Psychiatry Research ■ (■■■■) ■■■–■■■

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Psychiatry Research

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Letter to the Editor

The brain-derived neurotrophic factor Val66-Met polymorphism is not associated with schizophrenia: An updated meta-analysis of 11,480 schizophrenia cases and 13,490 controls

To the Editors:

Of the known polymorphisms in the BDNF gene, the most extensively investigated single nucleotide polymorphism is Val66-Met, also known as G196A or rs6265. Accumulating evidence suggests a potential relationship between the rs6265 polymorphism and schizophrenia; however, the results of such studies have been inconsistent. Thus, we performed an updated meta-analysis to explore the association between the rs6265 polymorphism and the risk of schizophrenia.

We used 'BDNF (Val66Met or G196A or rs6265)' and 'schizophrenia' as search words to identify full texts in the PUBMED and EMBASE databases before July 2014. Only case-control studies of patients who fulfilled the DSM-IV or the ICD-10 diagnostic criteria for schizophrenia were included in the analysis. The reference lists of each article were further examined to include studies not listed in above databases. In the case of studies using overlapping populations, only the study with the larger sample was included. The data analysis and statistical methods were carried out according to the methods described in our previous study (Zhao et al., 2013).

Database searches identified 44 studies met the inclusion criteria (Egan et al., 2003; Hong et al., 2003; Nanko et al., 2003; Skibinska et al., 2004; Anttila et al., 2005; de Krom et al., 2005; Gourion et al., 2005; Neves-Pereira et al., 2005; Schumacher et al., 2005; Szeszko et al., 2005; Tan et al., 2005; Agartz et al., 2006; Chen et al., 2006; Hashimoto and Lewis, 2006; Ho et al., 2006; Jönsson et al., 2006; Tochigi et al., 2006; Watanabe et al., 2006; Zhang et al., 2006, 2012; Donohoe et al., 2007; Huang and Lee, 2007; Naoe et al., 2007; Numata et al., 2007; Qian et al., 2007; Xu et al., 2007; Han et al., 2008; Rybakowski, 2008; Takahashi et al., 2008; Chang et al., 2009; Kawashima et al., 2009; Park et al., 2009; Koolschijn et al., 2010; Zhou et al., 2010; Sun et al., 2011, 2013; Yi et al., 2011; Zakharyan et al., 2011; Gruber et al., 2012; Loh et al., 2012; Lu et al., 2012; Sotiropoulou et al., 2013; Suchanek et al., 2013; Chen et al., 2014). Previous studies have demonstrated the Val allele is associated with higher activity of the BDNF system compared with the Met allele; we therefore grouped the data for this meta-analysis according to the law of dominant or recessive modeling. We hypothesize the Met/Met genotype is required to confer susceptibility to schizophrenia.

The between-study heterogeneity results suggested the effect size of each study was not significant (I^2=4.5%, P=0.39). The pooled OR from these studies was 0.96 (95% CI=0.89–1.03, z=1.15, P=0.25), indicating there was no association between the Met/Met genotype and schizophrenia (Fig. 1). We speculated the Met/Met genotype is associated with schizophrenia in different populations, and performed separate analyses. The between-study heterogeneity results suggested the effect of study size was not significant in the Chinese population (I^2=39.2%, P=0.07); the pooled OR from these studies was 0.97 (95% CI=0.88–1.06, z=0.71, P=0.48), indicating there was no association between the Met/Met genotype and schizophrenia in the Chinese population. Similarly, no association was found in the Caucasian (OR=0.81, 95% CI=0.63–1.03, z=1.70, P=0.10) and Japanese (OR=1.00, 95% CI=0.87–1.14, z=0.06, P=0.95) populations. Following above analysis, we hypothesize the Met allele is a risk factor for schizophrenia. The between-study heterogeneity results suggested the effect size of each study was not significant (I^2=20.5%, P=0.12); the pooled OR from these studies was 0.99 (95% CI=0.95–1.03, z=0.46, P=0.65), indicating there was no association between the Met allele and schizophrenia. Similarly, we also compared the Met versus Val alleles in the Chinese, Caucasian and Japanese populations separately. However, the results did not change (OR=0.97, 95% CI=0.91–1.03, z=1.12, P=0.26; OR=1.00, 95% CI=0.93–1.09, z=0.05, P=0.96; OR=1.03, 95% CI=0.96–1.12, z=0.86, P=0.39).

Thirteen studies (Hong et al., 2003; Anttila et al., 2005; Szeszko et al., 2005; Tan et al., 2005; Agartz et al., 2006; Hashimoto and Lewis, 2006; Han et al., 2008; Takahashi et al., 2008; Koolschijn et al., 2010; Zakharyan et al., 2011; Gruber et al., 2012; Sotiropoulou et al., 2013; Suchanek et al., 2013) assessing the Val66Met polymorphism had small sample sizes, indicating possible population stratification. Therefore, a sensitivity analysis was performed excluding these studies. However, the sensitivity analysis did not alter the results of this meta-analysis (OR=0.97, 95% CI=0.90–1.05, z=0.83, P=0.41). Both the Begg–Mazumdar test (z=0.66, P=0.51) and Egger's test (t=−0.98, P=0.37) showed no significant results. Thus, we concluded that no publication bias existed.

In agreement with our findings, previous meta-analyses have also suggested the Val66Met polymorphism is not associated with schizophrenia (Xu et al., 2007; Kawashima et al., 2009). In contrast, Gratacòs et al. (2007) demonstrated the Met/Met carriers showed a 19% increased risk of schizophrenia compared with the heterozygous subjects. However, our updated meta-analysis, included 44 studies with 11,480 patients and 13,490 cases, is greater than the previous studies. We speculated the greater number of studies and larger sample sizes might explain the heterogeneity across these studies.

