



## Smoking and BDNF Val66Met polymorphism in male schizophrenia: A case-control study



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### ABSTRACT

Some recent studies show an association between a functional polymorphism of BDNF gene (Val66Met) and the susceptibility to nicotine dependence and we hypothesized that this polymorphism was associated with smoking in both schizophrenia patients and healthy controls. The *BDNF* Val66Met gene polymorphism was genotyped in 690 chronic male schizophrenia patients (smoker/nonsmoker = 522/169) and 628 male controls (smoker/nonsmoker = 322/306) using a case-control design. Nicotine dependence (ND) was assessed by the cigarettes smoked per day (CPD), the Heaviness of Smoking Index (HSI), and the Fagerstrom Test for ND (FTND). Patients also were rated on the Positive and Negative Syndrome Scale (PANSS). The results showed no significant differences in *BDNF* Val66Met genotype and allele distributions between the patients and healthy controls or between smokers and nonsmokers in either patients or healthy controls alone. In patient groups, however, the smokers with the Met allele had significantly higher HSI scores (Met/Met:  $2.8 \pm 1.7$  vs. Met/Val:  $2.2 \pm 1.7$  vs. Val/Val:  $2.0 \pm 1.6$ ,  $p < 0.01$ ) and a trend toward a significantly higher FTND score ( $p = 0.09$ ) than those with the Val/Val genotype. In addition, the smokers showed significantly lower PANSS negative symptom and total scores, longer duration of illness and more hospitalizations (all  $p < 0.05$ ). In the control group, the smokers with the Met allele started smoking significantly earlier than those with the Val/Val genotype (both  $p < 0.05$ ). These results suggest that the *BDNF* Val66Met polymorphism may affect a smoker's response to nicotine in both schizophrenia and healthy controls from a Chinese Han population, but with differential effects in different aspects of smoking behaviors.

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### 1. Introduction

Schizophrenia is associated worldwide with a higher rate of smoking than that observed among the general population or those with other severe mental illnesses (Llerena et al., 2003; de Leon and Diaz, 2005). The reasons for such high rates of smoking in this psychiatric population are not well understood. A number of

theories have been proposed, and two main hypotheses have become popular. The self-medication hypothesis suggests that smoking might have a beneficial effect by decreasing negative symptoms or extrapyramidal side-effects of antipsychotics, and/or ameliorating cognitive deficits associated with schizophrenia (Adler et al., 1998; Dalack et al., 1998; Kumari and Postma, 2005). The genetic hypothesis proposes a shared genetic vulnerability (de Leon, 1996; de Leon and Diaz, 2012) that exerts pleiotropic effects (i.e., the same DNA sequence causing both phenotypes of schizophrenia and smoking). Two specific pleiotropic associations between smoking and schizophrenia may involve genetic variations in the alpha-7 nicotine receptor gene (Freedman et al., 1997; Mexal et al., 2010) and in the brain-derived neurotrophic factor (BDNF) gene (Li, 2006).

Molecular epidemiological studies suggest that genetic factors play a role in the etiology of smoking behavior (Vink et al., 2005;

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Li, 2008). According to twin studies, heritability for smoking initiation has been estimated to be in males: 22–75%, and in females: 32–72% (Tyndale, 2003; Li et al., 2004). Heritability for smoking persistence has been estimated to be in males 50–71%, and in females 4–49% (Tyndale, 2003; Li et al., 2004). Heritable predisposition to smoking may be mediated, in part, by genetic variation in the mesolimbic dopamine (DA) pathway, a pathway that mediates the reinforcing effects of all drugs of abuse (Lerman and Berrettini, 2003). Preclinical studies show that nicotine activates dopaminergic neurons in the mesolimbic reward pathway enhancing DA release (Pontieri et al., 1996), which is associated with the pleasurable effects of the drug.

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophic factor family, is widely expressed in the adult mammalian brain, playing a critical role in the development, regeneration, survival, maintenance and function of neurons (Altar and DiStefano, 1998). Studies show that BDNF and DA systems interact within a number of neurobiological processes (Altar et al., 1997; Guillin et al., 2001). For example, *in vitro* and *in vivo* evidence shows that BDNF is vital for the growth, functionality and neurodevelopment of dopaminergic neurons (Hyman et al., 1991; Thoenen, 1995). Moreover, dopaminergic neurons are regulated and receive neuroprotection through BDNF (Hyman et al., 1991). In addition, BDNF facilitates normal expression of the dopaminergic receptor subtypes in drug-reward brain areas during development and in adulthood (Guillin et al., 2001). BDNF's influence on DA responsiveness might be an important determinant in the etiopathology and/or treatment of several conditions implicating DA such as drug abuse and psychiatric disorders (Guillin et al., 2001, 2007).

