; Ngan et al., 2002), different changes in the frontal metabolism after the administration of aripiprazole suggested the possibility of the present results.

The present results are also in accordance with the findings of previous studies regarding the effects of the DRD2 Taq1A polymorphism on the clinical response to antipsychotic drugs. Schafer et al. (2001) reported that patients without the A1 allele showed poorer clinical responses to haloperidol than patients with the A1 allele. Moreover, nemonapride, a selective dopamine antagonist, also exhibited more favorable therapeutic effects in schizophrenic patients with the A1 allele (Suzuki et al., 2000).

In contrast to the PANSS score, the change in the CGI score did not appear to be influenced by the DRD2 Taq1A genotype. This may be ascribed to the CGI itself, as it only consists of one item on a 7-point scale and may therefore be too crude to detect a genotypic effect on the clinical response to...
aripiprazole; in contrast, the PANSS includes 30 items on a 7-point scale. In other words, the clinical impact of the DRD2 Taq1A genotype may be not enough to be observed by the CGI.

In a recent report, the Taq1A polymorphism was found to reside within a novel kinase gene, designated ankyrin repeat and kinase domain containing 1 protein (ANKK1). The Taq1A polymorphism was reported to substitute an amino acid within the 11th ankyrin repeat of ANKK1, which might affect substrate-binding specificity (Neville et al., 2004).

An association between the DRD2 density in the brain and the Taq1A polymorphism has been reported (Jonsson et al., 1999; Noble et al., 1991; Pohjalainen et al., 1998; Thompson et al., 1997). However, the mechanism by which the ANKK1 gene, having the Taq1A polymorphism, influences the DRD2 gene remains obscure. A recent study suggested that the Taq1A polymorphism might affect the DRD2 gene through other polymorphisms. The Taq1A polymorphism was reported to be in linkage disequilibrium with C957T, a synonymous mutation in the DRD2 gene (Duan et al., 2003; Hirvonen

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**Figure 5** The changes in Simpson–Angus Scale (SAS) score from the baseline to week 4 after the treatment with aripiprazole. A: week: $F = 6.589$, $df = 1,120$, $p = 0.011$; genotype: $F = 1.289$, $df = 1,120$, $p = 0.258$; week×genotype: $F = 5.150$, $df = 1,120$, $p = 0.025$. B: week: $F = 13.038$, $df = 1,64$, $p = 0.001$; genotype: $F = 6.575$, $df = 1,64$, $p = 0.013$; week×genotype: $F = 8.452$, $df = 1,64$, $p = 0.005$. C: week: $F = 0.644$, $df = 1,46$, $p = 0.427$; genotype: $F = 3.352$, $df = 1,46$, $p = 0.074$; week×genotype: $F = 0.644$, $df = 1,46$, $p = 0.427$. 

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et al., 2004). Although the C957T polymorphism does not affect the amino-acid sequence, it alters messenger ribonucleic acid (mRNA) folding, resulting in decreased mRNA stability and translation, and dramatically diminishes dopamine-induced up-regulation of DRD2 expression. This molecular mechanism could explain the previous finding that individuals with the A1 allele had a reduced density of the brain DRD2 (Jonsson et al., 1999; Noble et al., 1991; Pohjalainen et al., 1998; Thompson et al., 1997).

As a result of fewer DRD2, patients with the A1A1 genotype may have more DRD2 occupied by aripiprazole and less free and unbound DRD2 at any dosage of the antipsychotic drug. Dopamine receptor drug occupancy and consequent receptor blockade by antipsychotic drugs are necessary to achieve an antipsychotic effect (Kapur and Remington, 2001; Kapur et al., 2000). In addition, the findings of an in vitro study indicated that partial agonists behaved like antagonists under lower receptor density conditions, and like agonists under higher receptor density conditions (McDonald et al., 2003). Considering the above (Kapur and Remington, 2001; Kapur et al., 2000; McDonald et al., 2003), as shown in the present results, patients with the A1A1 genotype may exhibit a more favorable therapeutic response to aripiprazole, and although we could not observe patients with symptomatic aggravations after the treatment with aripiprazole, there is a possibility that some patients with the other genotypes, which are related with higher dopamine receptor density compared to the A1A1 genotype, might show symptomatic aggravations as in the previous reports (DeQuardo, 2004; Raja, 2006; Ramaswamy et al., 2004; Reeves and Mack, 2004), by the medium of dopamine agonism of aripiprazole under higher receptor density conditions.

