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Original Article

PDLIM5 gene polymorphisms and short term antidepressant response in Chinese major depressive disorders

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Abstract: Several investigations have suggested that PDLIM5 plays a key role in the pathophysiology of major depressive disorder (MDD), and that PDLIM5 might be a therapeutic target for the action of antidepressant. In this study, we sought to investigate whether variations of PDLIM5 gene sequence could predict response to antidepressants in MDD patients. We selected 3 SNPs (rs10008257, rs2433320, 2452600) of PDLIM5 gene, and performed an association analysis of PDLIM5 and the efficacy of fluoxetine treatment in 185 Han Chinese MDD patients. The results show that the rs2433320 of PDLIM5 gene are associated with fluoxetine therapeutic response in MDD patients (X^2 = 8.2960, df = 2, P = 0.0145) after correction with the Bonferroni multiple test, the HAMD score of the GG genotype group was significantly lower than that of the AA and AG genotype group at 1, 2, 4 and 6 weeks. The results support the idea that the PDLIM5 gene is likely to be involved in the antidepressant response in MDD.

Keywords: PDLIM5, antidepressant, pharmacogenetics, major depressive disorder

Introduction

Major depressive depression (MDD) is one of the most common and debilitating psychiatric disorders. The response to antidepressant treatment varies markedly between individuals. Up to 63% of patients are expected to improve to certain degree clinically, but only 36.8% of patients return to their premorbid levels of function without any significant depressive symptoms after treatment with a single antidepressant [1, 2], others exhibit partial, refractory or intolerant responses to treatment. As there are no clinical or biomarker predictors of treatment response, the assignment of a depressed patient to a drug is based solely on chance or on attempts to minimize side effects that are more likely to occur with a specific medication. Among those possible causes, genetic variation is known to contribute to individual response to many drugs including antidepressants [3]. Identification of genetic factors underlying response to antidepressant therapy may help to predict therapeutic response and facilitate determination of optimal drug selection [4].

PDLIM5 is expressed in various regions of brain such as hippocampus, thalamus, hypothalamus, cortex and amygdala. Its cellular localization is identical to synapsin I, which is known to be involved in neurotransmitter release [5]. Pharmacological evidence suggested that the monoaminergic neurotransmitter systems and intracellular second messenger systems involved in response of antidepressant. PDLIM5 is known to interact specifically with N-type calcium channel alpha-1B subunit and protein kinase C-ε, and is critical for rapid, efficient potentiation of the calcium channel activation by PKC in neurons [6]. Down-regulation of PDLIM5 in the peripheral leukocytes may reflect the impairments of calcium signaling and neuronal plasticity in neurons. Clinical literatures also considered that calcium homeostasis play a key role in the pathophysiology of MDD and

the action of antidepressant [7]. PDLIM5 may play an essential role in the process of regulation of the nervous system by interfering with the molecular cascade from PKC to the calcium channel that controls intracellular calcium levels.

PDLIM5 might be involved in the pathophysiology of MDD and other psychiatric disease [8]. Iwamoto et al used an oligonucleotide microarray to achieve comprehensive gene expression analysis of frontal lobes and found that the expression of the PDLIM5 gene was significantly altered. The gene was upregulated in postmortem brain tissues and downregulated in the immortalized lymphoblastoid cell lines derived from patients with bipolar disorder, schizophrenia and MDD [9]. They further confirmed the downregulation of PDLIM5 in lymphoblastoid cells in a replication study [9]. Iga et al reported that PDLIM5 mRNA levels in the peripheral leukocytes of depressive patients were significantly lower than in the control subjects, PDLIM5 mRNA significantly increased after selective serotonin reuptake inhibitors (SSRIs) treatment [10]. The increase of PDLIM5 expression after treatment may be a consequence of statedependent factors such as clinical improvement and pharmacological effects of antidepressant.

PDLIM5 gene localizes on chromosome 4q22.3. It was known that PDLIM5 gene has two splicing isoforms, the long gene spans 216.3 Kb with one non-coding and 12 coding exons while the short gene spans 136.3 Kb with one non-coding and 9 coding exons. The PDLIM5 gene encodes an enigma-homologue (ENH) protein containing a postsynaptic density-95/discs large/zone occludens-1 (PDZ) domain and three LIM (Lin-11, Isl-1, and Mec-3) domains [11]. Genetic studies have suggested that PDLIM5 gene might be a potential candidate gene of MDD. Genome-wide linkage studies have confirmed that this region is associated with bipolar disorder and MDD [12, 13]. Kato et al found a positive association between 3 single nucleotide polymorphisms (SNPs) in the upstream region of PDLIM5 gene and bipolar disorder has been confirmed [14, 15]. In a previous paper by our group, we tested for association between three PDLIM5 SNPs (rs10008257, rs2433320, 2452600) and MDD in a Chinese population, and found an association of rs2433320 and recurrent MDD [16]. Iga observed a negative result between there SNPs of PDLIM5 and MDD in a Japanese population [10]. Geographical and ethnic variablity might contribute to inconsistent results in genetic association studies.

