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The interaction of combined effects of the *BDNF* and *PRKCG* genes and negative life events in major depressive disorder

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A B S T R A C T

Major depressive disorder (MDD) is a mental disorder that results from complex interplay between multiple and partially overlapping sets of susceptibility genes and environmental factors. The brain derived neurotrophic factor (BDNF) and Protein kinase C gamma type (*PRKCG*) are logical candidate genes in MDD. Among diverse environmental factors, negative life events have been suggested to exert a crucial impact on brain development. In the present study, we hypothesized that interactions between genetic variants in BDNF and PRKCG and negative life events may play an important role in the development of MDD. We recruited a total of 406 patients with MDD and 391 age- and gender-matched control subjects. Gene–environment interactions were analyzed using generalized multifactor dimensionality reduction (GMDR). Under a dominant model, we observed a significant three-way interaction among BDNF rs6265, PRKCG rs3745406, and negative life events. The gene–environment combination of PRKCG rs3745406 C allele, BDNF rs6265 G allele and high level of negative life events (C-G-HN) was significantly associated with MDD (OR, 5.97; 95% CI, 2.71–13.15). To our knowledge, this is the first report of evidence that the BDNF–PRKCG interaction may modify the relationship between negative life events and MDD in the Chinese population.

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1. Introduction

Major depressive disorder (MDD) is one of the most complex, prevalent, and costly brain diseases, with affective, motivational, cognitive, physical, and behavioral symptoms. The etiological risks and the understanding mechanisms of MDD were far from being elucidated. Studies taking into account of gene–environment interactions have shown that through moderating the effects of the environmental factors, such as stressful life events (SLEs), genetic variation explains why some individuals are vulnerable and others are resistant to the effects of adversity (Kendler et al., 1995; Paykel, 2003).

The brain impairments correspond with depression and may be via neurotrophic factors and related signaling cascades (Duman and Monteggia, 2006; Covington et al., 2010) which regulate neural growth and differentiation during development and regulate the plasticity and survival of adult neurons and glia (Nestler et al., 2002) Neuroimaging and postmortem studies in depressed adult patients demonstrated the involvement of decreased neurogenesis in the underlying pathophysiology of MDD (Karege et al., 2005; Dwivedi et al., 2006; Janssen et al., 2007) . The brain derived neurotrophic factor (BDNF) protein is the most common neurotrophins and has an important role in synaptic plasticity, neurogenesis, neural growth and differentiation (Maisonpierre et al., 1990; McAllister et al., 1999). Several studies pointed to the specific role of the BDNF system in MDD. Decreased levels of BDNF were shown in animal models of depression and humans with depression (Karege et al., 2005). Some studies reported strong support serum BDNF levels in depressed patients decreased and increased with antidepressant treatment (Lee and Kim, 2009; Pandey et al., 2010; Serra-Millas et al., 2011). In addition the BDNF polymorphism has been linked with an increased incidence of MDD (Verhagen et al., 2010).

Protein kinase C gamma type (*PRKCG*) is another important candidate gene of the *BDNF* system that has been reported to associate with MDD. Results from a series of recent studies suggest that *PRKC*G, which is a subtype of PKC (Protein kinase C), may be present in MDD. PKC plays a major role in the regulation of neuronal excitability, neurotransmitter release, and alterations in plasticity (Huang et al., 2000; McDonald et al., 2001) , and reduced PKC activity was showed in human peripheral and post mortem brain of depressed patients and hippocampal postmortem tissue from teenage suicide victims showed decreased membrane(incorporate PKC-γ) and cytosolic fraction PKC activity, and of their respective m-RNA's (Pandey et al., 2004). In a previous study, we found that PKCgamma rs3745406 polymorphism is not

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significantly associated with MDD, but is significantly associated with suicidal symptoms in MDD (Wang et al., 2010).

Furthermore, recent studies identified a strong functional link between *PRKCG* and *BDNF*. Jovanovic et al. found that acute application of BDNF rapidly enhances miniature IPSC (induced pluripotent stem cell) amplitude in cortical and hippocampal cell cultures, with switching in the direction of effect of PKC-mediated phosphorylation simultaneously (Jovanovic et al., 2004). Zhao and Levine (2014) reported that the effect of BDNF-endocannabinoid interactions at neocortical inhibitory synapses require PKC signaling. In addition, combined treatment with ketamine and imipramine significantly increased BDNF protein levels in the prefrontal cortex, hippocampus and amygdala, and PKC phosphorylation in prefrontal cortex (Reus et al., 2011).

