Association between *ABCB1* Polymorphisms and Antidepressant Treatment Response in Taiwanese Major Depressive Patients

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Objective: The multidrug resistance 1 (*ABCB1*, *MDR1*) gene, encoding P-glycoprotein, is extensively distributed and expressed in various tissues, such as a blood-brain barrier transporter. P-glycoprotein plays an important role in controlling the passage of substances between the blood and brain. The current study aimed to investigate possible associations of functional *ABCB1* polymorphisms (C3435T, G2677T and C1236T) with response to antidepressant treatment and serum cortisol levels in Taiwanese patients with major depressive disorder (MDD).
Methods: We recruited 112 MDD patients who were randomized to fluoxetine (n=58, mean dose: 21.4±4.5 mg/day) or venlafaxine (n=54, 80.2±34.7 mg/day) treatment for 6 weeks. The 21-item Hamilton Depression Rating Scale (HDRS) was administered initially and biweekly after treatment, and cortisol levels were assessed initially and after 6-week antidepressant treatment.
Results: The initial HDRS scores and the HDRS scores after six weeks of antidepressant treatment were not significantly different among the different genotypes in each polymorphism of *ABCB1*. The percentage changes of HDRS scores over time were significantly different in the polymorphisms of *ABCB1* G2677T ($p=0.002$). MDD patients with the G/G genotype of *ABCB1* G2677T had a worse antidepressant treatment response. However, the polymorphisms of *ABCB1* genotypes were not significantly associated with cortisol levels before and after antidepressant treatment in MDD patients.
Conclusion: The results suggested that the variants of *ABCB1* may influence the short-term antidepressant response in MDD patients. Further details of the underlying mechanisms of *ABCB1* in antidepressant treatment remain to be clarified.

KEY WORDS: P-Glycoproteins; Antidepressive agents; Hydrocortisone; Major depressive disorder; Polymorphism.

INTRODUCTION

The ATP-binding cassette, sub-family B, member 1 (*ABCB1*) gene encodes P-glycoprotein (P-gp), which is extensively expressed in the intestinal epithelium, hepatocytes, renal proximal tubular cells, the adrenal gland and capillary endothelial cells comprising the blood-brain and blood-testis barriers.[1] As P-gp is located at the blood-brain barrier, it plays an important role in controlling the passage of substances into the brain and limits brain accumulation of many drugs, such as chemotherapy drugs and psychotropic drugs.[1-4]

The central nervous system bioavailability of anti-depressants may also be influenced by P-gp, which could result in an insufficient intracerebral concentration and a poor response to antidepressants.[5,6] In addition, previous studies have indicated that *ABCB1* gene polymorphisms may alter the P-gp efficiency with P-gp substrate antidepressants at the blood-brain barriers.[5] The three major single nucleotide polymorphisms (SNPs) at C3435T, G2677T, and C1236T of *ABCB1* have been associated with efflux pump efficiency and with predicting changes in the function of P-gp,[7] although these SNPs were controversially associated with substrates of selective serotonin reuptake inhibitors (SSRI) and with the serotonin norepinephrine reuptake inhibitors (SNRI) dose and response for major depressive disorder (MDD).[2,8-11] Moreover, as accumulating reports have shown interactions between P-gp and cortiso[1,12,13] the *ABCB1* genotype polymorphisms could influence the serum levels of cortisol in healthy controls.[12] Although the interaction may influence the antidepressant treatment response, there are few studies of

the relationship between *ABCB1* polymorphisms and cortisol in MDD patients treated with antidepressants.

Therefore, it has to be noted that so far no prospective study has proven a superior clinical effects of *ABCB1* polymorphisms on treatment and cortisol level. The current study not only aimed to investigate possible associations of functional *ABCB1* polymorphisms (C3435T [rs1045642], G2677T [rs2032582], and C1236T [rs1128503]) with response to antidepressant treatment, but also aimed to investigate the influence of *ABCB1* polymorphisms on cortisol levels before and after antidepressant treatment in Taiwanese patients with MDD.

