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LETTER

Association Between rs1344706 of *ZNF804A* and Schizophrenia: A Meta-analysis

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Abstract Schizophrenia is one of the most serious mental diseases found in humans. Previous studies indicated that the single nucleotide polymorphism (SNP) rs1344706 in the gene *ZNF804A* encoding zinc finger protein 804A was associated with schizophrenia in Caucasian population but not in Chinese Han population. However, current results are conflicting in Asian population. In the present study, a meta-analysis was performed to revisit the association between rs1344706 and the risk of schizophrenia in Asian, Caucasian and other populations. Electronic search of PubMed database identified 25 case–control studies with available genotype frequencies of rs1344706 for the meta-analysis, involving a total of 15,788 cases and 22,654 controls. A pooled odds ratio (OR) with 95% confidence interval (CI) was used to assess the association. The current meta-analysis showed an association between rs1344706 and schizophrenia in Caucasian populations ($P = 0.028$, OR = 1.138, 95% CI: 1.014–1.278; $P = 0.004$ for heterogeneity) and Asian populations ($P = 0.008$, OR = 1.092, 95% CI: 1.023–1.165; $P = 0.001$ for heterogeneity), but not in other populations ($P = 0.286$, OR = 1.209, 95% CI: 0.853–1.714, $P = 0.120$ for heterogeneity). Egger's test ($P > 0.05$) and Begg's test ($P > 0.05$) are both suggestive of the lack of publication bias for the included studies. Thus, the absence of association in other populations suggests a genetic heterogeneity in the susceptibility of schizophrenia and demonstrates the difficulties in replicating genome-wide association study findings regarding schizophrenia across different ethnic populations. To validate the association between rs1344706 and schizophrenia, further studies with larger participant populations worldwide are needed.

Introduction

Schizophrenia is a common, serious psychotic disorder. The main features of schizophrenia include various psychotic symptoms such as delusions, auditory hallucinations, altered emotional reactivity, disorganized behavior, social isolation and cognitive

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impairment [1]. Many studies based on families, twins and adopted individuals have consistently demonstrated the importance of genetic factors and of the combination of environmental and genetic factors to the etiology of schizophrenia, among which heritability estimates are approximately 80% [2–4].

Genetic variants in the gene *ZNF804A* have been found to be associated with schizophrenia in a genome-wide association study (GWAS) [5]. In particular, the intronic single nucleotide polymorphism (SNP) rs1344706 (A/C) has been associated with schizophrenia in several studies, with the A allele being the risk allele [5–8]. *ZNF804A* (OMIM: 612282) is located on chromosome 2q32.1 and consists of 4 exons and 3 introns [6]. *ZNF804A* encodes zinc finger protein 804A, which contains a C2H2-type zinc finger domain, and is distributed throughout the human brain especially in the developing medial temporal lobe and brain cortices [9–11]. Proteins with zinc finger domains play a variety of roles, including binding to DNA, transcriptional regulation, gene expression and DNA–protein interactions [10,12,13]. However, the exact functions of ZNF804A remain unknown [11]. Some studies suggested that rs1344706 may be associated with brain structure and function [14–16]. To further explore whether the risk allele A of rs1344706 would increase the risk of schizophrenia in different populations, the present meta-analysis was performed to evaluate the association between rs1344706 and the risk of schizophrenia in Asian, Caucasian and other populations.

Results

Eligible studies

A total of 25 studies that reported the association between rs1344706 and schizophrenia were identified from the literature and included in this meta-analysis (**Figure 1**), including 15,788 schizophrenia cases and 22,654 controls. The detailed characteristics of eligible studies are summarized in **Table 1**.