The clinical response to aripiprazole was influenced by the previous clinical course as well as the genotype. Patients with the first episode may be different from patients with recurrent episodes in many clinical aspects such as the duration of illness, history of exposure to antipsychotic drugs, and so on. Among them, the history of exposure to antipsychotic drugs was definitely different between the first episode group and the recurrent episode group. Therefore, our results suggest that the previous exposure to antipsychotic drugs might affect the clinical response to aripiprazole. It was reported that the dopamine receptor density increased after the treatment with antipsychotic drugs (Silvestri et al., 2000). Given the finding, patients with recurrent episodes, who had much exposure to antipsychotic drugs, may have higher dopamine receptor density than patients with the first episode, which may lead to the different clinical response to aripiprazole according to the previous clinical course. This finding can be a supportive evidence for the mechanism of the DRD2 Taq1A genotypic effect on the clinical response to aripiprazole.

We could observe the difference in the SAS score change from baseline to week 4 between the two genotype groups. Although the difference is statistically significant, it is not enough to draw any definite conclusion from the result, as the significant difference was not observed in the other EPS scales and prolactin level. The inconsistent results might be partly attributed to the study design, which was primarily intended to detect the difference in the symptomatic change. However, the result deserves attention, because the different changes in the SAS score appear to result from the higher scores at baseline of patients with the A1A1 genotype and recurrent episodes. Although it cannot be conclusive, the finding raises a possibility that patients with the A1A1 genotype may be more vulnerable to extrapyramidal symptoms after long-term exposure to antipsychotic drugs. Guzey et al. (2007) found an association between the A1 allele and extrapyramidal symptoms, which is a supportive result. In addition, Alenius et al. (2007) reported that patients with the A1 allele more often had significant side effects from strong DRD2 antagonistic drugs. In contrast, Zai et al. (2006) reported a conflicting result that the T957 variant was associated with a decreased incidence and severity of tardive dyskinesia and speculated that the decreased DRD2 levels resulting from the T-allele might decrease tardive dyskinesia susceptibility and severity. Consequently, the findings reported to date encourage further pharmacogenetic research regarding extrapyramidal symptoms and DRD2 polymorphisms.

In summary, the Taq1A polymorphism status may be associated with the clinical response to aripiprazole. Our results suggest that the Taq1A polymorphism can, in part, explain inter-individual variation in the clinical response to aripiprazole.

This is the first prospective study to show an association between the Taq1A polymorphism status and the variation in the clinical response to aripiprazole. However, the present study has some limitations. As seen in the changes of the SAS score, we could not exclude the effects of previous medication on the clinical response to aripiprazole. In addition, although we reported the effect of the Taq1A polymorphism on the clinical response to aripiprazole, our sample size does not appear to be sufficient to confirm the result. In the future, a pharmacogenetic study that is not a subgroup study needs to be designed to evaluate the genotypic effect in a larger patient group. Finally, most of the studies that reported an effect of the Taq1A polymorphism on the clinical response to antipsychotic drugs analyzed the response in Asian patients (Mihara et al., 2000, 2001; Suzuki et al., 2001, 2000). To verify the results of the present study, it should be replicated in other ethnic groups.

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Contributors

Kwon J.S. designed the study, interpreted the results, and wrote the first draft of the manuscript. Kim E. managed the literature search and analysis, and participated in the interpretation of the results. Kang D.H. helped design the study. Choi J.S. helped the analysis of data. Yu K.S. performed the determination of the DRD2 Taq1A polymorphism. Jang I.J. and Shin S.G. helped design the study and supervised the determination of the polymorphism. The APLUS group collected data. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors have no conflict of interest.
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