Association of BDNF Val66Met Polymorphism with both baseline HRQOL scores and improvement in HRQOL scores in Chinese major depressive patients treated with fluoxetine

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Objective To explore the association of brain-derived neurotrophic-factor (BDNF) Val66Met polymorphism with both baseline health related quality of life (HRQOL) scores and improvement in HRQOL scores in Chinese major depressive patients treated with fluoxetine.

Methods Patients with major depressive disorder (MDD) took fluoxetine (20 mg/day) for 6 weeks. The HRQOL was measured with the Medical Outcomes Study Short Form-36 (SF-36) at baseline and at 6th week. Patients were genotyped for BDNF Val66Met polymorphism.

Results There was a significant association between social function (SF) and BDNF Val66Met polymorphism, and patients with Met/Met genotype had better SF (compared with Val/Val P = 0.004; compared with Val/Met P = 0.005). A significant association was found between improvement in SF and BDNF Val66Met polymorphism, and patients with Met/Met genotype had poorer improvement in SF (compared with Val/Val P = 0.010; compared with Val/Met P = 0.001). Similar association was found between improvement in mental component summary (MCS) and BDNF Val66Met polymorphism, and patients with Met/Met genotype had poorer improvement in MCS (compared with Val/Val P = 0.066; compared with Val/Met P = 0.006).

Conclusions These results indicate that there may be association between BDNF Val66Met polymorphism and both baseline HRQOL (SF) scores and improvement in HRQOL (SF, MCS) scores in Chinese major depressive patients treated with fluoxetine. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS—health related quality of life; major depressive disorder; brain-derived neurotrophic factor; polymorphism; SSRIs

INTRODUCTION

Major depressive disorder (MDD) is a common and serious clinical problem that reduces patients’ productivity, quality of life, and increases their mortality (Ustun, 2001). Selective serotonin reuptake inhibitors (SSRIs) are frequently used as first-line antidepressants for MDD, but many patients with MDD do not achieve full remission with SSRIs, or else improve very slowly (Driscoll et al., 2005; Lotrich and Pollock, 2005; Whyte et al., 2004). Interindividual variations in the response to antidepressants are possibly due to the genetic background. Pharmacogenetic prediction of the response is one possibility for improving the efficiency of antidepressant treatment. A number of
pharmacogenetic predictors of antidepressant efficacy have been reported over the last few years (Serretti et al., 2005).

Health related quality of life (HRQOL) is defined as “individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns” (Ware and Sherbourne, 1992). It is a multidimensional construct that typically includes four broad categories: physical, functional, social, and emotional well-being. HRQOL assessment is nowadays considered as an important component of evaluation in chronic disease and its treatment response (Whoqol Group, 1993).

Brain-derived neurotrophic factor (BDNF) is a member of the nerve growth factor family, and is widely expressed in the adult mammalian brain. The accumulating evidence suggests a role for BDNF in the pathophysiology and treatment of MDD (Nibuya et al., 1995; Siuciak et al., 1997). The human BDNF gene maps to chromosome 11p13 and contains a functional 196G/A single-nucleotide polymorphism (rs6265) causing an amino-acid substitution from valine to methionine in exon 1 (Val66Met; Mowla et al., 2001). Recently, a meta-analysis has shown that BDNF Val66Met polymorphism was of greater importance in the development of MDD in men than in women (Verhagen et al., 2010). Meanwhile, many studies have examined the association between BDNF Val66Met polymorphism and antidepressant treatment outcome (Choi et al., 2006; Domschke et al., 2009; Huuhka et al., 2007; Kang et al., 2009; Licinio et al., 2009; Rajewska-Rager et al., 2008; Tsai et al., 2003; Wilkie et al., 2007; Yoshida et al., 2007), and these studies have found that the BDNF Val66Met polymorphism may play a major role in antidepressant treatment outcome. However, these studies did not examine the association of BDNF Val66Met polymorphism and HRQOL of patients.

The purpose of this study was to explore the association of BDNF Val66Met polymorphism with both baseline HRQOL scores and improvement in HRQOL scores in Chinese major depressive patients treated with fluoxetine.