Meta analysis

The evaluation of the association between rs1344706 and the heterogeneity test is shown in **Table 2**. Since the genetic

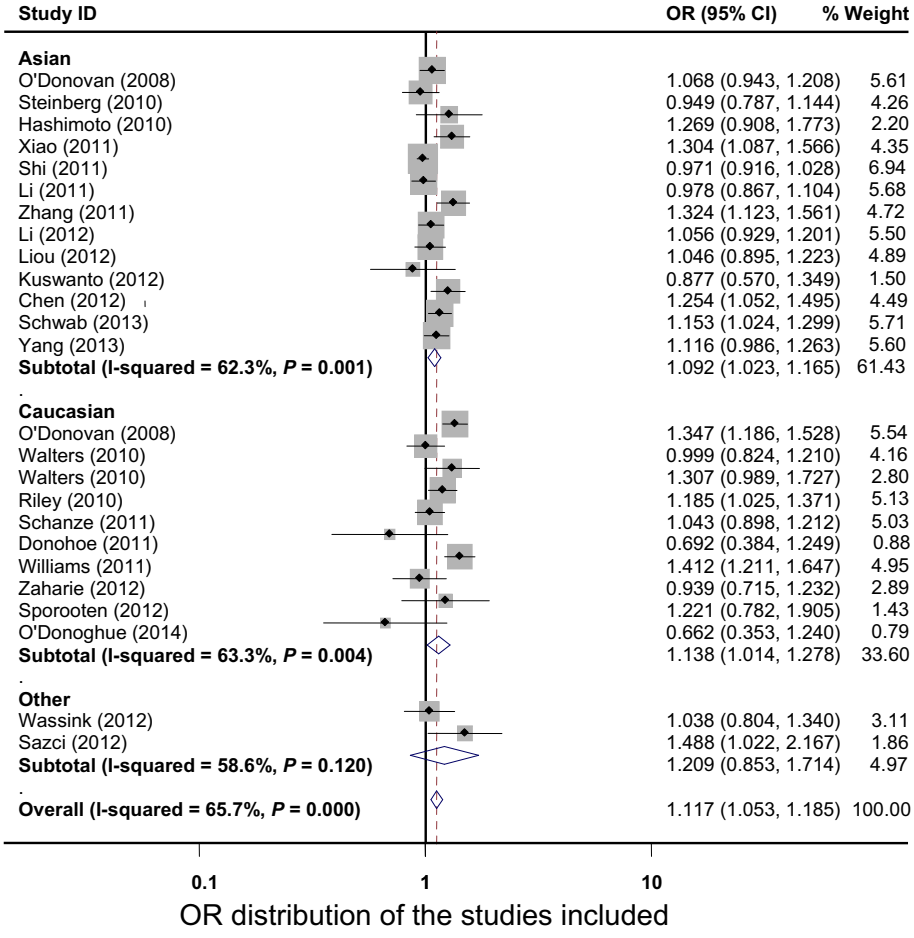

Figure 1 Forest plot of association between rs1344706 and schizophrenia in different ethnic populations
Forest plot of odds ratio (OR) of schizophrenia A allele when compared to the C allele (additive model) was generated. The OR of each study was plotted. The vertical black line indicates that OR equals to 1 and the dashed line in red indicates the overall OR for all 25 studies. The solid diamond and horizontal line correspond to the study-specific OR and 95% CI of each individual study, respectively. The area of the gray box reflects the study-specific weight, which was calculated from random effects analysis. The open diamond represents the pooled OR and 95% CI. The studies included in the meta analysis are listed according to the time of publication.

