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Association between the Alu Insertion/Deletion Polymorphism in the Tissue-Type Plasminogen Activator Gene and Mirtazapine Response in Koreans with Major Depression

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Objectives To determine the relationship between the Alu insertion/deletion (I/D) polymorphism in the tissue-type plasminogen activator (tPA) gene and the clinical outcome of mirtazapine treatment in Korean major depressive disorder (MDD) patients.
Methods We enrolled 422 patients in this study. Symptoms were evaluated using the 21-item Hamilton Depression Rating (HAMD-21) Scale. After 1, 2, 4, and 8 weeks of mirtazapine treatment, the association between the Alu I/D polymorphism in the tPA gene and remission/response outcomes were evaluated.
Results The proportion of I/I homozygotes in responders was higher than that in non-responders, whereas the proportion of D/D homozygotes in responders was lower than that in non-responders at 8 weeks of treatment ($p = 0.032$, OR = 1.57). The percentage decline of HAMD-21 scores in I allele carriers was larger than that of D/D homozygotes at 2 and 8 weeks of treatment ($p = 0.035$ and 0.007, respectively). I allele carriers were associated with remission at 8 weeks of treatment ($p = 0.047$, OR = 2.2).
Conclusions These results show that treatment response and remission to mirtazapine were associated with the Alu I/D polymorphism of the tPA gene. This suggests the Alu I/D polymorphism may be a potential genetic marker for the prediction of therapeutic response to mirtazapine treatment in patients with MDD.

Key Words Major depressive disorder · Tissue type plasminogen activator · Alu insertion/deletion · Genetic polymorphism · Mirtazapine treatment response.

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Introduction

Evidence has been accumulating regarding the role of brain-derived neurotrophic factor (BDNF) in the pathophysiology of psychiatric disorders in recent years. In both the central nervous system (CNS) and peripheral nervous system (PNS), BDNF plays a critical role in the differentiation and survival of neurons during embryonic development as well as in the maintenance of neuronal viability during adulthood.[1-3] BDNF expression may also be associated with the mechanisms of action of antidepressants; multiple studies have suggested that BDNF gene expression can be a downstream target of various antidepressants.[4-7] In addition, the BDNF gene is known to play a critical role in the development of the serotonergic system, a major neurotransmitter system and a target in the treatment of patients with major depressive disorder (MDD).[8] Thus, BDNF may have a role in therapeutic improvement in depression and may protect from stress-induced neuronal damage.[9-12]

Recent evidence suggests that tissue-type plasminogen activator (tPA) and the plasminogen system play a key role in the proteolysis of proBDNF in the brain.[13][14] The mature form of BDNF is derived from proBDNF by proteolytic cleavage.[15] Therefore, in addition to the role of BDNF in the pathogenesis of MDD, a hypothesis that implicates tPA dysfunction in MDD may also explain the reason antidepressants increase BDNF transcription,[16][17] and occasionally cannot improve or can even worsen symptoms of major depression. Recently, associations between tPA and MDD have also been demonstrated in clinical, as well

as animal, studies. In mice subjected to acute restraint stress, tPA activity was rapidly up-regulated in the central and medial amygdala, while mice in which the tPA gene had been disrupted did not show anxiety and showed attenuated neuronal remodeling after repeated stress.[18] As stress is a major factor affecting mood states and tPA is also critical for the stress reaction, this finding implies the role of tPA in MDD following stressful life events. In fact, the association between patients with MDD and lower plasma levels of tPA has been previously reported. One study revealed that subjects with depression showed significantly lower plasma tPA concentrations when compared with healthy controls.[19] Another study showed that baseline plasma tPA levels were significantly lower in geriatric patients with depression compared to controls.[20] These findings suggest that the tPA gene and its relationship with susceptibility to depression and antidepressant response should be further studied.