MATERIALS AND METHODS

Subjects and treatment

In order to elucidate genetic and environmental influence on individualized response to antidepressant, a pharmacogenetic study of antidepressants, at Anhui Medical University, was conducted in 14 hospitals in China. In total, 1038 ethnic-Chinese patients suffering from MDD were recruited to the prospective study cohort. Three hundred five of 1038 patients were genotyped for BDNF Val66Met polymorphism. Therefore, 305 patients were included in the current study from the Sixth Affiliated Hospital of Peking University, Peking Union Medical College Hospital, People’s Hospital of Wuhan University, the First Affiliated Hospital of China Medical University, the Seventh Hospital of Hangzhou City, the Second Affiliated Hospital of Zhejiang University School of Medicine, the Sixth People’s Hospital of Hebei Province, the First Affiliated Hospital of Harbin Medical University, the Suzhou Guangji Hospital, and the First Hospital of Shanxi Medical University in China. The study was approved by the ethical committee of Anhui Medical University. Written informed consent was obtained from each subject after detailed explanation to each subject before any study procedure happened.

The subjects met the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) criteria for MDD. Other inclusion criteria were age ≥ 18 years, minimum baseline score of 16 on the 17-item Hamilton depression rating scale (HAM-D; Hamilton, 1967), presence of depressive symptoms for at least 2 weeks before entry into the study, no additional diagnoses on Axis I of the DSM-IV (including substance abuse, and generalized anxiety, panic, and obsessive compulsive disorders). There has no antidepressant treatment and electroconvulsive therapy in the last 6 months. The diagnoses were made by two independent senior psychiatrists and confirmed by a third psychiatrist, blind to the previous evaluations.

Fluoxetine (20 mg/day) was administered for 6 weeks. HRQOL was measured using the Medical Outcomes Study Short Form-36 (SF-36) questionnaire (Ware et al., 1993) at baseline and at 6th week. The SF-36 is a generic instrument with scores that are based on responses to individual questions, which are summarized into eight scales, each of which measures a health concept. These scales include function domains and aspects of well-being, as follows: physical function (PF), limitations in physical activities because of health problems; role-physical (RP), limitations in usual role activities because of physical health problems; bodily pain (BP), limitations in social activities because of physical or emotional problems; general health (GH), influence of pain on daily activities; vitality (VT), energy level and fatigue; social function (SF), subjective perception of health status; role-emotional (RE), limitations in usual role activities because of emotional problems; mental health (MH), psychologi-
cal distress and well-being. In addition, the scores of the eight subscales were computed into two summary scores, physical component summary (PCS) and mental component summary (MCS) score. We used the improvement in PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS score to assess the efficacy of fluoxetine (score at 6 week-score at baseline). Concomitant psychotropic drugs were not allowed. For patients with obvious sleep disorder, a low dose of sleep-inducing hypnotic agents were allowed in short term (not more than 1 week) at bedtime, but were not allowed in the last 2 weeks of therapy.

Three hundred five of 1038 patients were genotyped. Of them, 295 patients (96.72%) completed the 6-week treatment trial. Ten patients dropped out of the study, four of whom due to lack of efficacy or side effect and six of whom due to failure of attending the scheduled visits. The clinical characteristics of the dropouts did not differ significantly from the completers (data not shown). These 10 dropouts were not included in the data analyses.

**Genotyping**

Genomic DNA was extracted from venous blood samples using the QIAamp 96 DNA Blood Kit (Qiagen Inc., Valencia, California) and stored at −20°C until analyzed. Genotyping for the presence of BDNF Val<sup>66</sup>Met polymorphism was performed using the Taqman genotyping assay ( Applied Biosystems, Foster City, California). Polymerase chain reaction (PCR) products were amplified in a 5-μl reaction employing 10 ng of genomic DNA; 1X master mix; 900 nmol/L of forward and reverse primers (forward primer: 5’-TTCTTCATTGGGCCGAACTTTT-3’; reverse primer: 5’-CTTGACATCATTGGCTGACACTTT-3’); and two 250-nmol/L Taqman MGB probes (Applied Biosystems; VIC-5’ CGAACACGTGATAGAA3’-NFQ, FAM-5’ CGAACACGTGATAGAA3’-NFQ) using 384-well plates on a PTC-225 Tetrad Thermal Cycler ( MJ Research, Watertown, Massachusetts) under the following conditions: 1 cycle at 95°C for 10 min, and 50 cycles at 92°C for 15 s and at 60°C for 1 min. After PCR amplification, an end-point plate reading of the intensity of fluorescence of each well was performed on an ABI Primer 7900 (Applied Biosystems). The genotype was scored automatically using SDS Plate Utility version 2.1 (Applied Biosystems) and inspected visually on the plot. Every 384-well plate included four non-DNA wells as negative internal controls for quality control within the plate. Additionally, 15% of total samples were randomly selected for duplicate assay for further quality control. The genotyping data were accepted only if the results for all internal controls were negative and the consistency of the duplicate assays was >99%.