METHODS

Subjects

We investigated 112 outpatients with MDD, all of whom fulfilled the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria and were interviewed using the Chinese version of the Mini International Neuropsychiatric Interview (MINI).[14] The institutional review board at the National Cheng Kung University Hospital approved the study proposal, and all patients signed an informed consent. The patients were excluded if they: (i) had taken monoamine oxidase inhibitors or any other antidepressants within two weeks prior to entering the study; (ii) matched the DSM-IV diagnosis criteria for substance abuse within the past three months; (iii) had organic mental disorders, mental retardation or dementia; (iv) had surgical conditions or major physical illnesses; (v) were pregnant or breast-feeding; and (vi) had any concomitant DSM-IV Axis I diagnoses together with somatic or neurologic illnesses interfering with psychiatric evaluation.

All of the patients were treatment-naive. Patients were randomly assigned to either the fluoxetine or venlafaxine extended-release treatment group. The dose of fluoxetine was initially 20 mg once daily and could be increased by 20 mg per day in divided doses to a maximal daily dose of 80 mg. The dose of venlafaxine was initially 37.5 mg once daily for 4 days, then titrated to 75 mg once daily, and could be increased by 75 mg in divided doses to a maximal daily dose of 225 mg. The average doses of fluoxetine and venlafaxine prescribed were 21.4±4.5 mg and 80.2±34.7 mg, respectively. Although the antidepressive mechanism of venlafaxine has both noradrenergic and serotonergic effects, it acts only on serotonergic transmission at low doses ($<$150 mg/day).[15] Thus, it suggested that fluoxetine and venlafaxine might act as the same mode of mechanism in this study. Lorazepam was the only concomitant medication allowed to be added, with a maximal dose of 6 mg per day.

All MDD patients were evaluated at weeks 0, 2, 4, and 6 using the 21-item Hamilton Depression Rating Scale (HDRS) by trained senior psychiatrists blind to the genetic data and treatment details. The therapeutic response was evaluated as the percentage of change in HDRS score (calculated by the difference in HDRS score before and after treatment divided by the score of HDRS before treatment). The same rater conducted the initial and the subsequent ratings for each patient.

SNP Detection

DNA was isolated using standard methods from blood drawn into K-EDTA tubes and stored at 4°C. Genomic DNA was extracted from each blood sample using a QIAamp DNA blood kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. The quality of the extracted genomic DNA was checked by agarose gel electrophoresis analysis. The DNA was stored at -80°C until use.

The SNPs of *ABCB1* (C3435T: rs1045642, G2677T: rs2032582 and C1236T: rs1128503) were analyzed using commercially-available TaqMan® SNP Genotyping Assays (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. Amplification and dis-

Table 1. Demographic characteristics of the patients

Characteristic	All (n=112)	Fluoxetine (n=58)	Venlafaxine (n=54)	*p* value*
Sex (male)	30 (26.8)	14 (24.1)	16 (29.6)	0.512
Age (yr)	39.7±12.4	41.7±12.0	37.5±12.5	0.074
Average daily dose (mg)	-	21.5±5.0	79.1±36.7	-
Initial HDRS score	25.1±5.8	24.3±5.7	25.9±6.0	0.135
After 6-week antidepressant treatment				
HDRS score	8.3±7.0	8.0±7.7	8.7±8.3	0.676
Change in HDRS score (%)	70.1±31.9	68.3±33.2	71.5±30.7	0.734

Values are presented as number (%) or mean±standard deviation.
HDRS, 21-item Hamilton Depression Rating Scale.
*Comparison between the fluoxetine and venlafaxine subgroups.

sociation were carried out using an ABI 7900HT fast re-al-time polymerase chain reaction (PCR) system (Applied Biosystems). The PCR system automatically calculated the negative derivative of the change in fluorescence. The SNP genotype of each tested sample was determined by a software program and was confirmed manually. In case of disagreement, the analysis was repeated.