Mature tPA, with an inferred sequence of 527 amino acids, is a single-chain glycoprotein.[21][22] The gene for human tPA has been mapped to 8p12-q11.2[23] and its complete sequence of 33 kilobases (kb) has been established.[24] Several polymorphisms of the tPA gene, which consists of the presence or absence of a 311-bp Alu sequence in intron 8, have been identified.[25] The Alu-repeat insertion probably arose early in human evolution, and a number of populations have been found to be dimorphic for its presence or absence.[26] The Alu-repeat insertion may also be closely linked to a mutation at or near the tPA gene that produces a functional effect, and an Alu-repeat insertion/deletion (I/D) event can alter mRNA stability and splicing.[27] Based on this, many studies have focused on the Alu I/D polymorphism's (rs4646972) association with several diseases, including ischemic stroke[28] and multiple sclerosis.[29][30] A similar polymorphism in the angiotensin converting enzyme (ACE) gene has been previously studied, demonstrating association with various neuropsychiatric disorders, such as dementia[31] and depression.[32][33] However, the Alu I/D genetic polymorphism in the tPA gene has not yet been studied in MDD. Thus, studies of genetic polymorphisms of the tPA gene, and their association with the risk of MDD and antidepressant treatment response, may provide genetic markers for predicting individual response to antidepressant treatment.

Mirtazapine is a tetracyclic antidepressant drug that is noradrenergic and a specific serotonergic antidepressant (NaSSa); it enhances noradrenergic transmission through blockade of α2-adrenoceptors.[34] Mirtazapine also enhances serotonergic transmission indirectly through noradrenergic stimulation of α1-adrenoceptors and blockade of α2-heteroreceptors.[35][36] In addition, mirtazapine blocking both 5-HT2 and 5-HT3 receptors leads to important advantages in both its therapeutic and tolerability profiles. For instance, the 5-HT2-blocking effect is thought to contribute to the anxiolytic effects of mirtazapine and its beneficial effects on sleep.[37] However, some patients still have intolerable side effects or poor response after mirtazapine treatment. In our previous study, we observed an increase in plasma BDNF after mirtazapine treatment in patients with MDD. However, BDNF polymorphism was not significantly associated with treatment response to mirtazapine.[38] Thus, the present study aimed to determine the relationship between the Alu I/D polymorphism in the tPA gene, which has a key role in regulation and expression of BDNF, and the clinical outcome of mirtazapine treatment in Korean MDD patients. We hypothesized that the Alu I/D polymorphism in the tPA gene may be associated with mirtazapine treatment response in patients with MDD.

Methods

Subjects

All subjects were recruited from outpatients visiting the Psychiatric Clinic of Korea University Anam Hospital and gave informed consent to participate in the study. Trained psychiatrists examined all subjects using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) and the Korean version of the Diagnostic Interview for Genetic Studies (K-DIGS). The severity of depression was assessed using the 21-item Hamilton Depression Rating (HAMD-21) Scale. As we intended to observe treatment response over the course of 8 weeks, subjects with moderate or severe depression were considered more appropriate for this study. Therefore, only subjects with a minimum score of 18 on the HAMD-21 Scale were enrolled.[39] The protocol was approved by the Ethics Committee of the Korea University Medical Center.

Patients with primary or comorbid diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, dementia, and alcohol or substance dependence based on DSM-IV criteria within the previous 6 months were excluded from the study. We also excluded patients with a personal or family history of substance abuse/dependence. Patients who were receiving psychotropic medications were subjected to a 2-week washout period. Demographic data, medical history, and laboratory data were documented. Patients with serious or unstable medical illness, such as seizures, brain lesions, cardiac problems, pregnancy, liver/kidney failure, and abnormal baseline laboratory values, were also excluded from the study. All subjects were at least 18 years of age.

Clinical assessment

A total of 422 patients were enrolled in this study from November 2009 to March 2012. During the study treatment period, all subjects took mirtazapine (Remeron® ; Schering-Plough, Kenilworth, NJ, USA) at a daily dose of 15–60 mg for 8 weeks. The daily dose was determined based on clinician judgment, considering the patient's initial tolerability, and potential adverse effects. Psychotropic drugs, such as benzodiazepines and mood stabilizers, were not permitted.