Preclinical data show that chronic nicotine increases BDNF mRNA levels in the hippocampus (Kenny et al., 2000). Interestingly, genome-wide linkage scans indicate that the region of chromosome 11p13 where the BDNF gene is located likely harbors susceptibility genes for polysubstance abuse in general (Uhl et al., 2001) and for nicotine dependence specifically (Li et al., 2003). Moreover, Beuten et al. (2005) provide evidence of an association between allelic variants of BDNF and nicotine dependence in male European-American smokers (Beuten et al., 2005). A single nucleotide polymorphism (SNP) that determines a valine-to-methionine variation at codon 66 of the BDNF coding sequence (rs6265) was found to be functional and alters intracellular trafficking and packaging of pro-BDNF, influencing the activity-dependent BDNF secretion (Egan et al., 2003). Consequently, secretion of the mature peptide has been implicated in human memory and hippocampal function. A recent study in Germany demonstrated that the frequency of both the Met/Met genotype and Met allele was significantly increased in current and in former smokers when compared to never smokers (Lang et al., 2007), although subsequent association studies did not corroborate these findings (Montag et al., 2008; Zhang et al., 2012). Other studies have linked this BDNF polymorphism with smoking initiation (Tobacco and Genetics Consortium, 2010), smoking cessation (Breetvelt et al., 2012) or the age of smoking initiation (Zhang et al., 2012). Taken together, these findings suggest that BDNF may play an important role in the etiology of nicotine dependence, and the BDNF Met allele is considered being the risk allele for smoking.

Also intriguing is the potential role of BDNF in the pathogenesis of schizophrenia. Conflicting results from postmortem studies show that BDNF mRNA is either reduced (Durany et al., 2001; Weickert et al., 2003) or increased (Takahashi et al., 2000) in the hippocampus and prefrontal cortex and other areas of the brain of patients with schizophrenia. The majority of studies report decreased serum BDNF levels in treated and first-episode schizophrenic patients (Rizos et al., 2008; Chen et al., 2009; Xiu et al., 2009; Pillai et al., 2010; Nurjono et al., 2012). Moreover, BDNF

levels have been associated with positive symptoms (Buckley et al., 2007; Chen et al., 2009; Xiu et al., 2009), negative symptoms (Rizos et al., 2008), and cognitive deficits (Zhang et al., 2012). In addition, some studies showed the association between the BDNF Val66Met polymorphism or BDNF haplotypes and schizophrenia (Hong et al., 2003; Neves-Pereira et al., 2005; Rosa et al., 2006), although several other studies did not replicate these results (Naoe et al., 2007; Xu et al., 2007; Kanazawa et al., 2007; Zintzaras, 2007; Varnas et al., 2008; Zhou et al., 2010).

In view of high rate of smoking in schizophrenia and the well-documented interaction of nicotine and BDNF, as well as the important role of BDNF in the pathogenesis of schizophrenia, we hypothesized that BDNF was associated with smoking in patients with schizophrenia. To test this we examined the relationship between the BDNF Val66Met polymorphism and nicotine dependence in schizophrenia using a case-control design in a Chinese population. In addition to studying the main effect of the above polymorphism, other possible mediating effects including demographic and clinical parameters, as well as clinical symptoms shown on the Positive and Negative Syndrome Scale (PANSS) were assessed. Because smoking is substantially more common among Chinese men than in women with schizophrenia (Zhang et al., 2010), as well as gender differences in smoking behaviors (de Leon and Diaz, 2005), we included only male subjects.

## 2. Methods

### 2.1. Subjects

We recruited 690 male inpatients with schizophrenia from Beijing HuiLongGuan Hospital and HeBei Province Veterans Psychiatric Hospital in BaoDing City, which is about 50 miles away from Beijing. All diagnoses of schizophrenia were confirmed by a consensus diagnosis of two independent experienced psychiatrists on the basis of the Structured Clinical Interview for DSM-IV (SCID). All schizophrenic patients were of the chronic type, with at least 5 years of illness and a mean illness course of  $24.5 \pm 9.3$  years, were Han Chinese, and between 25 and 75 years old. All patients had been receiving stable doses of oral antipsychotic drugs for at least 12 months before entry into the study. Antipsychotic drug treatment consisted mainly of drug monotherapy including: clozapine ( $n = 331$ ), risperidone ( $n = 139$ ), chlorpromazine ( $n = 57$ ), sulpiride ( $n = 38$ ), perphenazine ( $n = 30$ ), aripiprazole ( $n = 23$ ), quetiapine ( $n = 19$ ), haloperidol ( $n = 18$ ), loxapine ( $n = 14$ ), olanzapine ( $n = 6$ ) and others ( $n = 15$ ). A mean daily dose of antipsychotics, including both first- and the second-generation antipsychotics, was converted to approximate daily mean chlorpromazine milligram equivalents for each subject using standard guidelines (Woods, 2003). The mean antipsychotic dose (in chlorpromazine equivalents) was  $449 \pm 427$  mg per day.

We also recruited 628 male normal controls from the local community. All participants were interviewed by trained investigators supervised by a research psychiatrist. A clinical interview was used to exclude potential controls with Axis I disorders by a research psychiatrist. Current mental status and personal or family history of any mental disorder was assessed by unstructured interviews. None of the healthy control subjects presented a personal or family history of psychiatric disorder.

A complete medical history, physical examination, and laboratory tests were obtained from patients and control subjects. All subjects were in good physical health, and any subjects with major medical illnesses or drug and alcohol abuse/dependence were excluded. All subjects were Han Chinese from the Beijing area. They gave written informed consent, which was approved by the Institutional Review Board of Beijing Hui-Long-Guan hospital.

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