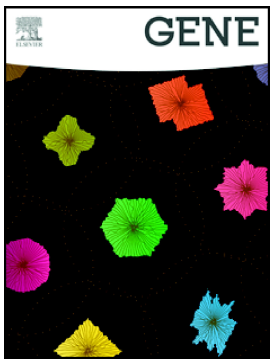

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Association between variations in the *disrupted in schizophrenia 1* gene and schizophrenia: a meta-analysis

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Abstract

Schizophrenia is a severe psychiatric disorder. Genetic and functional studies have strongly implicated the *disrupted in schizophrenia 1* gene (*DISC1*) as a candidate susceptibility gene for schizophrenia. Moreover, recent association studies have indicated that several *DISC1* single nucleotide polymorphisms (SNPs) are associated with schizophrenia. However, the association is hardly replicate in different ethnic group. Here, we performed a meta-analysis of the association between *DISC1* SNPs and schizophrenia in which the samples were divided into subgroups according to ethnicity. Both rs3738401 and rs821616 showed not significantly association with schizophrenia in the Caucasian, Asian, Japanese or Han Chinese populations.

Key words: *DISC1*, polymorphisms, schizophrenia, meta-analysis

Schizophrenia is a devastating mental illness, with a worldwide prevalence of approximately 1% (Sullivan et al., 2003). It is characterized by emotional impairment, cognitive deficits, and social dysfunction. Evidence from multiple studies indicated that genetic factors play an important role in the etiology of schizophrenia (Faraone et al., 2002).

The 414 kb *disrupted in schizophrenia 1* gene (*DISC1*), first identified at the site of a balanced translocation (1;11)(q42.1;q14.3), co-segregates with schizophrenia and other psychiatric disorders in a Scottish pedigree (Millar et al., 2000; Blackwood et al., 2001). Subsequently, the association of several coding or non-coding *DISC1* single nucleotide polymorphisms (SNPs) with schizophrenia was independently reported in different ethnic groups (Ekelund et al., 2004; Zhang et al., 2005; Zhang et al., 2006; Chen et al., 2007; Qu et al., 2007; Saetre et al., 2008; Hennah et al., 2009).

DISC1 acts as a scaffold protein that interacts with or regulates multiple molecules in neurogenesis, neurodevelopment, neuronal migration, and signaling (Brandon and Sawa, 2011; Porteous et al., 2011; Soares et al., 2011). Mouse models carrying *DISC1* mutations show behavioral deficits, and abnormalities in brain morphology, cognitive function, and sociability, which are reminiscent of the findings in schizophrenia (Clapcote et al., 2007; Hikida et al., 2007; Li et al., 2007; Kvajo et al., 2008; Lee et al., 2011; Zhou et al., 2013). Thus, the evidence seems strong for a role of *DISC1* in the etiology of schizophrenia. However, genome-wide association studies failed to identify an association between *DISC1* and schizophrenia (Brandon and Sawa, 2011; Schizophrenia Working Group of the Psychiatric Genomics, 2014),

and this was confirmed by two previous meta-analyses in the same year (Kinoshita et al., 2012; Mathieson et al., 2012).

In the present study, we conducted a meta-analysis covering several recent genetic studies focusing on the association of *DISC1* variants with schizophrenia (Ratta-Apha et al., 2013; Luo et al., 2015; He et al., 2016; Luo et al., 2016), in which we divided the genetic studies into groups according to ethnicity for subgroup analysis. This meta-analysis revealed no significant association of the *DISC1* with schizophrenia.

Materials and methods

Literature search

We searched the PubMed database for all English-language publications up until July 12, 2017, using the keywords “schizophrenia”, “DISC1”, and “association”. Articles were included in the meta-analysis if they met all of the following criteria: 1) studying the association between *DISC1* single nucleotide polymorphisms and schizophrenia in human subjects; 2) including healthy control individuals; 3) including sufficient data to calculate odds ratios (ORs), 95% confidence intervals (CIs), and a *p* value; and 4) diagnosing schizophrenic patients according to the International Classification of Diseases, and Diagnostic and Statistical Manual of Mental Disorders. Reviews and meta-analyses were excluded.

Selection of candidate polymorphisms

Human *DISC1* contains 21,557 SNPs listed in the NCBI SNP database (build 141, http://www.ncbi.nlm.nih.gov/SNP/). However, because none of these SNPs were covered in all previous studies, we selected those reported in at least three cohorts in each ethnic to conduct a comprehensive meta-analysis. Only two missense variants, rs3738401 (R264Q) and rs821616 (S704C), matched this criterion. Both SNPs were checked against the HapMap database to determine the frequency of major/minor alleles.

