A major single nucleotide polymorphism of the *PDLIM5* gene associated with recurrent major depressive disorder

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**Objective:** The *PDLIM5* gene is known to interact specifically with the N-type calcium channel α-1B subunit and protein kinase Cε and is critical for rapid, efficient potentiation of the calcium channel activation by protein kinase C in neurons. Increasing amounts of data suggested that *PDLIM5* might be involved in the pathophysiology of major depressive disorder (MDD). The aim of this study was to examine whether genetic variations in the human *PDLIM5* gene might contribute to the liability to develop MDD. **Method:** We undertook a gene-based association analysis of single nucleotide polymorphisms (SNPs). Three SNPs (rs10008257, rs2433320, and rs2452600) were identified in the *PDLIM5* gene and genotyped in patients diagnosed with recurrent MDD and in matched control subjects. **Results:** We observed significant allele (*p* = 0.007) and genotype (*p* = 0.007) association with rs2433320, and the G allele of rs2433320 was significantly overrepresented in control subjects in comparison with MDD patients. **Conclusion:** These results support the hypothesis of a protective effect for the G allele of rs2433320 in the *PDLIM5* gene in recurrent MDD.

**Objectif :** On sait que le gène *PDLIM5* agit spécifiquement avec la sous-unité α-1B du canal calcique de type N et la protéine kinase Cε et joue un rôle critique dans la potentiation efficace rapide de l’activation du canal calcique par la protéine kinase C dans les neurones. De plus en plus de données indiquent que le *PDLIM5* pourrait jouer un rôle dans la pathophysio logie du trouble dépressif majeur (TDM). Cette étude visait à déterminer si des variations génétiques du gène humain *PDLIM5* pouvaient contribuer au risque d’apparition du TDM. **Méthode** : Nous avons entrepris une analyse par association à base de gènes de polymorphismes d’un nucléotide simple (PNS). Nous avons identifié trois PNS (rs10008257, rs2433320 et rs2452600) dans le gène *PDLIM5* et nous en avons déterminé le génotype chez des patients qui avaient un TDM récurrent diagnostiqué et chez des sujets témoins jumelés. **Résultats** : Nous avons observé une association allèle (*p* = 0.007) et génotype (*p* = 0.007) importante avec rs2433320 et l’allèle G de rs2433320 était sur représenté considérablement chez les sujets témoins comparativement aux patients qui avaient un TDM. **Conclusion** : Ces résultats appuient l’hypothèse d’un effet protecteur pour l’allèle G du rs2433320 dans le gène *PDLIM5* des sujets qui ont un TDM récidivant.

**Introduction**

Major depressive disorder (MDD) is one of the most prevalent and costly brain diseases. Severe forms of depression affect 2%–5% of the population worldwide; up to 20% suffer from milder forms of the disease, and recurrent attacks are common. Despite the high morbidity and mortality associated with MDD, its etiology and pathophysiology have not been precisely defined. Although environmental components have been demonstrated, genetic

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factors account for 40%–70% of the risk for developing MDD. However, specific genes or relevant DNA sequence variations involved in the pathogenesis of MDD have not yet been identified.

Recent findings suggest that the PDLIM5 gene might be involved in the pathophysiology of MDD. PDLIM5 is expressed in various regions of the brain, such as the hippocampus, thalamus, hypothalamus, cortex and amygdala. Its cellular localization is identical to synapsin I, which is known to be involved in neurotransmitter release. Pharmacologic evidence suggests that the monoaminergic neurotransmitter systems and intracellular second messenger systems are involved in MDD. PDLIM5 is known to interact specifically with N-type calcium channel α1B subunit and protein kinase Cε (PKCε) and is critical for rapid, efficient potentiation of the calcium channel activation by PKC in neurons. Clinical literature considers that calcium homeostasis plays a key role in the pathophysiology of MDD and the action of antidepressants, which suggests that abnormal calcium signalling cascade induced by the altered expression of PDLIM5 might be involved in the pathophysiology of MDD.

