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# Effects of polymorphisms of serotonin transporter promoter (5-HTTLPR) and brain derived neurotrophic factor gene (G196A rs6265) on the risk of major depressive disorder in the Chinese Han population

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**Abstract. – OBJECTIVE: The etiology of Major depressive disorder (MDD) is multifactorial but the genetic risk is an important factor. Previous studies have shown a significant interaction between serotonin and brain-derived neurotrophic factor (BDNF) in brain function. The serotonin transporter protein promoter polymorphism (5-HTTLPR) and BDNF (rs6265) are two of the most studied candidate gene polymorphisms in relation to MDD. However, the effect of 5-HTTLPR-BDNF (rs6265) interaction on MDD-risk is not consistent.**

**PATIENTS AND METHODS: This study recruited 459 patients with MDD and 412 healthy volunteers in a Chinese Han population. Polymerase chain reaction (PCR)-based genotyping was used to detect polymorphisms. Logistic regression was applied to estimate the effect of polymorphisms of 5-HTTLPR, BDNF (rs6265), and their interaction.**

**RESULTS: We observed a significant correlation between the heterozygous genotype of 5-HTTLPR and MDD [odds ratio (OR) = 1.42, 95% CI: 1.05~1.91; p = 0.02]. The BDNF (rs6265) polymorphism showed that there is no correlation with MDD. When interaction with BDNF was modeled, for individuals with BDNF (rs6265), genotype GG, cases in the heterozygous group had even higher odds of MDD than those in the combined homozygous group of 5-HTTLPR polymorphism (OR = 2.92, 95% CI: 1.43-5.95; p = 0.003).**

**CONCLUSIONS: Our results suggested that 5-HTTLPR, may be associated with the susceptibility of MDD in an overdominant mode, and there may be a significant interaction between 5-HTTLPR and BDNF (rs6265) polymorphisms in relation to MDD.**

Key Words:
Major depressive disorder, Serotonin transporter protein promoter, Brain-derived neurotrophic factor, Gene polymorphism, Overdominant model.

## Introduction

Major depressive disorder (MDD) is a prevalent form of mental illness and a leading cause of disability worldwide. The etiology of MDD is multifactorial but the genetic risk is an important factor[1-4]. A most studied genetic risk in MDD manifested that neuroticism is the repeat-length polymorphism within promoter region (5-HTTLPR) of genes encoding serotonin transporter (5-HTT)[5,6]. 5-HTTLPR is made up of 44-bp repeats. Insertion/deletion variable-number tandem repeats leads to 5-HTTLPR polymorphism, which is primarily either as a shorter allele (S) of a segment of 14 complex repeats or a longer allele (L) with 16 repeats, which are associated with low and higher 5-HTT transcription, respectively. 5-HTT plays an important role in serotonergic signaling. Thus, polymorphism of 5-HTTLPR is expected to be of clinical significance for psychiatric illnesses including MDD. However, the correlation between 5-HTTLPR polymorphism and MDD with and other behavioral traits of neuroticism is still controversial. A large scale meta-analysis by Clarke[7], involving approximately 7800 cases and 16000 controls, revealed a significant, but modest effect of the S allele (odds ratio = 1.076) using recessive model. Odgerel et al[8] did not find any significant association between 5-HTTLPR and another serotonin transporter polymorphism (rs25531) and MDD, anxiety disorders, or neuroticism scores in either European Americans or African Americans. Moreover, some studies suggested that the 5-HTTLPR polymorphism plays an overdominant role in MDD[9] or neuroticism[10].