**Statistical analysis**

Continuous variables were presented as mean ± standard deviation (SD) for variables normally distributed or median and interquartile range (P<sub>25</sub>–P<sub>75</sub>) for variables not normally distributed. Categorical variables were presented as number (percentage). The categorical data were analyzed using χ<sup>2</sup> test. Differences for continuous variables were evaluated using one-way analysis of variance for variables normally distributed, the Mann–Whitney or Kruskal–Wallis tests for variables not normally distributed. All statistical analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, North Carolina). Within this report, the term “significant” is used to denote statistical significance (P < 0.05; P < 0.017 for multiple comparisons).

**RESULTS**

**Genotype frequencies, demographic, and clinical characteristics**

Among 295 subjects, 81 with the Val/Val genotype, 144 with the Val/Met genotype, and 70 with the Met/Met genotype, the Val/Met allele frequencies were in Hardy–Weinberg equilibrium (χ<sup>2</sup> = 0.148 P = 0.701). The distribution of the genotypes: Val/Val, Val/Met, and Met/Met were 27.46, 48.82, and 23.72%, respectively. The Val- and Met- alleles frequencies were 51.86 and 48.14%, respectively. The frequency of the Met-allele in Han Chinese was higher than that in Caucasian populations, which is 22–32% (Cargill et al., 1999; Gratacos et al., 2008; Shimizu et al., 2004), and is similar with other studies in Asian populations, which is 40–52% (Choi et al., 2009; Kang et al., 2009; Tsai et al., 2003; Yoshida et al., 2007). The population characteristics of each genotypic group were showed in our another study (Zou et al., 2010). There were no significant differences in age, sex, height, weight, age at onset, smoking status, alcohol consumption, antidepressant medication history, and type of episode in patients with the Val/Val, Val/Met, and Met/Met genotypes (P > 0.05).

**BNDF Val<sup>66</sup>Met polymorphism and baseline HRQOL scores (Table 1)**

The HRQOL scores were not normally distributed and the results were presented as median and interquartile range (P<sub>25</sub>–P<sub>75</sub>). There was a significant association between SF and BDNF Val<sup>66</sup>Met polymorphism, and patients with Met/Met genotype (37.5(25.0-62.5)) had
better SF (compared with Val/Val (25.0(25.0-50.0)) P = 0.004; compared with Val/Met (37.5(25.0-50.0)) P = 0.005), and the boxplot is shown in Figure 1. A trend to higher total score of SF-36 at baseline was noted for Val/Met heterozygote patients (54.3(42.7-72.2)) and Met/Met homozygote patients (44.6(29.6-54.8)) in comparison to those bearing the Val/Val homozygote (39.2(27.7-48.9)), but not significantly (P = 0.061). No significant association was found between PF, RP, BP, GH, VT, RE, MH, PCS, MCS, and BNDF Val66Met polymorphism (P > 0.05).

**BNDF Val66Met polymorphism and improvement in HRQOL scores at 6th week (Table 2)**

The HRQOL scores were not normally distributed and the results were presented as median and interquartile range (P25–P75). There was a significant association between improvement in SF and BDNF Val66Met polymorphism, and patients with Met/Met genotype (6.3(12.5-25.0)) had worse improvement in SF (compared with Val/Val (25.0(0.0-37.5)) P = 0.010; compared with Val/Met (25.0(12.5-37.5)) P = 0.001), and the boxplot is shown in Figure 2. Similar association was found between improvement in MCS and BDNF Val66Met polymorphism, and patients with Met/Met genotype (10.4(3.3-26.5)) had worse improvement in MCS (compared with Val/Val (20.4(7.8-34.5)) P = 0.066; compared with Val/Met (22.5(12.6-36.6)) P = 0.006), and the boxplot is shown in Figure 3. A trend to poorer improvement in total score of SF-36 at 6th week was noted for Met/Met homozygote patients (10.4(3.3-26.5)) in comparison to those bearing the Val/Val homozygote (16.4(5.6-27.0)) and Val/Met heterozygote patients (18.3(8.4-28.8)), but not significantly (P = 0.081). No significant associ-
ation was found between PF, RP, BP, GH, VT, RE, MH, PCS and BNDF Val66Met polymorphism \((P > 0.05)\).