Cortisol Level

All the MDD patients, who had fasted since midnight, reported to the research site at the Department of Psychiatry, National Cheng Kung University Hospital, and at 9:00 a.m. had blood drawn for analysis of the corti-sol level. The cortisol level was assessed using a commer-cial radioimmunoassay kit (sensitivity: 0.2 ng/dl) (Immulite Cortisol; DPC-Biermann GmbH, Bad Nauheim, Germany). The inter- and intra-assay coefficients of variation were <7.8% and <7.7%, respectively.

Statistical Analysis

We analyzed the data using the Statistical Package for Social Sciences software version 12.0 (SPSS Inc., Chicago, IL, USA). The observed and expected genotype frequen-cies were compared in order to ensure that the loci were in Hardy-Weinberg equilibrium using a chi-square good-ness-of-fit test. The Golden Helix® software (Golden Helix Inc., Bozeman, MT, USA) was applied to estimate pairwise linkage disequilibrium (LD) measures r^2 and D'. LD was assumed if a pair of SNPs had r^2 and D' values > 0.80. Categorical variables were expressed as numbers and percentages, and continuous variables as means±standard deviation unless otherwise specified. Categorical variables were assessed using chi-square tests, and continuous variables were assessed using *t*-tests or one-way ANOVA (followed by a *post hoc* LSD test). Data were analyzed using a last observation carried for-ward method, in which the last observation was entered for missing visits, and an observed-case method, which included only data available at each observation based on intent-to-treat sample (patients who received at least one

dose of study medication and had at least one HDRS eval-uation during therapy). The genotypes associated with a percentage change in the HDRS score over time and with cortisol level over time were analyzed using re-peated-measure ANOVA. The level of significance was set at 0.05 unless otherwise specified.

RESULTS

We consecutively enrolled 30 male (28.2%) and 82 fe-male patients, and the mean age was 39.7±12.4 years. The initial HDRS score was 25.1±5.8. The demographic char-acteristics of whom are shown in Table 1. The demo-graphic characteristics did not differ significantly be-tween the patients receiving fluoxetine and those receiv-ing venlafaxine. Moreover, the initial depressive symp-toms or treatment response were also not significantly dif-ferent between groups.

The genotype frequencies of *ABCB1* C3435T, G2677T, and C1236T in the current study did not depart sig-nificantly from Hardy-Weinberg equilibrium (*p*=0.661, *p*=0.089, and *p*=0.367). In addition, pairwise LD analysis showed that all three SNPs were at independent loci (r^2 and/or D' <0.80, Table 2). Thus, haplotype analysis was not performed. The genotype frequencies of the three *ABCB1* polymorphisms were not significantly different between the patients receiving fluoxetine and those re-ceiving venlafaxine (Table 3).

Although the initial total HDRS scores nor the HDRS scores after six weeks of antidepressant treatment were significantly different among the different genotypes in

Table 2. Linkage disequilibrium for *ABCB1* SNPs

ABCB1	Linkage disequilibrium	1	2	3	
C3435T	1	-	0.68	0.35	
G2677T	2	0.33	-	0.74	D'
C1236T	3	0.16	0.53	-	
			r^2		

SNP, single nucleotide polymorphism.

Table 3. Genotype frequencies of *ABCB1*

Genotype	All (n=112)	Fluoxetine (n=58)	Venlafaxine (n=54)	*p* value*
C3435T CC/CT/TT	29/52/31 (25.9/46.4/27.7)	16/25/17 (27.6/43.1/29.3)	13/27/14 (24.1/50.0/25.9)	0.607
G2677T GG/GT/TT	26/37/49 (23.2/33.0/43.8)	13/19/26 (22.4/32.8/44.8)	13/18/23 (24.1/33.3/42.6)	0.842
C1236T CC/CT/TT	21/42/49 (18.7/37.5/43.8)	11/25/22 (19.0/43.1/37.9)	10/17/27 (18.5/31.5/50.0)	0.197

Values are presented as number (%).
*Comparison between the fluoxetine and venlafaxine subgroups.