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Besides 5-HTTLPR, another widely studied risk factor for susceptibility of MDD is a brain-derived neurotrophic factor (BDNF), as a neurotropic factor in the brain and spinal cord that promotes the survival of neurons[11]. The Val66Met (G196A, rs6265) polymorphism is the most important genetic variant within an exon of BDNF gene which changes an amino acid at codon 66 from Val to Met. Some investigations[12-14] have suggested that Val66Met is positively associated with MDD risk, although these have not been confirmed in meta-analysis[15,16]. By recruiting 447 patients with MDD and 432 controls, we found a significant effect of three-locus BDNF/GSK3β interaction (GSK3β rs6782799, BDNF rs6265 and BDNF rs7124442) with MDD were found in Chinese population and individuals carrying the combination of three risk alleles gave the largest OR value of 4.46[17].

Previous researches showed a significant interaction between BDNF and serotonin in brain function. Serotonergic transmission exerts powerful control over BDNF gene expression, and BDNF promotes the survival, differentiation and maintenance of serotonergic neurons[18]. However, the effect of 5-HTTLPR-BDNF (rs6265) interaction on MDD-risk is not consistent. In this paper, it is aimed to explore 5-HTTLPR polymorphism and the BDNF (rs6265) polymorphism and to their possible interaction in relation to MDD-risk by using case-control data collected in the Han Chinese population. We were specifically interested in whether the effect of 5-HTTLPR polymorphism is overdominant, and how the effect is influenced by BDNF polymorphism.

## Patients and Methods

### Patients

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

Cases were collected from March 2004 and February 2008 in Shanxi Province of China. Sample collection and diagnosis for subjects had been previously described in detail[17,19]. The sample of Zhang's study included 401 patients with MDD and 391 controls in 2009, 447 patients with MDD and 432 controls in 2010. In the present study, our sample completed were overlapped those in Zhang's study. Among subjects, 459 patients (male, n = 229; female, n = 230; age range, 18-60 years old) were recruited from clinical settings of the Department of Psychiatry, First Hospital of Shanxi Medical University. The diagnosis was made by at least two consultant psychiatrists according to criteria for MDD in "Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV)" (American Psychiatric Association, 1994). All patients were also diagnosed with the Chinese Version of the Modified Structured Clinical Interview for DSM-IV TR Axis I Disorders Patient Edition (SCID-I/P, 11/2002 revision). Among these patients, 81.3% were suffering their first major depressive episode (n = 373), while the remaining 18.7% were experiencing a relapse (n = 86). Patients 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 were excluded.

The control was consisted of 412 healthy volunteers (male, n = 172; female, n = 240; age range, 18-60 years old). They were without any history of neuropsychiatric disorders and recruited from the community or regular health screening visiting as controls.

### Genotyping

Two types of polymorphisms were selected from the NCBI database (http://www.ncbi.nlm.nih.gov) and the HapMap database (http://www.hapmap.org), including 5-HTTLPR polymorphism in the 5-HTT gene and rs6265 polymorphism in the BDNF gene. Genomic DNA was extracted from peripheral blood leukocytes by the phenol-chloroform extraction. Polymerase chain reaction (PCR)-based genotyping was used to detect polymorphisms.

Primers were designed with Primer 5.0 software. The primer pair for detecting 5HTTLPR polymorphism are forward 5'-GGCGTTGCCGCTCTGAATGC-3' and reverse 5'-GAGGGACTGAGCTGGACAACCAC-3'. The primer pair for detecting BDNF (rs6265) polymorphism are forward 5'-GCTTTCTCCCTACAGTTCCAC-3' and reverse 5'-TCTGCTGCCGTTACCCAC-3'. PCR was performed in 25 μl volume containing 60 ng of genomic DNA, 200 μM dNTPs, 0.2 μM each primer, 2.5 μl 10×PCR buffer, and 1 U of Taq DNA polymerase (Tiangen,

Beijing, China). PCR included initial denaturation at 94 °C for 5 min, followed by 35 cycles of 94 °C for 30 s, 60 °C for 5HTTLPR or 56 °C for BDNF (rs6265) annealing for 30 s, 72 °C for 30 s, and a final elongation at 72 °C for 10 min. Products of 5HTTLPR were electrophoresed on 12% polyacrylamide gels and products of rs6265 were sequenced with the ABI 3730 DNA analyzer (Perkin-Elmer, Applied Biosystems, Foster City, CA, USA).