One of the best-known established environmental risk factors for MDD is negative life events (Brown et al., 1973; Dohrenwend and Dohrenwend, 1974). Several studies showed that negative life events are associated with the onset of MDD, and have a positive correlation with the severity of depression (Kendler et al., 1998, 1999; Rice et al., 2003). In addition, a meta-analysis confirmed the association between negative life events and MDD (Kraaij et al., 2002). However, the quality and availability of social supports were found to modify the risk for depression in individuals with a history of maltreatment or with long-term negative squeal and with a specific serotonin transporter gene promoter polymorphism (Barbazanges et al., 1996; Kaufman et al., 2000; Huot et al., 2004; Kaufman et al., 2004). Moreover, studies revealed significant gene-environment (GxE) interactions in relation to MDD for negative life events and genetic factors including polymorphisms in the serotonin transporter, brainderived neurotrophic factor (BDNF), and HPA axis-related genes (Juhasz et al., 2011; Karg et al., 2011; Kranzler et al., 2011). *BDNF* has also been associated with the vulnerability for depression following predisposing environmental factors (Kaufman et al., 2006; Wichers et al., 2008; Aguilera et al., 2009; Bukh et al., 2009). In addition, a significant interaction between stressful life events and 5-HTTPR and BDNF genotypes were observed in patients with depression (Kim et al., 2007).

In this study, we hypothesize that an interaction between the *BDNF-PRKCG* genes and negative life events and/or social supports plays a role in the development of MDD. We conducted a case-control study in a Han Chinese population to examine the relationships among MDD, the BDNF gene, PRKCG and negative life events and objective social supports as assessed using standard rating scales.

2. Materials and methods

2.1. Subjects

In the present study, 406 patients (male, $n=194$; female, $n=212$; mean age, 28.42 ± 7.73 years old; age range, 18–60 years old) were recruited from clinical settings (inpatients, $n=89$; outpatients, $n=317$) of the Department of Psychiatry, First Hospital of Shanxi Medical university. The detailed process of collection and diagnosis for subjects was described previously (Zhang et al., 2010) where 447 patients with MDD and 432 controls were included. All patients recruited for this study were interviewed by trained psychiatrists using the Structured Clinical Interview for DSM-IV disorders (SCID-I) and diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (SCID-I/P, 11/2002 revision). Among these patients, 80.05% were experiencing their first major depressive episode ($n=325$), while the other 19.95% were experience a relapse ($n=81$). Potential participants did not include those with pregnancy, significant medical conditions, abnormal laboratory baseline values, unstable psychiatric features (e.g., suicidal), a history of alcoholism or drug abuse, seizures or epilepsy, head trauma with loss of consciousness, neurological illness, or concomitant additional Axis I psychiatric disorders.

The age- and sex-matched control group consisted of 391 healthy volunteers (male, $n=170$; female, $n=221$; mean age, 28.36 ± 6.42years old; age range, 18–60 years old). They were recruited from the same community or via regular health screening visiting and did not have a history of neuropsychiatric disorders.

All subjects were from the same geographical areas in Northern China and were all of Chinese Han origin. All participants provided written informed consent. This study was approved by the Ethical Committee for Medicine of the First Hospital of Shanxi Medical University, China.

2.2. Clinical assessments

Negative life events were assessed using the life events scale (LES) created by Desen Yang and Yalin Zhang, in which a total of 48 items are classified into three categories, including 28 items on family life, 13 items on working problems, and 7 items on social and other aspects, and has been assessed in a Chinese population (Yang and Zhang, 1999). All participants carefully read the questionnaires and described life events occurring in the previous one-year period. A number of negative life events, including illness, housing problems, relationship breakdowns, unemployment, and financial difficulty were determined by the interviewers. Each life event was given a score that indicates the amount of readjustment a person had to make as a result of the event. This scale of LES thus indicates that change in one's life requires an effort to adapt and then an effort to regain stability. These event scores have demonstrated high reliability and validity, as shown in Yang and Zhang (1999). The data showed skewed distribution; therefore, the 95% percentile (score of 50.4) in the control sample was selected as the cutoff value for categorizing results into high or moderate levels of negative life events.