In this study, we sought to investigate whether variations of PDLIM5 gene sequences could predict response to antidepressants in Han Chinese population with MDD.

Materials and methods

Subjects

The study population consisted of 252 unrelated Chinese MDD patients (male/female: 91/161; mean age: 29.67 ± 0.6295 (Mean ± SEM)), who were outpatients and inpatients from the Psychiatric Department of Renmin Hospital of Wuhan University. Patients were interviewed by trained psychiatrists using the Structured Clinical Interview for DSM-IV disorders (SCID-I), the diagnosis according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Severity of depression was assessed using the 21-item Hamilton Rating Scale for Depression (HAMD) [17]. The inter-rater reliability kappa values were 0.82 of SCID. Only subjects with a minimum score of 18 on the HAMD-21 were selected, this definition is commonly used in short-term antidepressant treatment response evaluation [18-20]. Exclusion criteria were additional current DSM-IV Axis I diagnoses (including schizophrenia, bipolar disorder, substance abuse, anxiety disorders), personality disorders, pregnancy, recent suicide attempt, and major medical and/or neurological disorders, electroconvulsive therapy in the last 6 months, current enrollment in psychotherapy or previous lack of response to fluoxetine. Presence depressive symptoms for at least 2 weeks before entry into the study without antidepressant treatment during that period (patients were fresh cases or had quit antidepressants for more than 2 weeks). All patients were Han people came from the same geographical region in China. The Medical Ethics Committees of Renmin Hospital of Wuhan University approved the research project, patients were included in the study after they gave written informed consent.

Study design

For the fluoxetine treatment, the daily doses were 20 mg/day in the beginning, with dose

Table 1. Clinical characteristics of MDD patients in fluoxetine treatment

	Responder	Non-responder	*P*-value
Number	98	87	
Age (Mean ± SEM)	28.68 ± 0.9064	30.15 ± 1.067	0.2936
Gender (males/females)	40/58	32/55	0.6509
Initial HAMD scores (Mean ± SEM)	27.32 ± 0.5492	28.60 ± 0.5654	0.1076

Table 2. Genotype distributions of PDLIM5 polymorphisms in responder and non-responder to 6-week fluoxetine treatment

SNP-ID		Genotype distribution			*P*-value	X^2	df
		AA	AG	GG			
rs10008257	Responder	39	43	16	0.6140	0.5859	2
	Non-responder	33	36	18			
rs2433320	Responder	2	28	68	**0.0145**[a]	8.2960	2
	Non-responder	7	36	44			
		CC	CT	TT			
rs2452600	Responder	35	43	20	0.6253	0.6486	2
	Non-responder	30	35	22			

[a]Bold numerals *p*-values after Bonferroni correction.

escalation based on clinical outcomes after 2-weeks treatment the investigator could increase the dosage to 40 mg/day. Concomitant psychotropic drugs were not allowed, except a low dose of sleep-inducing hypnotic agents at bedtime. Treatment efficacy was evaluated by one investigator, who administered the HAMD Scale before and after the 6-week fluoxetine treatment. The subjects were considered 'responders' if they had a least 50% decrease in HAMD total score after 6-week fluoxetine treatment. Ratings were assigned blind to genotyping.

SNP genotyping

Genomic DNA was extracted from EDTA anticoagulated venous blood samples. In this study, three SNPs were assayed in PDLIM5 gene corresponding to the following dbSNP identifiers: rs10008257, rs2433320 and rs2452600. SNPs were genotyped with TaqMan technology (Assay-by-Design) on an ABI 7900 system (Applied Biosystems). The standard PCR reaction was carried out using TaqManR Universal PCR Master Mix reagent kit. Fluorescence data files from each plate were analyzed by using automated software (SDS 2.1; Applied Biosystems). All laboratory procedures were carried out blind to case–control status.

Statistical analysis

The GENEPOP program was used to compare the overall genotype distributions for each SNP in response and non-response groups, and to test Hardy-Weinberg equilibrium [21]. A total of 10,000 permutation tests were performed in each analysis. Bonferroni correction was used for multiple testing, using the total number of SNPs as correction factor. Differences in patient characteristics were analysed with the use of the unpaired t-test or chi-square test where appropriate. Differences in the HAMD scores at each evaluation point were examined with the one-way factorial ANOVA followed by the Fisher's PLSD test. Statistical analysis was carried out by using SPSS software for windows (version 13.0). Power analysis was carried out by G*Power program. All tests were two-tailed, alpha was set at 0.05.