### Statistical Analysis

Genotype frequencies of the 5-HTTLPR and BDNF polymorphisms in both cases and controls and tested for departure from Hardy-Weinberg equilibrium (HWE)[20]. Specifically, for the 5-HTTLPR polymorphism, the previously observed heterosis might imply a selective advantage or disadvantage conferred on the heterozygous genotype, which in turn may result in a departure from HWE[9,10].

Logistic regression was performed to assess the effects of 5-HTTLPR and BDNF polymorphisms and their interaction in relation to MDD. For both 5-HTTLPR and BDNF polymorphisms, we first conducted the analysis using a co-dominant model. Based on the results of the co-dominant model, we repeated the analysis with some reduced genetic models. For 5-HTTLPR, we were specifically interested in the overdominant model in order to test whether our data support the heterosis reported in the literature. If an interaction between the two polymorphisms was modeled, we reported Odds ratios (ORs), the corresponding 95% confidence intervals (95% CIs), and *p*-values for each polymorphism within the strata of the other polymorphism, in addition to the *p*-values for the test of the interaction effect. In all analyses, age and gender were adjusted. All analyses were performed using the SAS software (SAS Institute Inc., 2011) and $p < 0.05$ was considered statistically significant.

## Results

### Hardy-Weinberg Equilibrium Analysis

Genotype frequencies of BDNF polymorphism rs6265 did not differ significantly from those expected under HWE. However, as shown in Table I, we observed a significant deviation from HWE for 5-HTTLPR in the control group, but not in the case group. In the control group, there were only 28% individuals carrying the heterozygous genotype (LS), which is far less than what should be expected (36%) based the observed allele frequency of the S-allele (76%) under HWE, leading to a significant deviation from HWE ($p = 1.62E-05$). In the case group, the expected heterozygous genotype frequency was 39%, which is very close to the observed value of 36%, and the deviation from HWE was not significant ($p = 0.11$).

### Genotypic and Allelic Distribution of SNPs

Table II shows the distribution of cases and controls in terms of gender, age and the genotypes of the two polymorphisms. A Chi-square test showed that gender, age and genotype of 5-HTTLPR were significantly different between cases and controls. Because an allelic association test requires an assumption of HWE, we only conducted association tests based on genotypes, which does not reply on the assumption of HWE. In Table III, we show the results of univariate analyses for the two polymorphisms by using logistic regression adjusted for gender and age. The analyses were performed using a co-dominant model for both polymorphisms, as an overdominant model for 5-HTTLPR, and a recessive model for BDNF, respectively. Individuals with the heterozygous genotype of 5-HTTLPR (LS) is significantly higher risk of MDD than those with homozygous SS genotype (OR = 1.46, 95% CI: 1.08-1.96; $p = 0.01$) or those with either homozygous SS or LL genotype (OR = 1.42, 95%

**Table I.** Allele and genotype frequencies of 5-HTTLPR and test for Hardy-Weinberg equilibrium.

| | Allele frequency (S) | Expected genotype frequency | | | Observed genotype frequency | | | HWE p-value |
|---|---|---|---|---|---|---|---|---|
| | | SS | LS | LL | SS | LS | LL | |
| Controls N (%) | 609 (76.1) | 231 (53.4) | 171 (39.4) | 32 (7.3) | 248 (54.8) | 113 (36.4) | 39 (8.8) | 1.62E-05 |
| Cases N (%) | 634 (73.1 ) | 232 (58.0) | 145 (36.3) | 23 (5.7) | 238 (62.0) | 158 (28.3) | 38 (9.8) | 1.14E-01 |