Genetic studies also suggest that PDLIM5 might be a potential candidate etiological factor in MDD. It has been reported that the expression level of PDLIM5 was significantly and commonly increased in the postmortem brain tissues of patients with bipolar disorder, schizophrenia and MDD and that it was decreased in the immortalized lymphoblastoid cells derived from patients with bipolar disorder. Iga and colleagues reported that PDLIM5 messenger ribonucleic acid levels in the peripheral leukocytes of depressed patients were lower than in control subjects but that it significantly increased after paroxetine treatment. The PDLIM5 gene is located at 4q22. Genome-wide linkage studies have confirmed that this region is associated with bipolar disorder and MDD. An association between single nucleotide polymorphisms (SNPs) in the upstream region of the PDLIM5 gene and bipolar disorder has been confirmed. The aim of this study was to examine whether genetic variations in the human PDLIM5 gene might contribute to the liability to develop MDD. We identified SNPs in PDLIM5 and subsequently analyzed them in a genetic association study in patients with recurrent MDD and healthy control subjects.

Method

The patient sample consisted of 181 unrelated Chinese MDD patients: 72 men and 109 women; mean age 33.68 (standard deviation [SD] 10.07) years; age of onset 29.34 (SD 9.63) years. They were recruited from outpatients and inpatients at the Psychiatric Department of the Renmin Hospital of Wuhan University. A trained psychiatrist made the diagnosis by interviewing patients. All patients had at least 2 well-defined episodes of MDD (average, 3.6 episodes) as defined by the DSM-IV. Severity of depression was assessed on the 21-item Hamilton Rating Scale for Depression (HAMD-21) and the Clinical Global Impression Scale (CGI). The HAMD-21 mean score was 29.11 (SD 5.89). Subjects with less than a minimum score of 18 on the HAMD-21 were excluded from the study. Patients with severe organic disorders or comorbidity with other psychiatric disturbances (e.g., substance or alcohol dependence, personality disorders, anxiety disorders and others) were also excluded. There were no significant differences between men and women for all other investigated variables (age and clinical variables such as CGI and HAMD-21 scores).

A total of 186 healthy control subjects (71 men and 115 women) matched for age (mean age 32.94 [SD 11.32] y), sex and ethnicity were selected from the general population. All patients and control subjects were Han people from the same geographical region in China. The Medical Ethics Committees of Wuhan University approved the research project. Patients were included in the study after they gave written informed consent.

Genomic DNA was extracted from EDTA-anticoagulated venous blood samples that were acquired as described by Miller and colleagues. In this study, 3 SNPs were assayed in the 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, Foster City, Calif.). All MGB TaqMan probes and PCR primers were designed by Applied Biosystems. The standard PCR reaction was carried out in 25-μL reactions containing 100 ng genomic DNA in a 96-well plate format. The patient sample consisted of 181 unrelated Chinese MDD patients: 72 men and 109 women; mean age 33.68 (standard deviation [SD] 10.07) years; age of onset 29.34 (SD 9.63) years. They were recruited from outpatients and inpatients at the Psychiatric Department of the Renmin Hospital of Wuhan University. A trained psychiatrist made the diagnosis by interviewing patients. All patients had at least 2 well-defined episodes of MDD (average, 3.6 episodes) as defined by the DSM-IV. Severity of depression was assessed on the 21-item Hamilton Rating Scale for Depression (HAMD-21) and the Clinical Global Impression Scale (CGI). The HAMD-21 mean score was 29.11 (SD 5.89). Subjects with less than a minimum score of 18 on the HAMD-21 were excluded from the study. Patients with severe organic disorders or comorbidity with other psychiatric disturbances (e.g., substance or alcohol dependence, personality disorders, anxiety disorders and others) were also excluded. There were no significant differences between men and women for all other investigated variables (age and clinical variables such as CGI and HAMD-21 scores).

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<th>Table 1: Allele and genotype distribution of PDLIM5 SNPs in MDD patients and control subjects</th>
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SNP = single nucleotide polymorphism; MDD = major depressive disorder; CON = control subjects; HWE = Hardy–Weinberg exact test; OR = odds ratio; CI = confidence interval.