Statistical analysis

Data for each SNP were extracted and entered into Review Manager 5.0 (RevMan 5.0) to analyze log-ORs and 95% CIs. Heterogeneity between individual studies was assessed by the χ^2-based Q test and I^2 statistic to ensure that each study was suitable for inclusion in the meta-analysis (Cochran, 1954; Colditz et al., 1995; Higgins and Thompson, 2002). Pooled effect sizes across studies were calculated using the random effects model if the p value for heterogeneity was <0.05; otherwise, a fixed effects model was performed. Publication bias was computed by a funnel plot and Egger's regression test (Egger et al., 1997). Sensitivity analysis was performed by removing included studies in turn, and re-calculating the remaining studies to assess the potential influences of a single study on the pooled effect size, and to ensure that no single study was entirely responsible for the combined data.

Results

The combined search yielded 205 references, of which only 20 matched the inclusion criteria (Devon et al., 2001; Hodgkinson et al., 2004; Kockelkorn et al., 2004; Thomson et al., 2005; Zhang et al., 2005; Hashimoto et al., 2006; Zhang et al., 2006; Chen et al., 2007; Qu et al., 2007; Kim et al., 2008; Sanders et al., 2008; Rastogi et al., 2009; Schumacher et al., 2009; Hotta et al., 2011; Ratta-Apha et al., 2013; Thomson et al., 2014; Hu et al., 2015; Luo et al., 2015; He et al., 2016; Luo et al., 2016). We manual searched studies analyzed by previous two meta-analysis (Kinoshita et al., 2012; Mathieson et al., 2012). Only two studies were enrolled (Song et al., 2008; Kinoshita et al., 2012). Since the SNPs investigated by the included studies rarely overlapped, only two missense variants, rs3738401 (R264Q) and rs821616 (S704C), were investigated in at least three individual cohorts in each ethnic; therefore, our meta-analysis was carried out against rs3738401 and rs821616. Five studies, which did not contain these two SNPs, were excluded (Hodgkinson et al., 2004; Kockelkorn et al., 2004; Sanders et al., 2008; Hu et al., 2015; Luo et al., 2016). At last, 17 researches were included in our study (Table 1). As shown in Table 1, seven studies were of Caucasians, while ten were of Asian populations. Among the ten studies of Asia populations, five studies were Japanese populations, four studies were Han Chinese populations and one study was Korean population.

rs3738401

Twelve independent studies of this SNP containing 10,751 schizophrenia patients and 15,076 healthy controls were included in the meta-analysis. Considering the

significant heterogeneity across studies, a random effects model was performed. The pooled effect size was 1.00, with 95% CI 0.90–1.12, $p = 0.98$ (Fig. 1), suggesting that the minor allele (A allele) of rs3738401 had not significant association with schizophrenia. We next divided the thirteen studies into two subgroups according to ethnicity (Caucasian and Asian populations). Five studies were Asian population, six studies were Caucasian. The rs3738401 A allele showed no association with schizophrenia either in the Caucasian subgroup (1.01 (0.83–1.22), $p = 0.95$) or in the Asian (1.01 (0.93–1.10), $p = 0.76$) (Fig. 2). In the Japanese subgroup, The A allele was still not significantly associated with schizophrenia (1.02 (0.93–1.11), $p = 0.73$) (Fig 3).

rs821616

Seventeen independent studies of this SNP containing 16,928 schizophrenia patients and 20,622 healthy controls were included in the meta-analysis. A random effects model was used because of the significant heterogeneity across studies. The pooled effect size was 1.06, with 95% CI 0.94–1.20, $p = 0.31$ (Fig. 4), indicating that the minor allele (T allele) of rs821616 showed no significant association with schizophrenia. As before, we divided the eighteen studies into two subgroups according to ethnicity (Caucasian and Asian populations). Ten studies were included in Asian subgroup, while eight studies in Caucasian subgroup. However, the rs821616 T allele showed no significant association with schizophrenia either in Caucasian (1.00 (0.92–1.09), $p = 0.97$) or Asian populations (1.11 (0.91–1.35), $p = 0.32$) (Fig. 5).

We next divided Asian subgroup into Japanese (five studies) and Han Chinese populations (four studies). The T allele was still not significantly associated with schizophrenia either in Japanese (0.97 (0.77–1.23), p = 0.82) or Han Chinese populations (1.37 (0.94–1.99), p = 0.1) (Fig. 6).