Clinical symptoms were evaluated using the HAMD-21 Scale at baseline and after 1, 2, 4, and 8 weeks of treatment. The HAMD-21 was performed and managed by a single trained rater, and the rater and genotyper were both blinded. At baseline, 422 patients with MDD were enrolled. At week 1, 329 patients of whom were initially enrolled participated, 282 patients remained at week 2, 240 patients at week 4, and 205 patients at week 8. The reasons for withdrawal included intolerable adverse effects (23.9%), insufficient improvement of symptoms (7.4%), non-attendance to scheduled visits (34.4%), economic problems (15.3%), another medical conditions (1.8%), and discontinuation of medication due to improvement of symptoms (17.2%). Responders were those who showed a ≥ 50% decrease in HAMD-21 score compared to baseline, and remission status was defined as a HAMD-21 total score of 7 points or less.[40)41)] Udvalg for Klinske Undersogelser (UKU) Side Effect Rating Scale (UKU-SERS) was used to evaluate the side-effect profile.[42)]

Genotyping for the tPA Alu I/D polymorphism

Genotypes of the tPA Alu I/D were analyzed using genomic DNA extracted from peripheral blood mononuclear cells of study subjects using polymerase chain reaction (PCR) with minor modifications to the methods described by Tishkoff et al.[26)] PCR was performed using the following primers : sense, 5'-GTG AAA AGC AAG GTC TAC CAG-3' ; antisense, 5'- GAC ACC GAG TTC ATC TTG AC-3'. The amplification mixture contained 10 pmol of each primer, 200 μM of each dNTP, 50 mM KCl, 10 mM Tris. HCl (pH8.4), 3 mM MgCl2, 0.5 units Taq DNA polymerase (iNtRON Biotechnology, Seoul, Korea), and 100 ng genomic DNA. The samples were subjected to 30 cycles consisting of 1 min at 94°C, 1 min at 60°C, and 1 min at 72°C in a thermal cycler (TaKaRa Bio Inc., Shiga, Japan). A 10 μl sample of the reaction product was analyzed on a 2.0% agarose gel. Following electrophoresis, the DNA was visualized with ethidium bromide. The amplified 570- and 260-bp fragments corresponded to the insertion and deletion allele, respectively.

Statistical analysis

The Hardy–Weinberg equilibrium for the tPA Alu I/D polymorphism was tested using the chi-square test. The genetic association of the polymorphism was analyzed using a multiple logistic regression and generalized linear model (GLM) type III for categorical data and continuous variables, respectively, controlling for age and sex as covariates. To compensate for the missing data caused by patient withdrawal, LOCF (last-observation-carried-forward) was applied for imputation of missing HAMD-21 scores. A p-value ≤ 0.05 was regarded as statistically significant. The power to detect associations given the sample size was analyzed using Power for Genetic Association Analyses (PGA).[43)] All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics of study subjects and hardy-weinberg equilibrium for the Alu I/D polymorphism

Table 1 summarizes patient data for mean age, age at onset, sex, previous history of depression, family history of depres-

Table 1. Demographic characteristics in the MDD intention-to-treat group

	tPA Alu genotype (n = 422)			p value
	Ins/Ins	Ins/Del	Del/Del	
Number of patients	153	192	77	0.221†
Age (year, mean ± gSE)	50.14 ± 1.15	51.78 ± 1.08	50.42 ± 1.64	0.551*
Onset age (year, mean ± nSE)	46.10 ± 1.25	47.81 ± 1.09	45.69 ± 1.68	0.454*
Sex (female, %)	122 (79.7)	138 (71.9)	61 (79.2)	0.182†
Previous history of depression (%)	57 (37.3)	74 (38.5)	38 (49.4)	0.216†
Family history of depression (%)	18 (11.8)	23 (12.0)	14 (18.2)	0.332†
Family history of other psychotic disease (%)	8 (5.2)	14 (7.3)	3 (3.9)	0.725†
Suicide attempt (%)	10 (6.5)	13 (6.8)	7 (9.1)	0.753†
Baseline HAMD-21 score (mean ± SE)	22.42 ± 0.37	22.91 ± 0.38	22.40 ± 0.56	0.538†