Table 1 Characteristics of the 25 studies included in the current meta-analysis

Population	Country	Year of publication	Number of cases	Number of controls	A allele frequency (%)		Authors	Refs.
					Case	Control		
Asian	China	2008	996	1015	0.530	0.514	O'Donovan	[5]
Asian	China	2010	439	446	0.533	0.546	Steinberg	[7]
Asian	Japan	2010	113	184	0.588	0.530	Hashimoto	[17]
Asian	China	2011	496	448	0.601	0.536	Xiao	[18]
Asian	China	2011	3617	6344	0.496	0.503	Shi	[19]
Asian	China	2011	891	1298	0.503	0.509	Li	[20]
Asian	China	2011	566	574	0.527	0.457	Zhang	[21]
Asian	Singapore	2012	885	976	0.520	0.506	Li	[22]
Asian	China	2012	522	793	0.512	0.501	Liou	[1]
Asian	China	2012	111	67	0.527	0.560	Kuswanto	[23]
Asian	China	2012	570	448	0.564	0.508	Chen	[24]
Asian	Indonesia	2013	1067	1111	0.525	0.489	Schwab	[25]
Asian	China	2013	1024	975	0.538	0.510	Yang	[26]
Caucasian	UK	2008	642	2937	0.660	0.590	O'Donovan	[5]
Caucasian	Germany	2010	251	1472	0.588	0.588	Walters	[27]
Caucasian	Ireland	2010	297	165	0.665	0.603	Walters	[8]
Caucasian	Ireland	2010	1021	626	0.650	0.610	Riley	[6]
Caucasian	Germany	2011	936	585	0.620	0.610	Schanze	[28]
Caucasian	Italy	2011	70	38	0.600	0.684	Donohoe	[29]
Caucasian	UK	2011	479	1445	0.670	0.590	Williams	[8]
Caucasian	Romania	2012	231	222	0.636	0.651	Zaharie	[30]
Caucasian	UK	2012	84	83	0.655	0.608	Sporooten	[31]
Caucasian	Ireland	2014	30	67	0.583	0.679	O'Donoghue	[32]
Other	USA	2012	335	198	0.622	0.614	Wassink	[33]
Other	Turkey	2012	105	137	0.676	0.584	Sazci	[34]

Note: Other populations include Turkish [34] and American [33].

Table 2 Meta-analysis of the association between rs1344706 and schizophrenia in different ethnic populations

Population	Pooled OR (95% CI)	*P* value	Heterogeneity *P* value	Publication bias *P* value	
				Begg's test	Egger's test
Asian	1.092 (1.023, 1.165)	0.008	0.001	0.464	0.058
Caucasian	1.138 (1.014, 1.278)	0.028	0.004	0.325	0.096
Others	1.209 (0.853, 1.714)	0.286	0.120	0.317	NA
Overall	1.117 (1.053, 1.185)	0.000	< 0.001	0.920	0.695

Note: NA, not applicable.

polymorphism model of ZNF804A is unclear, we used the additive model (A allele *vs.* C allele) for analysis. Our data showed an association with risk of schizophrenia in Caucasian populations ($P = 0.028$, OR = 1.138, 95% CI: 1.014–1.278; $P = 0.004$ for heterogeneity) and Asian populations ($P = 0.008$, OR = 1.092, 95% CI: 1.023–1.165; $P = 0.001$ for heterogeneity), but not in other populations ($P = 0.286$, OR = 1.209, 95% CI: 0.853–1.714, $P = 0.120$ for heterogeneity) (Figure 1).

Publication bias

The main purpose of meta-analysis is to extract information from published studies. However, selective publication of studies in a meta-analysis could lead to bias in the conclusions [35,36]. Therefore, Egger's test and Begg's test were performed to evaluate whether there exists publication bias in the previous studies on schizophrenia selected for this meta-analysis. As shown in Table 2, the *P* values from Egger's test and Begg's test for publication bias were in the range 0.058–0.92, which are all above the significance threshold. These data indicate no publication bias ($P > 0.05$ for both) for the studies included for the meta-analysis, which is further evidenced by the symmetry of the funnel plot as shown in **Figure 2**.

Discussion

Several SNPs such as rs1344706, rs4667001 and rs728534 in *ZNF804A* have been associated with schizophrenia in a GWAS of European population in 2008 [5]. Later on, three independent laboratories also demonstrated that rs1344706 in *ZNF804A* was associated with schizophrenia in European populations [37–39]. However, a previous meta-analysis suggested that rs1344706 is not associated with schizophrenia in Chinese Han population [40]. Thus, further studies are necessary to explore whether the risk allele A of rs1344706 would increase the risk of schizophrenia in different populations. Our present meta-analysis showed that rs1344706 is associated with schizophrenia in both Caucasian ($P = 0.028$) and Asian populations ($P = 0.008$), but not in other populations ($P = 0.286$). Two studies were classified as "others", including