Table 4. Association between HDRS scores and the genotypes of *ABCB1*

	C3435T			p value	G2677T			p value	C1236T			p value
	C/C	C/T	T/T		G/G	G/T	T/T		C/C	C/T	T/T	
Age (yr)	39.9±15.2	42.2±11.1	40.8±10.6	0.834	39.2±12.8	44.7±10.1	41.0±12.0	0.420	39.3±16.0	41.3±11.6	14.8±10.8	0.860
Initial HDRS score	25.2±6.6	25.7±5.9	25.9±5.5	0.946	24.3±6.2	26.3±5.7	26.9±5.4	0.331	22.7±5.7	26.0±6.3	26.6±5.4	0.206
HDRS score after treatment	6.0±5.7	9.1±8.3	6.1±5.0	0.303	5.2±5.6	6.5±5.7	10.6±8.5	0.050	6.6±7.0	6.7±6.8	8.3±7.5	0.715
HDRS change (%)				0.908*				0.002*,†				0.554*
Week 2	-43.6±30.5	-36.5±30.7	-39.4±33.7		-26.3±34.3	-44.3±24.9	-53.8±29.5		-36.1±30.2	-48.7±31.0	-36.1±31.4	
Week 4	-43.4±30.5	-54.7±28.7	-61.5±24.3		-34.3±28.5	-60.9±39.5	-68.3±23.1		-48.2±53.2	-60.2±26.8	-50.7±31.7	
Week 6	-77.7±23.6	-62.1±40.1	-76.6±17.9	0.363†	-56.5±42.1	-74.6±22.9	-79.9±20.2	0.151†	-73.9±23.9	-70.7±38.9	-68.8±28.8	0.531†
Cortisol (ng/ml)												
Initial	11.1±4.6	14.9±6.1	16.2±7.3		13.2±6.3	16.4±5.9	14.1±6.6		10.9±6.0	15.7±6.2	14.6±6.3	
Week 6	13.2±5.7	13.5±5.7	13.0±6.7		11.4±5.8	14.8±6.2	14.4±5.4		14.3±6.4	12.3±6.1	13.7±5.8	

Values are presented as mean±standard deviation.
HDRS, 21-item Hamilton Depression Rating Scale.
*Repeated measurements analysis was used to determine changes in HDRS scores over time after adjustment by initial HDRS score, age, and gender.
†Repeated measurements analysis was used to determine cortisol level over time after adjustment by initial HDRS score, age, and gender.
‡Significant after Bonferroni correction ($p<0.017$ needed).

each polymorphism of *ABCB1* (Table 4), the percentage changes of HDRS scores over time were significantly different in the polymorphisms of *ABCB1* G2677T after adjustment by initial HDRS score, age, and gender ($p=0.002$). MDD patients with the G/G genotype of *ABCB1* G2677T had a worse antidepressant treatment response. However, cortisol levels did not change significantly after antidepressant treatment. In addition, the polymorphisms of the *ABCB1* genotypes were neither significantly associated with the cortisol levels before and after antidepressant treatment, nor with cortisol level changes in the MDD patients (Table 4).

DISCUSSION

In the current study, the results suggested a possible association of *ABCB1* variants with antidepressant response regardless of whether the patients were taking fluoxetine or venlafaxine. MDD patients with the G/G genotype of *ABCB1* G2677T had a worse antidepressant treatment response. However, we did not find a significant association between the polymorphisms of *ABCB1* genotypes and cortisol levels in MDD patients.