**DISCUSSION**

HRQOL is impaired in patients with MDD, especially when compared to the general population and patients with other chronic diseases such as arthritis, diabetes or cardiovascular disease (Hays *et al.*, 1995; Wells *et al.*, 1989; Wells and Sherbourne 1999). Recently, there is increasing interest in HRQOL as a measure of response to antidepressant treatment because it encompasses not only symptoms, but also physical, mental, and social functioning as well as role performance (Demyttenaere *et al.*, 2002). Assessment of HRQOL may provide a more comprehensive evaluation of treatment response than one based solely on improvement in emotional symptoms of depression. The SF-36 is a 36-item short form test derived from 245-item Medical Outcomes Study questionnaire, which was devised to measure general health status in population surveys and evaluative studies of health policy (Ware *et al.*, 1993). The SF-36 survey has been used in over 700 studies to assess HRQOL, and it has been validated in many diverse populations, including Chinese population (Liu *et al.*, 2001; Manocchia *et al.*, 1997; Ware *et al.*, 1995). Therefore, HRQOL of MDD patients was assessed by the SF-36 in this study.

The present study revealed that there was a significant association between SF and BDNF Val66Met polymorphism at baseline and patients with Met/Met genotype had better SF. A trend (but not significant) was found between PF, RP, BP, GH, VT, RE, MH, PCS and BNDF Val66Met polymorphism \((P > 0.05)\).

**Table 2. Comparison of improvement in health related quality of life of patients between genotypes**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Val/Val ((N = 81))</th>
<th>Val/Met ((N = 144))</th>
<th>Met/Met ((N = 70))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>5.0(0.0-20.0)</td>
<td>7.5(0.0-15.0)</td>
<td>5.0(0.0-15.0)</td>
<td>0.874</td>
</tr>
<tr>
<td>Role-physical</td>
<td>0.0(0.0-25.0)</td>
<td>0.0(0.0-50.0)</td>
<td>0.0(0.0-25.0)</td>
<td>0.427</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>12.2(0.0-25.6)</td>
<td>11.1(0.0-22.2)</td>
<td>11.7(0.0-24.4)</td>
<td>0.692</td>
</tr>
<tr>
<td>General health</td>
<td>10.0(0.0-30.0)</td>
<td>17.5(0.0-35.0)</td>
<td>12.5(0.0-30.0)</td>
<td>0.076</td>
</tr>
<tr>
<td>Vitality</td>
<td>20.0(10.0-35.0)</td>
<td>25.0(15.0-25.0)</td>
<td>20.0(5.0-35.0)</td>
<td>0.143</td>
</tr>
<tr>
<td>Social function</td>
<td>25.0(0.0-37.5)</td>
<td>25.0(12.5-37.5)</td>
<td>6.3(-12.5-25.0)(b)</td>
<td>0.004</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>0.0(0.0-33.3)</td>
<td>0.0(0.0-66.7)</td>
<td>0.0(0.0-33.3)</td>
<td>0.311</td>
</tr>
<tr>
<td>Mental health</td>
<td>24.0(12.0-36.0)</td>
<td>24.0(2.0-36.0)</td>
<td>20.0(4.0-32.0)</td>
<td>0.135</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>13.3(0.0-19.9)</td>
<td>12.5(0.0-25.6)</td>
<td>8.7(-1.3-20.7)</td>
<td>0.388</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>20.4(7.8-34.5)</td>
<td>22.5(12.6-36.6)</td>
<td>10.4(3.0-26.5)(d)</td>
<td>0.022</td>
</tr>
<tr>
<td>Total Score</td>
<td>16.4(5.6-27.0)</td>
<td>18.3(8.4-28.8)</td>
<td>10.4(3.0-26.5)</td>
<td>0.081</td>
</tr>
</tbody>
</table>