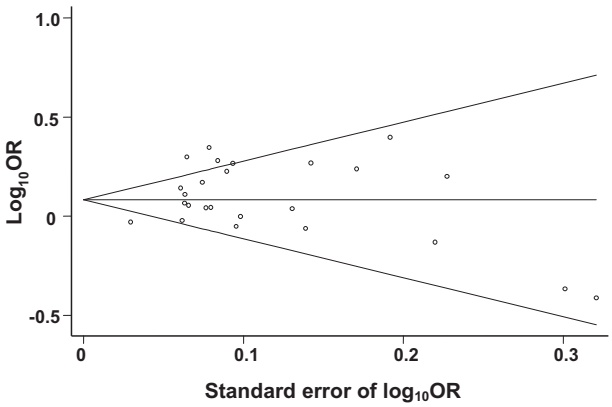

Figure 2 Begg's funnel plot for meta-analysis of rs1344706
The funnel plot is a scatter plot testing publication bias by determining if there is a significant correlation between the estimated effect sizes and their variances. The funnel graph plots log OR *vs*. their standard error. The horizontal line in the funnel plot indicates the summary estimate, while the sloping lines indicate the expected 95% CI for a given standard error, assuming no heterogeneity between studies. The statistical analysis was performed with pseudo 95% confidence limits using Stata software.

one performed by Wassink et al. in the United States [33] since the components of the study population were not described in the report. The other study is on Turkish population [34], since we cannot determine whether Turkish belongs to Asian population or Caucasian population. Our data agree well with the reported association of rs1344706 with the Caucasian. Nonetheless, these data are inconsistent with the previous study in Chinese populations. Such discrepancy could be explained by the number of studies included for Asian populations. In their report, Li et al. [40] included 8 studies (8982 cases and 12,342 controls) while we have 13 studies (11,297 cases and 14,679 controls) in the present meta-analysis, which included not only Chinese population but also other Asian populations like Japanese, Singaporeans and Indonesian. The difference in association of rs1344706 with schizophrenia between Caucasian, Asian and other populations may be due to the genetic heterogeneity of different ethnic populations [26]. The current findings suggest that genetic associations observed in complex psychiatric disorders may not be generalizable to different populations. Several studies have suggested that intelligence quotient (IQ) may modulate the association between *ZNF804A* gene polymorphism and cognitive function in schizophrenia patients [24,27]. Therefore, IQ may be a confounding factor and may modulate the association between rs1344706 and schizophrenia in other populations, which might explain our failure to find a significant association between rs1344706 and schizophrenia in other populations. Further association studies with more patients from more ethnic background would be required to determine the details.

Materials and methods

Literature search

The PubMed database was surveyed using search terms "ZNF804A", "SNP" and "schizophrenia" (the last search update was on May 14, 2014). Case–control studies with genotype frequencies of rs1344706 available were chosen without language restrictions. Additional studies were identified using review articles and manual searches of the reference section of original studies.

Statistical analysis

The strength of association between rs1344706 and schizophrenia was assessed by calculating crude additive ORs and 95% CIs for each study. The pooled ORs were calculated based on an additive genetic model (A allele *vs*. C allele). Due to the significant heterogeneity observed between studies ($P = 0.001$ for heterogeneity in Asian, and $P = 0.004$ for heterogeneity in Caucasian), the random effects model was used to calculate the pooled ORs.

Publication bias was examined using Begg's test rank correlation method (funnel plot method) and Egger's weighted regression method ($P < 0.05$ was considered significant) [35,36]. All statistical analyses were performed using Stata software (version 9.0; STATA Corporation, College Station, TX).

Authors' contributions

YL and WT conceived the idea and participated in study design. TL and JZ were involved in the study design. MZ carried out electronic search of PubMed database, performed the statistical analysis and drafted the manuscript. SJ, YL and WT revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that there are no competing interests.

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