The major limitation of this study is we did not explore the potential association between the Val66Met polymorphism and the subclinical heterogeneity of schizophrenia. It has been proposed that investigating the subclinical specific phenotypes of a complex disorder such as schizophrenia, may increase the power to detect genes involved in these diseases. Therefore, it is of great importance

http://dx.doi.org/10.1016/j.psychres.2014.11.015

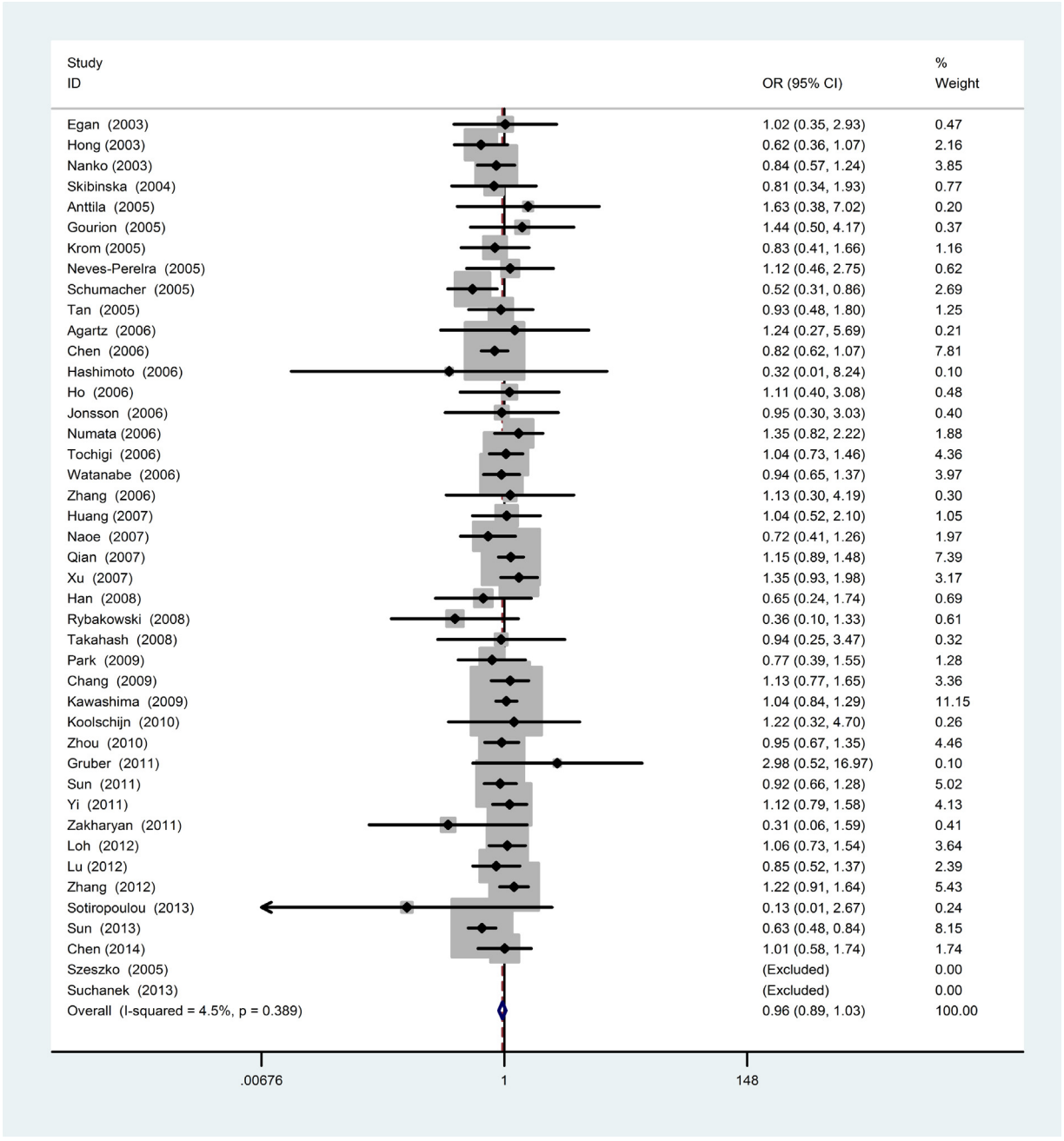

Fig. 1. Forest plot for the association between BDNF Val66Met polymorphism and schizophrenia risk (Met/Met versus Met/Val+Val/Val).

to test for an association between the Val66Met polymorphism and subgroups of patients with schizophrenia. In conclusion, this updated meta-analysis did not support the hypothesis that the BDNF Val66-Met polymorphism may confer susceptibility to schizophrenia.

Conflict of interest

All authors declare they have no conflict of interest.

Acknowledgment

This study was supported by grants from the National Natural Science Foundation of China (U1304804).

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Xiaofeng Zhao, Duolu Li, Chao Han, Quancheng Kan*
Clinical Pharmacology Base, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450002, Henan Province, PR China
E-mail address: kanqc@zzu.edu.cn (Q. Kan)

Yinglin Huang
Department of Psychology, Shengjing Hospital of China Medical University, Shenyang 110022, Liaoning Province, PR China

Kaiyuan Chen
Mental Health Center, Shantou University Medical College, Shantou 515065, Guangdong Province, PR China

Received 21 June 2014
3 November 2014
7 November 2014

* Corresponding author. Tel.: +86 371 66913114.