\(a\)Values are expressed as median and interquartile range \((P_{25}-P_{75})\); \(b\)Compared with Val/Val \(P\)-value = 0.010; \(c\)Compared with Val/Met \(P\)-value = 0.001; \(d\)Compared with Val/Met \(P\)-value = 0.006.

significant) to higher total score of SF-36 at baseline was found for the patients with Met-allele in comparison to those bearing the Val/Val homozygote. Meanwhile, there was a significant association between improvement in SF and BDNF Val66Met polymorphism, and patients with Met/Met genotype had worse improvement in SF and similar association was found between improvement in MCS and BDNF Val66Met polymorphism. A trend (but not significant) to poorer improvement in total score of SF-36 at 6th week was found for Met/Met homozygote patients in comparison to those bearing the Val/Val homozygote and Val/Met heterozygote patients.

Clinical and pharmacological studies have established a crucial role of BDNF in antidepressant treatment (Aydemir et al., 2006; Gonul et al., 2005; Karege et al., 2002; Kuipers and Bramham, 2006). BDNF Val/Met polymorphism is a significant genetic factor that affects the prefrontal and hippocampal function which in turn have not only negative impact on cognitive performance but may also increase the risk for developing of depression. Frodl et al. (2007) showed that in patients with MDD, BDNF Val66Met polymorphism has negative impact on hippocampal and amygdala volumes, while healthy persons carrying the Met-allele also showed smaller hippocampal volumes than subjects who are homozygous for the Val-allele (Pezawas et al., 2004). This is suggested by studies which indicated a significant association between the BDNF Val/Met polymorphism and memory deficits during depression. In this respect, Met-carriers have been shown to exhibit abnormal hippocampal activity during episodic memory performance (Egan et al., 2003; Hariri et al., 2003). Additionally, greater number of depressive episodes has been also found to be associated with smaller hippocampal volumes that is shown to increase the risk for developing of MDD (Sheline et al., 1996, 2003). These findings are suggested by neuroimaging studies indicating to reduced gray matter volume in the hippocampus and dorsolateral prefrontal cortex which have been implicated in mood regulation and cognitive performance (Pezawas et al., 2004; Phillips et al., 2003). A recent study in schizophrenic patients reported that Met-carriers had lower N-acetyl aspartate, a marker of neuronal viability, in the left hippocampus as measured by proton magnetic resonance spectroscopy (1H-MRS; Egan et al., 2003). Taken together, our result that the patients with Met/Met genotype (but not Met-carrier) had worse improvement in quality of life, especially in SF and MCS, is not well explained by these findings. Further studies are needed to explore the reason. Recently, Foltynie et al. (2005) revealed that the Met-allele of the BDNF Val/Met polymorphism was associated with better performance at the Tower of London (TOL) task in Parkinson’s disease. The TOL task was reported to increase relative regional cerebral blood flow in the dorsolateral prefrontal cortex, lateral premotor cortex, rostral anterior cingulate cortex, and dorsal caudate nucleus (Dagher et al., 1999). Therefore, it is possible that the functional effects of the BDNF Val/Met polymorphism differ among areas of the brain, and this regional difference may contribute to the better quality of life, especially SF, in patients with
the Val/Met heterozygote patients and Met/Met homozygote patients. Of course, further studies are needed to explore the detailed mechanism.

Our results may result from the direct effect of the polymorphism itself or through linkage disequilibrium with another functional polymorphism in the structural part of the gene or in regulatory regions. Our results may also result from the effect of interactions between BDNF gene and many different genes in the structural part of the gene, for example, serotonin transporter gene. Mossner et al. (2000) have demonstrated that BDNF may influence serotonin uptake lymphocytes, and preferential regulation of the serotonin transporter has been observed in cells of the long/long genotype of the polymorphism in the serotonin transporter gene promoter. It may be helpful for explaining our finding, therefore, to explore the interaction of BDNF and serotonin transporter genetic polymorphism in treatment outcome of SSRIs.

In conclusion, the present study suggests that there may be association between BDNF Val66Met polymorphism and both baseline HRQOL (SF) scores and improvement in HRQOL (SF, MCS) scores in Chinese major depressive patients treated with fluoxetine. To reach a definitive conclusion, further gene–gene and gene–environment interactions studies based on larger sample size are still needed.

ACKNOWLEDGEMENTS

We thank all patients for their enthusiastic participation in the pharmacogenomics study and all the people who give the help for the study.

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