**Table II.** Distribution of MDD cases and controls in terms of gender, age and the genotypes of the two polymorphisms.

| Variables | Categories | | MDD Cases N (%) | Controls N (%) | p-value |
|---|---|---|---|---|---|
| Gender | Male | | 229 (49.9) | 172 (41.7) | |
| | Female | | 230 (50.1) | 240 (58.3) | 0.02 |
| Age (years) | Age < 25 | | 191 (41.6) | 215 (52.2) | |
| | Age > 25 | | 268 (58.4) | 197 (47.8) | <0.01 |
| Genes | 5-HTTLPR | LL | 38 (8.8) | 39 (9.8) | |
| | | LS | 158 (36.4) | 113 (28.2) | 0.04 |
| | | SS | 238 (54.8) | 248 (62.0) | |
| | BDNF (rs6265) | AA | 88 (22.0) | 93 (23.2) | |
| | | AG | 215 (48.9) | 202 (50.2) | 0.64 |
| | | GG | 128 (29.1) | 107 (26.6) | |

CI: 1.05-1.91; $p = 0.02$). Any significant association was observed between the BDNF (rs6265) polymorphism and MDD ($p > 0.05$).

### Gene-Gene Interaction

Then, multivariable analyses were conducted by using logistic regression to investigate a possible interaction between 5-HTTLPR and BDNF. Based on the results obtained from the univariable analyses, we used an overdominant model for 5-HTTLPR was used. For BDNF, a co-dominant model was firstly used and a significant interaction was observed between these two polymorphisms ($p = 0.0039$). As shown in Table IV, for individuals carrying genotype GG for BDNF, the heterozygous genotype (LS) group for 5-HTTLPR is significantly higher risk of MDD than the two homozygous groups (SS and LL) (OR = 2.91, 95% CI: 1.42-5.93; $p = 0.003$). For individuals carrying heterozygous genotype of 5-HTTLPR, the GG genotype group had significantly higher risk of MDD than the AG and GG genotype groups (for the AA group, OR = 4.02, 95% CI: 1.73-9.37; $p = 0.001$; for the AG group, OR = 2.27, 95%CI: 1.08-4.76; p = 0.03). These results seemed to suggest a recessive model for BDNF (that is, GG *vs*. AA/AG). Therefore, a logistic regression was conducted using an overdominant model for 5-HTTLPR and a recessive model for BDNF and observed a significant interaction was observed again between these two polymorphisms ($p = 0.0064$). The results for ORs were also shown in Table IV and were similar to what we observed using a co-dominant model for BDNF.

## Discussion

In this study, we investigated the effects of 5-HTTLPR and BDNF (rs6265) polymorphisms and their potential interaction in relation to MDD in a Han Chinese population. Our re-

**Table III.** Association between genotypes of 5-HTTLPR and BDNF (rs6265) and MDD case status using univariable logistic regression model.

| Variables | OR | 95%CI for OR | | p-value |
|---|---|---|---|---|
| 5-HTTLPR | LS vs. LL | 1.43 | (0.86, 2.39) | 0.16 |
| | LS vs. SS | 1.46 | (1.08, 1.96) | 0.01 |
| | LS vs. LL/SS | 1.42 | (1.05, 1.91) | 0.02 |
| BDNF (rs6265) | AG vs. AA | 1.03 | (0.75, 1.40) | 0.88 |
| | GG vs. AA | 1.08 | (0.77, 1.50) | 0.66 |
| | AG/GG vs. AA | 1.05 | (0.78, 1.41) | 0.77 |
| | GG vs. AA/AG | 1.19 | (0.90, 1.58) | 0.22 |