Discussion

The present meta-analysis analyzed the association between *DISC1* SNPs rs3738401 and rs821616 with schizophrenia. We found that rs3738401 did not show association with schizophrenia in the Caucasian, Asian or Japanese subgroups. Like rs3738401, no positive association was identified between rs821616 and schizophrenia in Caucasian, Asian, Japanese or Han Chinese subjects, which is consistent with the two previous meta-analyses conducted by Mathieson et al. and Kinoshita et al. in Caucasian and Japanese populations, respectively (Kinoshita et al., 2012; Mathieson et al., 2012).

DISC1 is located at chromosomal breakpoint 1q42.1. Compared with such major gene interruptions, the contribution of SNPs to the pathogenesis of schizophrenia may only be minor, even if the SNP is located in a coding region (Bae et al., 2013). However, considering the much higher frequency of SNPs relative to translocations, there is still a need to analyze the association of *DISC1* SNPs with schizophrenia. Many previous genetic studies have investigated the association between *DISC1* and schizophrenia; however, the results are inconsistent, including SNP and haplotype findings. Previous meta-analyses failed to identify positive associations between

DISC1 variants and schizophrenia (Kinoshita et al., 2012; Mathieson et al., 2012), although differences in sample sizes, population, allelic heterogeneity, or genetic heterogeneity of disease could all cause difficulties in replicating data (Munafo and Flint, 2004). Considering the allelic heterogeneity and different genetic background between Caucasians and Asians, we divided the studies included in our meta-analysis into subgroups based on the ethnic population to minimize heterogeneity. However, rs3738401 and rs821616 showed no association with schizophrenia either in the Caucasian or Asian subgroup. Since gene expression regulated by genetic variants shows difference between Japanese and Han Chinese (Yuan et al., 2013), we divided Asia population into Japanese and Han Chinese subgroups with more specific. However, the association between rs3738401 or rs821616 and schizophrenia was still not found.

Genetic association studies between *DISC1* and schizophrenia are inconsistent in their findings among different groups and populations, which arise a question, whether *DISC1* is a real risk gene of schizophrenia. Some researchers convinced it is and others supported it is not (Sullivan, 2013; Porteous et al., 2014). For now, in addition to genetic studies, biological function studies provide evidence that DISC1 participates in multiple steps during neural development, including neuronal migration, neuronal architecture, synaptic plasticity, intracellular transport, and neural signaling (Li et al., 2007; Chubb et al., 2008; Kvajo et al., 2008; Brandon and Sawa, 2011; Porteous et al., 2011; Bradshaw and Porteous, 2012; Thomson et al., 2013). This supports a neural development hypothesis for schizophrenic etiology. Moreover,

a mouse model carrying a *DISC1* mutation presents with a schizophrenia-like phenotype, endophenotype, and behavior, including an impaired working memory, prepulse inhibition deficit, reduced sociability, and higher anxiety (Kvajo et al., 2008; Abazyan et al., 2010; Lipina et al., 2010; Ayhan et al., 2011; Lee et al., 2011; Lipina et al., 2013).

In summary, we found no evidence that DISC1 associated with schizophrenia. The association between *DISC1* and schizophrenia needs genetic evidence improvement and the precise molecular mechanism by which DISC1 participates in the etiology of schizophrenia should be investigated in a future study.

Conflict of Interest:

The authors declare that there are no conflicts of interest.

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Table 1. Chracteristics of articles on the association between *DISC1* and schizophrenia

Authors	Year	Diagnostic criteria	Ethnicities	n (SCZ)	n (CTR)
Devon et al.	2001	DSM-III-R/DSM-IV	Caucasian	267-328	426-726
Zhang et al.	2005	DSM-IV	Japanese	338	338
Thomson et al.	2005	DSM-IV	Caucasian	394	478
Hashimoto et al.	2006	DSM-IV	Japanese	658	717
Zhang et al.	2006	DSM-IV	Scottish	677	648
Chen et al.	2007	DSM-IV	Han Chinese	560	576
Qu et al.	2007	ICD-10	Han Chinese	313	317
Kim et al.	2008	DSM-IV	Korean	303	300
Song et al.	2008	DSM-IV	Caucasian	288	288
Rastogi et al.	2009	DSM-IV	Caucasian	210	210
Schumacher et al.	2009	DSM-IV	Caucasian	782	839
Hotta et al.	2011	DSM-IV	Japanese	485	660
Kinoshita	2012	DSM-IV	Japanese	915	1708
Ratta-alpha et al.	2013	DSM-IV	Japanese	503	511
Thomson et al.	2014	DSM-IV	Caucasian	240	889
Luo et al.	2015	DSM-IV	Han Chinese	1413	1120
He et al.	2016	ICD-10	Han Chinese	248	236

Figure legends

Fig. 1 Meta-analysis of *DISC1* rs3738401.

