



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

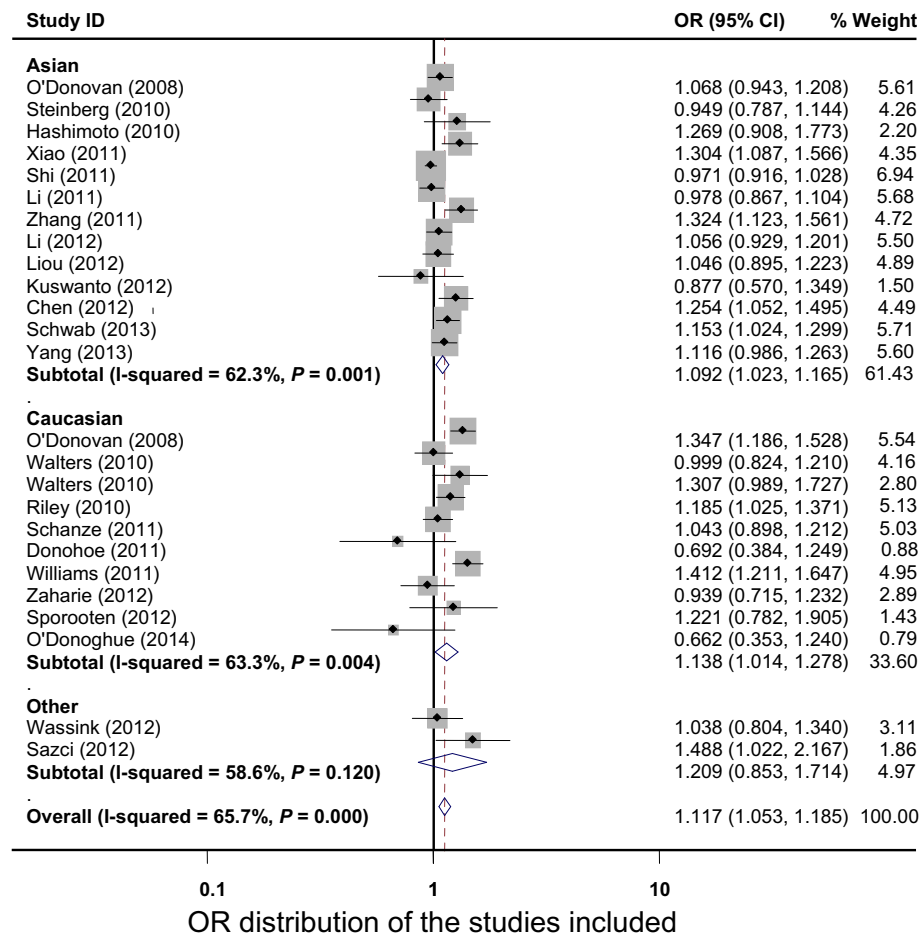


Figure 1 Forest plot of association between rs1344706 and schizophrenia in different ethnic populations

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.

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