Genotype comparisons were made by *ANOVA and †chi-square test, ‡ : p values for Hardy-Weinberg Equilibrium (chi-square test, d.f. = 1). MDD : major depressive disorder, tPA : tissue-type plasminogen activator, Ins : insertion, Del : deletion, HAMD-21 : 21-item Hamilton Depression Rating

sion, family history of other psychotic disease, frequency of suicidal attempts, and baseline HAMD-21 scores. None of these parameters differed significantly among the three tPA Alu genotypes (I/I, I/D, and D/D). In addition, baseline HAMD-21 scores showed no significant differences between the three genotypes. Chi-square tests were applied to the three genotype frequencies, and the result revealed that the subjects were in Hardy-Weinberg equilibrium ($\chi^2 = 1.497$, p = 0.221). The clinical characteristics of the withdrawn subjects were not significantly different from the completers, and the tPA Alu I/D genotype of the withdrawn subjects did not significantly differ between reasons for withdrawal.

Association between Alu I/D polymorphism and mirtazapine treatment response in patients with MDD

Statistical analysis of the association between the Alu I/D polymorphism in the tPA gene and mirtazapine treatment response was performed. As shown in Table 2, a significant association between the Alu I/D genotype and treatment response was found after 8 weeks of mirtazapine treatment. In the codominant model, the proportion of I/I homozygote in responders was higher than that in non-responders, whereas the proportion of D/D homozygote in responders was lower than that in non-responders at 8 weeks of treatment [p = 0.032, odd ratio (OR) = 1.57 (1.04−2.38)]. This association was also found in allelic analysis [p = 0.029, OR = 1.59 (1.06−2.39) ; 59.4% vs. 47.9%, respectively]. In the recessive model, there was a trend of better response in I allele carriers compared to D/D homozygotes, but the result was not significant [p = 0.052, OR = 1.99 (0.99−3.99)]. There was no significant difference in treatment response among genotypes in the dominant model (between I/I genotype and I/D+D/D genotype). No significant difference was found in dropout rate among genotypes (data not shown).

In addition, we compared the percent decline of HAMD-21 scores following mirtazapine treatment between patients having D/D genotype and I allele carriers (Fig. 1). In the recessive model, the percent decrease of HAMD-21 scores was significantly larger in I allele carriers compared to that in patients having D/D genotype at 2 weeks of mirtazapine treatment, as well as at 8 weeks of treatment.

Association between the Alu I/D polymorphism and remission status by mirtazapine treatment

We also investigated the relationship between the tPA gene Alu I/D polymorphism and remission status following mirtazapine treatment. As shown in Table 3, tPA Alu I/D genotypes were associated with remission status at 8 weeks of treatment, with I allele carriers achieving a better remission status

Table 2. Association analysis of Alu I/D polymorphism in tPA gene with treatment response to mirtazapine in patients with MDD