Fig. 2 Meta-analysis of *DISC1* rs3738401 in Asian and Caucasian subgroups.

Fig. 3 Meta-analysis of *DISC1* rs3738401 in Japanese population.

Fig. 4 Meta-analysis of *DISC1* rs821616.

Fig. 5 Meta-analysis of *DISC1* rs821616 in Asian and Caucasian subgroups.

Fig. 6 Meta-analysis of *DISC1* rs3738401 in Japanese and Han Chinese populations.

Fig. 1 Meta-analysis of *DISC1* rs3738401.

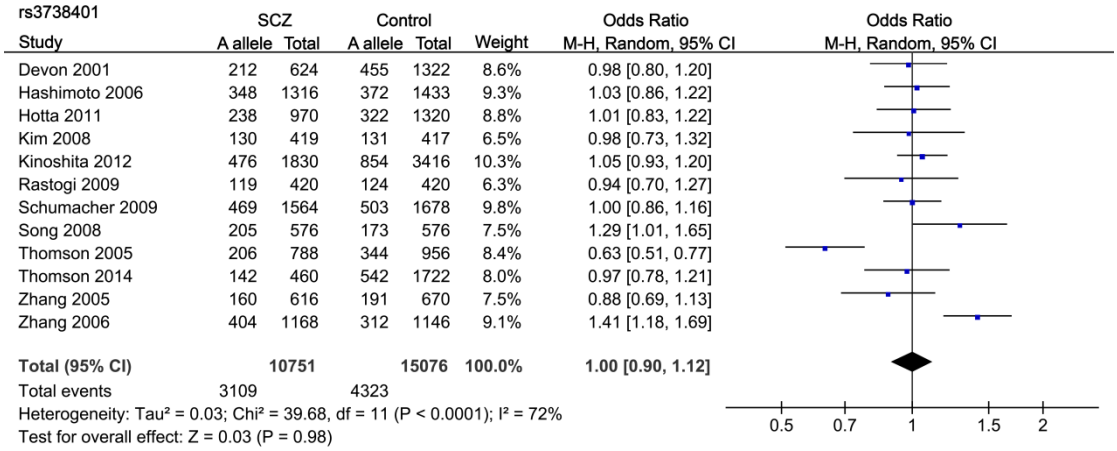


Fig. 2 Meta-analysis of *DISC1* rs3738401 in Asian and Caucasian subgroups.