*GENEPOP software was used to estimate p values.
†p < 0.05.
ried out using TaqMan Universal PCR Master Mix reagent kit in a 5-μl volume. Fluorescence data files from each plate were analyzed with automated software ( SDS 2.1; Applied Biosystems). All laboratory procedures were carried out blind to case–control status.

The GENEPOL program was used to compare the overall allele and genotype distributions for each SNP in both MDD patients and control subjects, as well as to test Hardy–Weinberg equilibrium.

Results

We performed an association study with 3 SNPs (rs10008257, rs2433320 and rs2452600) in the PDLIM5 gene and compared 181 patients suffering from recurrent MDD with 186 healthy control subjects. None of the 3 SNP genotype frequencies showed any significant deviations from Hardy–Weinberg equilibrium in either MDD patients or control subjects.

The results of single SNP association analysis are presented in Table 1. A significant difference in allele distribution between patients and control subjects was observed for rs2433320 (p = 0.007) and was due to an increase of the G allele in the control subjects. In the genotype distributions, which were reflected by a significant increase of GG homozygotes in control subjects (p = 0.007), carrying the G allele decreased the probability of developing MDD in this population (odds ratio 1.747, 95% confidence interval 1.172–2.604). The other 2 SNPs were not found to be associated with the disorder (Table 1).

Discussion

Given the higher heritability of recurrent MDD, compared with single-episode MDD, it was important to analyze this group. We studied the PDLIM5 gene in 181 patients suffering from recurrent MDD and 186 healthy control subjects. We describe the analysis of 3 SNPs in the PDLIM5 gene and compare allele and genotype frequencies of the 3 SNPs in MDD patients and healthy control subjects.

The investigated SNPs are common in the general population and with regard to the heterogeneity of MDD. In the single SNP evaluation in this study, we found the G allele more frequently in control subjects than in patients and observed a statistically significant association with rs2433320 (p = 0.007) in the genotype distributions, which were reflected by a significant increase of GG homozygotes in control subjects (p = 0.007). This suggests that carrying the G allele of rs2433320 might decrease the recurrent probability of MDD. Iga and colleagues found no difference in allele, genotype and haplotype frequencies of the 3 SNPs in the PDLIM5 gene between MDD and control subjects. Horiuchi and colleagues reported that the rs2433320 of the PDLIM5 gene was associated with schizophrenia. The study results suggest that polymorphisms in the G allele of rs2433320 in the PDLIM5 gene represent protective factors in the development of MDD in a Han Chinese population, which shows a marked geographical and ethnic variability of MDD. Since the SNPs are intronic, it is likely that none of them were the actual protective mutation. It is more likely that the associated SNPs are in linkage disequilibrium with a sequence variant in the 5’ regulatory region that influences the expression of the PDLIM5 gene. Therefore, the possibility that the susceptibility locus lies in other parts of the PDLIM5 gene needs to be studied with more polymorphisms.

These interpretations are certainly very speculative at the moment. PDLIM5 should also be considered involved in the modulating mechanisms of the pathogenesis of MDD and disorders related to disturbances of the serotonin system. The potential functional consequences of the investigated SNPs need further study to understand the genetic factors underlying MDD as well as possible interactions between the PDLIM5 gene and other plausible candidate genes.

Although genotype distributions for all 3 SNPs were in Hardy–Weinberg equilibrium in the control group, it is possible that they do not fully represent the genotype frequencies in the general population. We think that our findings might be preliminary and should be replicated in large samples and in other ethnic populations.

Conclusion

Allele and genotype association with the rs2433320 G allele was significantly overrepresented in control subjects, compared with subjects with MDD. The G allele in the PDLIM5 gene has a protective effect for recurrent MDD in a Han Chinese sample.

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Competing interests: None declared.

Contributors: Drs. Z. Liu, G. Wang, He and Li designed the study. Drs. Z. Liu, W. Liu, Xiao and Yin participated in the acquisition of data, which Drs. H. Wang, Cheng, Zhu and X. Wang analyzed. Drs. Z. Liu, W. Liu, Yin, Cheng and Xiao wrote the article, and Drs. G. Wang, H. Wang, X. Wang, Zhu, Li and He critically reviewed it. All authors gave approval for the final version of the article to be published.

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