Duration	Response status	Genotypes, n				Codom.		Dom.		Rec.		Allele frequencies, n				
		I/I	I/D	D/D	Total	p	OR	p	OR	p	OR	I	D	Total	p	OR
Week 1	Non-R	91 (33.1%)	129 (46.9%)	55 (20.0%)	275 (100%)	0.363	0.82 (0.54−1.25)	0.357	0.75 (0.41−1.38)	0.585	0.81 (0.37−1.75)	311	239	550	0.397	1.21 (0.79−1.84)
	R	21 (38.9%)	24 (44.4%)	9 (16.7%)	54 (100%)							66	42	108		
Week 2	Non-R	54 (30.5%)	84 (47.5%)	39 (22.0%)	177 (100%)	0.260	0.82 (0.58−1.16)	0.531	0.85 (0.50−1.42)	0.202	0.66 (0.35−1.25)	192	162	354	0.254	1.24 (0.88−1.75)
	R	37 (35.2%)	51 (48.6%)	17 (16.2%)	105 (100%)							125	85	210		
Week 4	Non-R	34 (35.4%)	40 (41.7%)	22 (22.9%)	96 (100%)	0.979	1.01 (0.69−1.46)	0.301	0.74 (0.42−1.30)	0.208	1.52 (0.79−2.93)	108	84	192	1.000	1.00 (0.69−1.45)
	R	42 (29.2%)	78 (54.2%)	24 (16.7%)	144 (100%)							162	126	288		
Week 8	Non-R	17 (23.6%)	35 (48.6%)	20 (27.8%)	72 (100%)	0.032*	1.57 (1.04−2.38)	0.108	1.71 (0.89−3.29)	0.052	1.99 (0.99−3.99)	69	75	144	0.029*	1.59 (1.06−2.39)
	R	47 (35.3%)	64 (48.1%)	22 (16.5%)	133 (100%)							158	108	266		

Obtained by logistic regression controlling for age and sex as covariates. Figures in parentheses indicate 95% confidence intervals unless stated otherwise. * : indicates p-value ≤ 0.05. I : insertion, D : deletion, Codom. : codominant model (I/I vs. I/D vs. D/D), Dom. : dominant model (I/I vs. I/D + D/D), Rec. : recessive model (I/I + I/D vs. D/D), OR : odds ratio, R : response, Non-R : nonresponse, MDD : major depressive disorder, tPA : tissue-type plasminogen activator

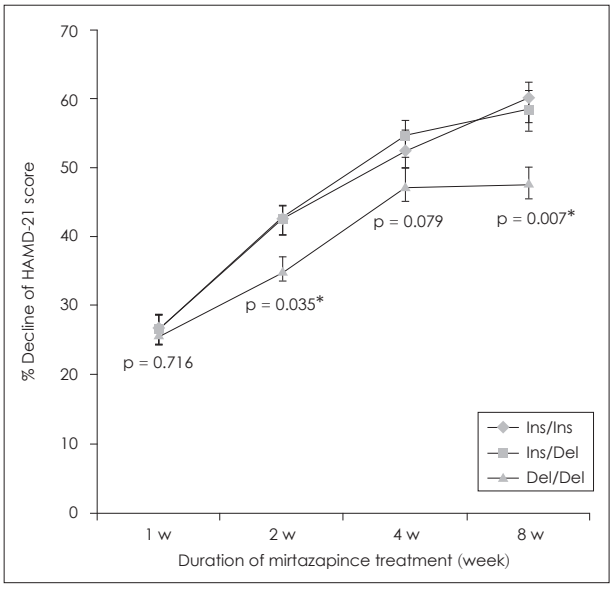

Fig. 1. Comparison of percent decline of Hamilton Depression Rating (HAMD-21) score following mirtazapine treatment at indicated period between tissue-type plasminogen activator Alu Ins/Del genotypes (Del/Del vs. Ins/Ins + Ins/Del). In the recessive model, the percent decrease of HAMD-21 scores was significantly larger in Ins allele carriers compared to that in patients having Del/Del genotype at 2 weeks of mirtazapine treatment (p = 0.035), as well as at 8 weeks of treatment (p = 0.007). The numbers above each time point indicate p-values, which were obtained using a type III generalized linear model age, with age of onset, sex, and starting dose of mirtazapine as covariates. * : p ≤ 0.05. Ins : insertion, Del : deletion.

compared to D/D homozygotes [p = 0.047, OR = 2.2 (1.01–4.80]. The proportion of I allele carriers was 86.8% in remitters at 8 weeks. In the allelic analysis, the frequencies of I allele were higher in remitters at 8 weeks than those in non-remitters, but no significant association was revealed [p = 0.123, OR = 1.40 (0.93–2.10)].