**Table IV.** Interaction between 5-HTTLPR and BNDF (rs6265) in relation to MDD.

| | Label | Stratum | OR | 95%CI for OR | *p*-value |
|---|---|---|---|---|---|
| | 5-HTTlpr LS vs. LL/SS | at BNDF=AA | 0.53 | (0.26, 1.07) | 0.08 |
| | 5-HTTlpr LS vs. LL/SS | at BNDF=AG | 1.25 | (0.75, 2.06) | 0.39 |
| | 5-HTTlpr LS vs. LL/SS | at BNDF=GG | 2.91 | (1.42, 5.93) | 0.003 |
| BNDF (rs6265) | BNDF AG vs. AA | at 5-HTTlpr=LL/SS | 0.76 | (0.46, 1.23) | 0.26 |
| co-dominant model | BNDF GG vs. AA | at 5-HTTlpr=LL/SS | 0.73 | (0.43, 1.25) | 0.26 |
| | BNDF GG vs. AG | at 5-HTTlpr=LL/SS | 0.97 | (0.61, 1.54) | 0.90 |
| | BNDF AG vs. AA | at 5-HTTlpr=LS | 1.77 | (0.87, 3.63) | 0.12 |
| | BNDF GG vs. AA | at 5-HTTlpr=LS | 4.02 | (1.73, 9.37) | 0.001 |
| | BNDF GG vs. AG | at 5-HTTlpr=LS | 2.27 | (1.08, 4.76) | 0.03 |
| | 5-HTTlpr LS vs. LL/SS | at BNDF=AA/AG | 0.93 | (0.62, 1.39) | 0.72 |
| BNDF | 5-HTTlpr LS vs. LL/SS | at BNDF=GG | 2.92 | (1.43, 5.95) | 0.003 |
| (rs6265) recessive Model | BNDF GG vs. AA/AG | at 5-HTTlpr=LL/SS | 0.88 | (0.57, 1.36) | 0.56 |
| | BNDF GG vs. AA/AG | at 5-HTTlpr=LS | 2.77 | (1.37, 5.57) | 0.004 |

sults showed that polymorphism of 5-HTTLPR significantly influences MDD risk in an overdominant way: the combination of the short and long allele of 5-HTTLPR when paired in heterozygous individuals will have a statistically significantly higher odds of MDD (OR = 1.42, $p = 0.02$) than those with either homozygous genotype. This overdominant effect of 5-HTTLPR became even more significant when an interaction with BDNF was taken into account: for individuals with the GG genotype of BDNF, the odds of MDD was nearly three times higher among those with a heterozygous genotype of 5-HTTLPR compared to those with a homozygous genotype (see Table IV).

The heterozygous genotype of 5-HTTLPR we observed for MDD is consistent with the so-called "heterosis" reported by Munafo et al[10] for neuroticism. Although the term "heterosis" usually refers to an improved or increased function of a hybrid organism, the meta-analysis by Munafo et al[10] implied that the highest personality scores were in the heterozygous group. Furthermore, in another study by Munafo et al[21], they found that there was a significant association among 5-HTTLPR genotype, neuroticism, and lifetime major depression, indicating that neuroticism is underlying the association between 5-HTTLPR and depression. Recently, a genome-wide sequencing study[22] of MDD for the Chinese Han women has been conducted by the CONVERGE consortium. We noticed that 5-HTTLPR was not reported as a significantly associated polymorphism. It is not possible to validate our findings using the results obtained by the CONVERGE consortium.

It has been believed that short allele of 5-HTTLPR is behaviorally deleterious because of the reduced transcriptional activity of 5-HTT[23,24]. However, our data revealed a higher frequency (75%) of the short allele of 5-HTTLPR in the Han Chinese population compared with the European American (43%) and African Americans (25%)[8]. The differences probably imply a complicated geographic dependence of natural selection on this polymorphism across human evolutionary history. It was likely that the short allele had some kind of evolutionary advantage in some regions East Asia. Our findings also showed that in the control group, the proportion of heterozygous genotype of 5-HTTLPR was significantly lower than the expected value under HWE (28% *vs*. 36%). Such deviation was not observed in the case group. Although the observed heterosis might be a statistical artefact or genotyping error, our results suggested that further investigation including replication studies using different data sets and/or from different populations are warranted. After all, simply discarding the data whenever deviation from HWE is observed may result in a loss of useful information[25].