Results

185 patients completed the 6-week study and no information loss. Among the clinical characteristics of patients in this pharmacogenetic study, no significant differences between either responders or nonresponders group were detected in the gender and age (**Table 1**). Genotype distributions for the three SNPs of PDLIM5 tested were in Hardy-Weinberg equilibrium. Among those 185 MDD patients, the mean fluoxetine dosage for all the patients was 25.91 ± 7.29 mg/day at week 6 and 98 (53.0%) of the patients had at least a 50% decrease in HAMD total score after 6 weeks of taking medication.

Table 2 shows the genotype distribution of responders and non-responders for all subjects receiving fluoxetine. In analysis of each SNP, we observed a significant association between rs2433320 of PDLIM5 gene and fluoxetine

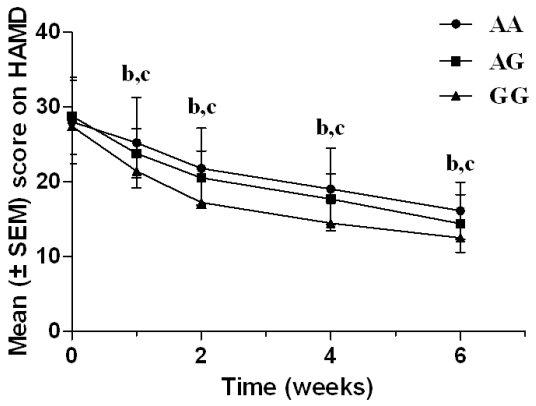

Figure 1. HAMD scores during 6 weeks of fluoxetine treatment in three PDLIM5 rs2433320 genotype groups[a]. [a]Each point represents the mean score ± SEM. Differences in the HAMD scores at each evaluation point were examined with the use of one-way factorial ANOVA followed by Fisher's PLSD test. [b]Significant differences at each point between the *AA* and *G/G* groups ($p = 0.0223$ at week 1, $p = 0.0005$ at week 2, $p = 0.0011$ at week 4 and $p = 0.0133$ at week 6). [c]Significant difference at each point between the *AG* and G/*G* groups ($p = 0.0001$ at week 1, p = 0.0001 at week 2, $p = 0.0001$ at week 4 and $p = 0.0032$ at week 6).

response ($X^2 = 8.2960$, df = 2, P = 0.0145) after correction with the Bonferroni multiple test. MDD patients with GG genotype had a better response to fluoxetine than patients who were A-allele carriers. No association was observed between the other two SNPs (rs2433320 and rs2433327) of PDLIM5 gene and the fluoxetine therapeutic response in MDD patients. **Figure 1** shows the HAMD scores over time in relation to the PDLIM5 rs2433320 polymorphism for fluoxetine treatment. There was no significant difference in baseline and 1 week HAMD scores among each genotype group. The HAMD score of the GG genotype group was significantly lower than that of the AA and AG genotype group at 1, 2, 4 and 6 weeks. There was no significant difference in the HAMD score at any evaluation point between the AA and AG genotype groups.

Power analysis for the samples was carried out by G*Power program, the sample size had a post-hoc power of 0.99 to detect an effect size of 0.5 (moderate) at the 0.05 significance level (2-tailed).

Discussion

To our knowledge, our results provide for the first time evidence that genetic variants of the PDLIM5 gene account for differences in the clinical efficacy of antidepressants. In this study, among 185 patients who completed a 6-week fluoxetine treatment, 98 (53%) patients were considered fluoxetine responders defined by a minimum 50% reduction in HAMD total score from baseline. Our studies suggested that MDD patients with GG genotype of the rs2433320 polymorphism predicted early response and over all response to SSRI treatment. This finding of interest that GG genotype of rs2433320 may be a predictor for efficacy of SSRIs treatment for MDD.

The findings reported here represent evidence that further strengthen the concept that PDLIM5 has a role in depression and that PDLIM5 is likely involved in antidepressant response. Since the SNP is intronic, it is also possible that the association of rs2433320 polymorphism and fluoxetine antidepressant response is due to linkage disequilibrium between this polymorphism and a nearby functional polymorphism.

In this study, we found a moderate liability effect of PDLIM5 polymorphisms in short-term fluoxetine antidepressant response. However, there are several limitations in this study. Firstly, the main limitation was that we did not recruit the patients who did not finish six weeks treatment of antidepressant. Some of them discontinued to take medicine before six weeks because they thought drug was useless for their emotional problems. Secondly, the plasma levels of fluoxetine were not analyzed. But this effect is minimal since a previous study had demonstrated that there were no significant relationships between fluoxetine blood levels and clinical response in depressed patients [22]. Furthermore, the relatively small sample size lacking of genomic control is liable for stratification bias, however the Han Chinese population is considered genetically homogenous and no patients from other regions were included in the study. The power of our study had a power of 0.99 to detect an effect size of 0.5 (moderate) at the 0.05 significance level (2-tailed).

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Disclosure of conflict of interest

None.

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