P-gp is expressed in the apical membrane of intestinal epithelial cells, the biliary canalicular membrane of hepatocytes and the luminal membrane of proximal tubular epithelial cells in the kidney.[16,17] In addition, it is also found in high levels in the luminal membranes of the endothelial cells that line the small blood capillaries that form the blood-brain and blood-testis barriers.[18] The association between polymorphisms of *ABCB1* genotypes and antidepressant response might result from the influence of intracerebral antidepressant concentrations, the disposal of antidepressant concentrations, or both. However, the serum concentration of the antidepressant does not correlate with the therapeutic response in human studies,[19] which may be because the brain concentrations depend on blood-brain efflux.[19] An animal study also reported that *ABCB1* knock-out mice had higher levels of antidepressant in the brain only, and not in other tissues.[5] Furthermore, the nonsynonymous G2677T sequence variation (Ala893Ser/Thr) of *ABCB1* gene polymorphisms may alter the P-gp efficiency to influence antidepressant efflux at the blood-brain barrier.[2,5] The T/T genotype of *ABCB1* G2677T has been reported to be associated with higher expression of P-gp,[20] though other reports have shown discrepancies.[21,22] In the current study, we found that the treatment response was associated with the polymorphism of *ABCB1* G2677T in MDD patients receiving

six weeks of antidepressant treatment, although not controlling for antidepressant serum levels was a limitation. Previous similar reports have also shown that it was associated with antidepressant treatment response in Caucasian and Asian populations.[2,6,11,23] These studies have showed same direction of that MDD patients with the G/G genotype of *ABCB1* G2677T had a worse antidepressant treatment response,[2,6,23,24] while there was an inconsistent result in another report.[25] The reason for these discrepancies is currently unclear but may be partly due to the enantiomeric effects of antidepressant.[25]

Moreover, as the access of endogenous cortisol to the brain is regulated by P-gp, the polymorphisms of *ABCB1* genotypes could exert a profound influence on the regulation of the hypothalamic-pituitary-adrenocortical (HPA) system,[6,12,26] and accumulating evidence has suggested that dysregulation of the HPA system would result in affective disorders, such as MDD and anxiety. In addition, antidepressants play a role in normalizing HPA axis hyperactivity in depressed patients, in which P-gp function mediates the negative feedback on the HPA axis.[6,27,28] The polymorphisms of the *ABCB1* C3435T genotype were shown to influence the serum levels of glucocorticoids corticosterone in an animal study, and also influence the cortisol level in healthy subjects.[12,26,27] However, few studies have investigated the possible association of the polymorphisms of *ABCB1* genotypes with cortisol in MDD patients treated with antidepressants. In the current study, we did not find an association between the polymorphisms of *ABCB1* genotypes and cortisol levels before and after antidepressant treatment in MDD patients.

There were some factors that limited the study results, including the phase of the normal menstrual cycle, lack of measurement using the corticosteroid suppression test, and polymorphisms of the glucocorticoid receptor gene. In addition, though the withdrawal rate in fluoxetine and venlafaxine groups were 24.1% (n=14) and 27.7% (n=15), the genotypes, allele frequencies, cortisol level were not significantly different between patients completed and those withdrawn from the study. Furthermore, although the relatively small sample size may limit the interpretation of results, the association between polymorphism of *ABCB1* G2677T and treatment response reached statistical power. We employed statistical power calculations for HDRS change between G/G and T/T genotype. Given 5% level of significance and set beta 0.2, power was 0.8. The estimates of the sample size for *ABCB1* G2677T polymorphism was 21. Large-scale study of the association between the *ABCB1* poly-

morphisms and the HPA system in MDD patients treated with antidepressants needs to be performed.

In summary, the findings of this study indicated that the polymorphisms of *ABCB1* may influence the short-term antidepressant response in MDD patients, but did not influence the cortisol levels before and after antidepressant treatment. In order to improve the clinical treatment response of MDD patients, further studies of the underlying mechanisms of the interaction of *ABCB1* and the HPA system with antidepressant response are needed.

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