In this work, we did not observe a significant association between BDNF (6265) polymorphism and MDD in Han ChineJTase people. Despite evidence for the role of BDNF in MDD, such as animal models of depression, brain tissue and blood samples of patients with depression, previous genetic association studies, including a meta-analysis[16], have not identified and associated between BDNF and MDD in human populations. In consistent with studies for European populations, our

data did not show that the BDNF gene plays a significant role by itself in MDD in Han Chinese population. Recently, the CONVERGE consortium[22] has conducted a genome-wide sequencing study and also it is found that BDNF (6265) polymorphism did not show association with recurrent MDD in Chinese Han women (OR = 1.015, $p = 0.591$). Some studies have reported a gender difference in the genetic association of BDNF (rs6265) and 5-HTTLPR with MDD. Clinically, depressions are clearly different according to gender in many ways. Replication study focused on gender-specific gene association will be necessary for our study in future.

Cumulating evidences have demonstrated a functional interplay between BDNF and 5-HT in mood disorders[18]. BDNF promotes the survival and differentiation of 5-HT neurons[26]. Conversely, 5-HTT knockout in rats consistently shows reduced BDNF mRNA and protein levels in the hippocampus and prefrontal cortex[27]. Using antidepressant selective serotonin reuptake inhibitors (SSRIs) can enhance BDNF gene expression[28]. We observed a significant interaction between 5-HTT and BDNF gene in MDD. Our result is consistent with Lee et al[29] recruited 186 Korea subjects and 1032 controls and found a significant interaction between BDNF (rs6265) polymorphism and 5-HTTLPR with age at onset of depression in the entire MDD patients group. The interaction between BDNF (rs6265) and 5-HTTLPR has been indicated as regulating environmental factor in MDD. Grabe et al[30] recruited 2035 Caucasian subjects and found that the S/S genotype of the 5-HTTLPR exerted a negative impact on MDD after childhood abuse only in the presence of the G/G genotype for BDNF (rs6265) polymorphism but not in the presence of the A allele. However, Gutiérrez et al[31] included 2679 Spanish participants, and observed that if they had previously experienced any kind of childhood abuse, those with both the 5-HTTLPR S allele and the BDNF (rs6265) A allele showed the highest risk of MDD. Harkness et al[32] included a community sample of 339 young adults, in the context of childhood neglect, and showed that individuals carrying A allele of BDNF (rs6265) and S allele carriers of 5-HTTLPR showed significantly more severe depression than those with L/L genotype, whereas a differential association of 5-HTTLPR genotype with depression was not observed among those with BDNF (rs6265) G/G genotype. The different interaction effects between 5-HTTLPR and BDNF may reflect some type of population heterogeneity and suggested 5-HTTLPR and BDNF (rs6265) polymorphisms may contribute to MDD in a complex way. Further exploration on the potential mechanism of the observed interaction between 5-HTTLPR and BDNF (rs6265) polymorphisms in relation to the susceptibility of MDD is warrant.

Our report had the following limitations. First, our data showed that the Han Chinese population had a higher frequency of S allele of 5-HTTLPR compared to the other populations. It is possible that this phenomenon is just a statistical artifact or genotyping error, and further studies involving more samples using different data sets and/or from different populations are needed. Second, the onset of MDD is influenced by both genetic and environmental factors, such as life events, maltreatment in childhood, and social support, etc. Another limitation is that environmental factors were not taken into account, because our sample size was too small for a three-way interaction analysis.

## Conclusions

We found that the 5-HTTLPR polymorphism may be associated with the susceptibility of MDD, and there may be a significant interaction between 5-HTTLPR and BDNF (rs6265) polymorphisms in relation to MDD. Replication study is warranted in order to explore the biological plausibility of the observed overdominant effect of 5-HTTLPR and its interaction with BDNF.

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**Conflicts of interest**

The authors declare no conflicts of interest.

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