Discussion

In the present study, we observed that the Alu I/D polymorphism of the tPA gene was associated with mirtazapine treatment response and remission status, along with the decline of HAMD-21 scores. We found a significant association between mirtazapine treatment response and the Alu-repeat polymorphism in I allele carriers in the codominant model, and a trend of better response in I allele carriers in the recessive model. A significant finding was also revealed in the recessive model of the remission group. The percentage decline of HAMD-21 score was also significantly larger in I allele carriers. Our results suggest that the I allele of the Alu-repeat I/D polymorphism in the tPA gene is a favorable factor in the treatment of MDD using mirtazapine. To our knowledge, this is the first study that

Table 3. Association analysis of Alu I/D polymorphism in tPA gene with the remission status in mirtazapine-treated patients with MDD

Duration	Remission status	Genotypes, n				Codom.		Dom.		Rec.		Allele frequencies, n				
		I/I	I/D	D/D	Total	p	OR	p	OR	p	OR	I	D	Total	p	OR
Week 1	Non-R	109 (34.7%)	145 (46.2%)	60 (19.1%)	314 (100%)	0.247	1.53 (0.74–3.15)	0.257	2.11 (0.58–7.68)	0.468	1.55 (0.48–5.03)	363	265	628	0.259	0.64 (0.31–1.33)
	R	3 (20.0%)	8 (53.3%)	4 (26.7%)	15 (100%)							14	16	30		
Week 2	Non-R	76 (32.2%)	111 (47.0%)	49 (20.8%)	236 (100%)	0.659	0.91 (0.58–1.41)	0.935	1.03 (0.52–2.04)	0.379	0.68 (0.29–1.61)	263	209	472	0.647	1.13 (0.72–1.78)
	R	15 (32.6%)	24 (52.2%)	7 (15.2%)	46 (100%)							54	38	92		
Week 4	Non-R	56 (31.5%)	84 (47.2%)	38 (21.4%)	178 (100%)	0.406	0.84 (0.55–1.27)	0.983	1.01 (0.54–1.89)	0.136	0.53 (0.23–1.22)	196	160	356	0.401	1.21 (0.80–1.83)
	R	20 (32.3%)	34 (54.8%)	8 (12.9%)	62 (100%)							74	50	124		
Week 8	Non-R	38 (29.5%)	59 (45.7%)	32 (24.8%)	129 (100%)	0.128	1.37 (0.91–2.06)	0.553	1.20 (0.65–2.22)	0.047*	2.20 (1.01–4.80)	135	123	258	0.123	1.40 (0.93–2.10)
	R	26 (34.2%)	40 (52.6%)	10 (13.2%)	76 (100%)							92	60	152		

Obtained by logistic regression controlling for age and sex as covariates. Figures in parentheses indicate 95% confidence intervals unless stated otherwise. * : indicates p-value ≤ 0.05. I : insertion, D : deletion, Codom. : codominant model (I/I vs. I/D vs. D/D), Dom. : dominant model (I/I vs. I/D + D/D), Rec. : recessive model (I/I + I/D vs. D/D), OR : odds ratio, R : remission, Non-R : nonremission, MDD : major depressive disorder

investigated the association between the Alu I/D polymorphism and mirtazapine monotherapy, for a period of 8 weeks in a single ethnic group of Koreans who were diagnosed with MDD.

tPA is involved in the expression of mature BDNF, and plasminogen activator inhibitor-1 (PAI-1) plays a key role in the regulation of tPA.[44] Recently, Eskandari et al.[45] found that women with MDD had higher serum PAI-1 levels than normal controls. Previous studies examining BDNF and PAI-1 polymorphisms in MDD have reported the following findings. There was no significant association between the BDNF V66M polymorphism, which is known to influence mature BDNF expression, and response to mirtazapine treatment in a previous study we had conducted.[38] Another study focusing on the association between the PAI-1 4G/5G polymorphism and treatment response to mirtazapine, also could not find significant associations.[46] Therefore, in this study, we analyzed the association between the Alu I/D polymorphism in the tPA gene and mirtazapine treatment response in patients with MDD directly.