Social support was assessed using the Chinese Social Support Rating Scale (SSRS) (Xiao, 1999). SSRS consists of a total of 10 items with three dimensions: objective social supports (3 items), subjective social supports (4 items), and the use of social supports (3 items). Each of these 10 items was classified into four grades ranging from completely disagree (1 point) to completely agree (4 points). The cutoff value for social support was determined by adding the mean score of 38.35 to the 1.96 standard deviation of 7.15; scores higher or lower than 51.00 were classified as high or moderate levels of social support, respectively.

2.3. XSNP selection and genotyping

In this study, three SNPs (BDNF rs6265, rs7124442 and PRKCG rs3745406) were included, which were selected from the NCBI SNP database (http://www.ncbi.nlm.nih.gov/SNP) and the HapMap database (http://www.hapmap.org). The method of selecting tag SNPs has been described in our previous publication (Zhang et al., 2010). In brief, SNPs were selected using the Haploview program (http://www.broad.mit.edu/mpg/haploview) (Barrett et al., 2005) with Gabriel's criteria (Gabriel et al., 2002), based on the HapMap database for a Chinese Han population of Beijing (CHB). The Haploview program indicated two haplotype blocks within the BDNF gene (Fig. 1). One tag SNP was selected from each haplotype block so that each SNP represented genetic information from its corresponding individual block. We selected two tag SNPs (rs6265 and rs7124442) from the BDNF gene for association analysis in our study.

For the PRKCG, based on the HapMap database for the Chinese Han population of Beijing (CHB), 9 tag SNPs were indicated as one haplotype blocks based on the Gabriel's criteria (Gabriel et al., 2002) using Haploview program. Therefore, one of the tag SNPs in the block (Fig. 1), rs3745406, was genotyped.

Using standard phenol-chloroform extraction, genomic DNA was extracted from peripheral blood leukocytes. All three SNPs were detected by a polymerase chain reaction (PCR)-based genotyping protocol. The primers used for PCR amplification were designed by the Primer 5.0 software, and their specificity was validated using NCBI BLASTN (http://www.Ncbi.nlm.nih.gov/BLAST/). PCR amplification was performed with the GeneAmp PCR 2700 system (Applied Biosystems) in a 25-μl reaction volume containing 10 mM Tris–HCl (pH=8.3), 50 mM KCl, 1.5 mM MgCl2, 0.001% (w/v) gelatin, 200 μM of each dNTP, 0.4 μM of each primer, 1.0 unit of Taq DNA polymerase (Tiangen, Beijing, China), and 60 ng of genomic DNA. The conditions used for PCR amplification included denaturation at 95 °C for 10 min, followed by 35 cycles of 94 °C for 30 s, 56 °C for 30 s, and 72 °C for 30 s, and then a final extension at 72 °C for 10 min. PCR products were purified using a Multi-Screen-PCR plate (Millipore, MA, USA). The purified PCR products were bi-directionally sequenced using the ABI 3700 DNA sequencer (Perkin-Elmer, Applied Biosystems, Foster City, CA, USA), and the genotype of the SNPs was read by the Chromas program (version 2.31). Primer sequences and detailed PCR-reaction conditions are shown in Table 1.

2.4. Statistical analysis

We tested the Hardy-Weinberg equilibrium (HWE) for genotypic distributions of the three SNPs using the chi-square (χ^2) goodness-of-fit test. $P<0.05$ was considered significant. Main effects for the risk of MDD were analyzed using SPSS for Windows (version 13.0; SPSS, Chicago, Illinois).

Gene–Gene, Gene–environment interactions were analyzed using generalized multifactor dimensionality reduction (GMDR) software (Lou et al., 2007) , which was an extension of the MDR methods (Hahn et al., 2003; Moore et al., 2006) for allowing covariate adjustment. GMDR has the ability to classify and predict disease risk status using CV. The null hypothesis was rejected when the upper-tail Monte

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