A previous study reported that, after 2 minutes of mental stress tPA release rates increased approximately 2-fold in all genotype groups. Moreover, subjects homozygous for the insertion polymorphism had a significantly higher release rate than both heterozygotes and subjects homozygous for the deletion polymorphism, with a graded increase in tPA release rate according to the number of I alleles.[47] This finding suggests that more tPA is released from subjects with the tPA Alu I/I genotype, compared to subjects with the deletion allele. A greater amount of mature BDNF is also produced in subjects homozygous for the insertion compared to subjects with the deletion allele. In line with these studies, our results suggest that higher levels of mature BDNF resulting from tPA expression in I allele carriers may facilitate response to mirtazapine treatment, and enhance therapeutic recovery rates from depression, compared to Alu D/D genotype carriers.

However, although we found a significant association between the Alu I/D polymorphism and remission status following mirtazapine treatment at 8 weeks, this association was not as significant in the allelic analysis. As both tPA and PAI-1 are involved in the tPA–plasminogen proteolytic cascade, this finding implies that the genetic interaction of tPA with PAI-1 or BDNF might have a decisive effect on remission, rather than tPA alone. As genetic variants of tPA and PAI-1 genes have been suggested to be risk factors for stroke, Babu et al.[28] investigated the association of the -7351 C/T polymorphism and Alu I/D polymorphism in the tPA gene and 4G/5G polymorphism in the PAI-1 gene. They reported that subjects with different tPA and PAI-1 genotype combinations displayed a significantly higher risk for overall ischemic stroke. However, when analyzed as independent covariates, no significant association was revealed. This result suggests how gene–gene interactions involving more variants may alter the susceptibility of particular subjects to a certain disease, and this may also be the case in MDD, since depression is a complex trait and does not follow Mendelian patterns.[48] In order to clarify this hypothesis, further research is required.

Our study has several limitations. Firstly, the total number of patients who completed the study (n = 205) was relatively low, along with the number of D allele homozygotes (n = 42). Thus, a similar analysis in a larger population group would be needed for replicating our results. Secondly, we investigated only the tPA Alu I/D polymorphism, and not all allelic combinations of the tPA Alu I/D polymorphism, which can be found in the Korean population. Therefore, to confirm the association between mirtazapine treatment response and tPA Alu I/D polymorphism, further genetic screenings and studies should be performed. Thirdly, as the study was conducted in a semi-naturalistic design, mirtazapine was titrated to a dosage considering treatment response and intolerable side effects. Finally, a placebo-controlled group was absent in this study.

Despite such limitations, the results of our study suggests the possibility that mirtazapine treatment response may be associated with tPA gene polymorphisms. Our study is meaningful as we have demonstrated the tPA Alu I/D polymorphism to be a favorable factor in predicting treatment response in MDD, which is a relatively novel finding. Due to several limitations and lack of previous related research, we cannot confirm the tPA Alu I/D polymorphism to be a definite predictor of mirtazapine treatment. Nevertheless, this is the first report on the association of tPA gene polymorphisms with clinical outcomes of mirtazapine treatment in patients with MDD. Moreover, our results suggest a better treatment response in I allele carriers, and support the hypothesis that this specific polymorphism influences the therapeutic action of mirtazapine in MDD. Future studies with larger sample sizes are needed in order to investigate the mechanistic hypotheses motivated by our results.

In conclusion, this study demonstrates that Alu I allele carriers of the tPA gene show better treatment response to mirtazapine monotherapy compared to D/D homozygotes. The determination of the genotype on the tPA Alu ID may be a useful genetic marker for predicting mirtazapine treatment response in patients with major depression, which may contribute when planning future treatment strategies.

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Conflicts of interest

The authors have no financial conflicts of interest.

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