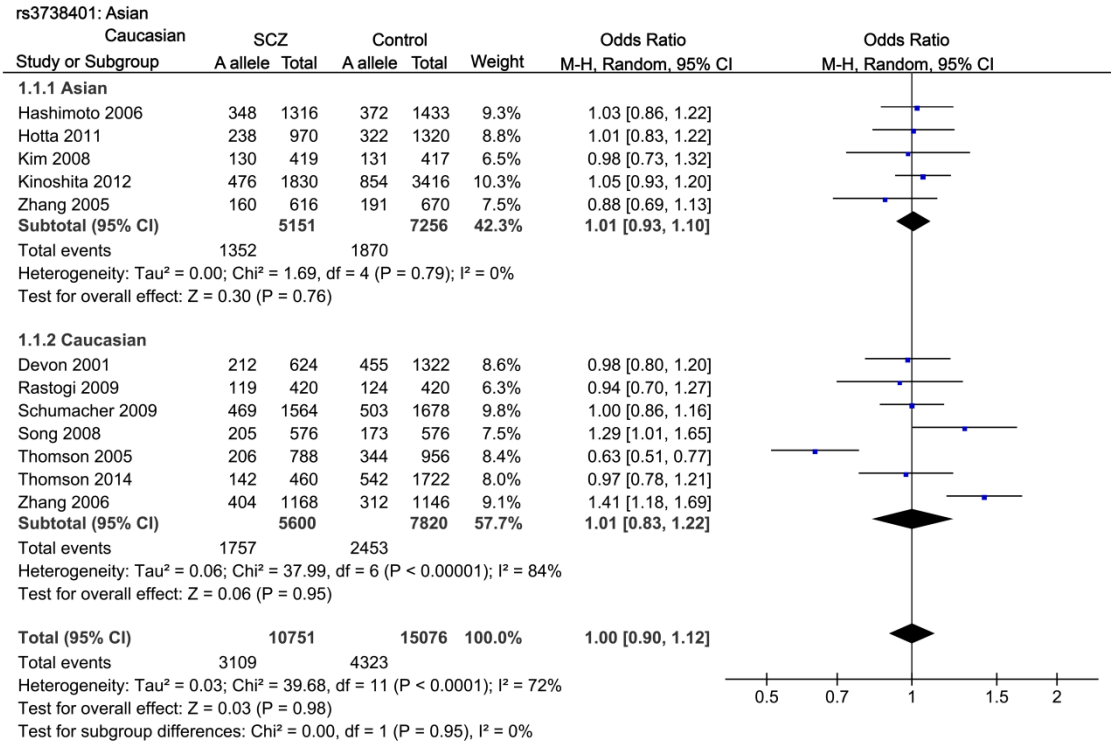


Fig. 3 Meta-analysis of *DISC1* rs3738401 in Japanese population.

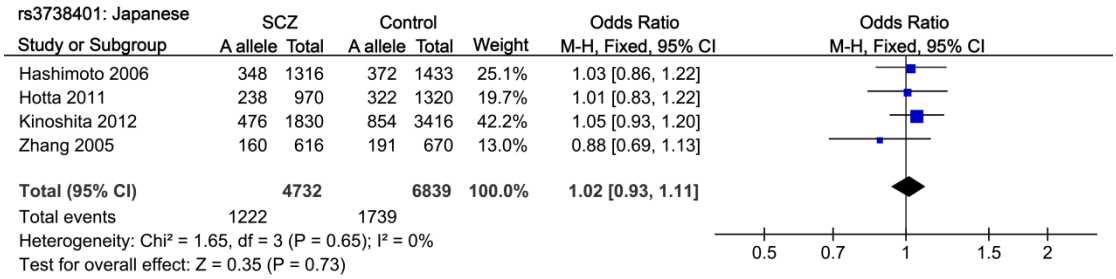


Fig. 4 Meta-analysis of *DISC1* rs821616.

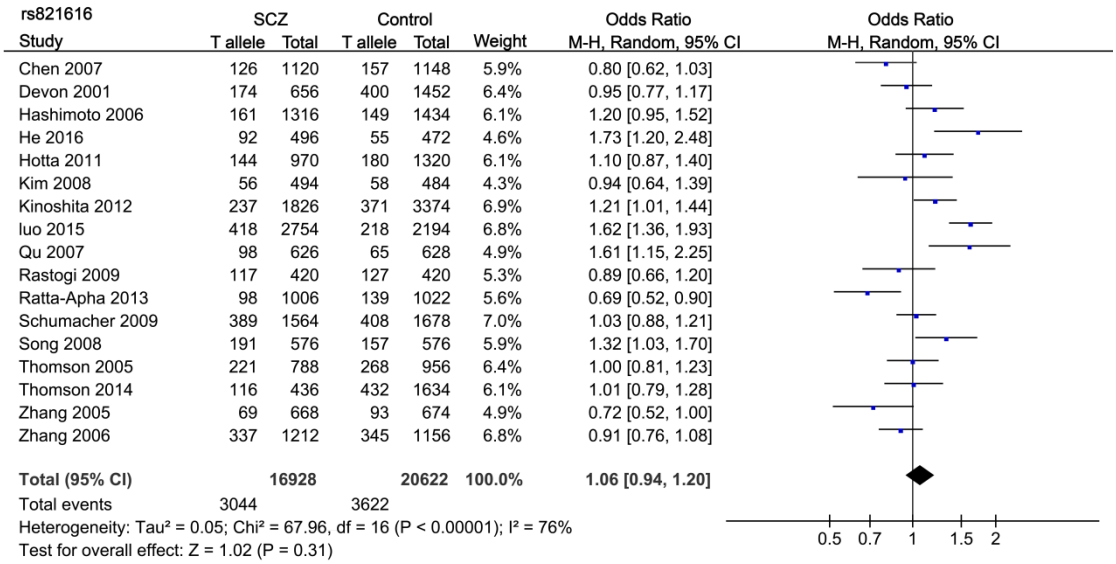


Fig. 5 Meta-analysis of *DISC1* rs821616 in Asian and Caucasian subgroups.

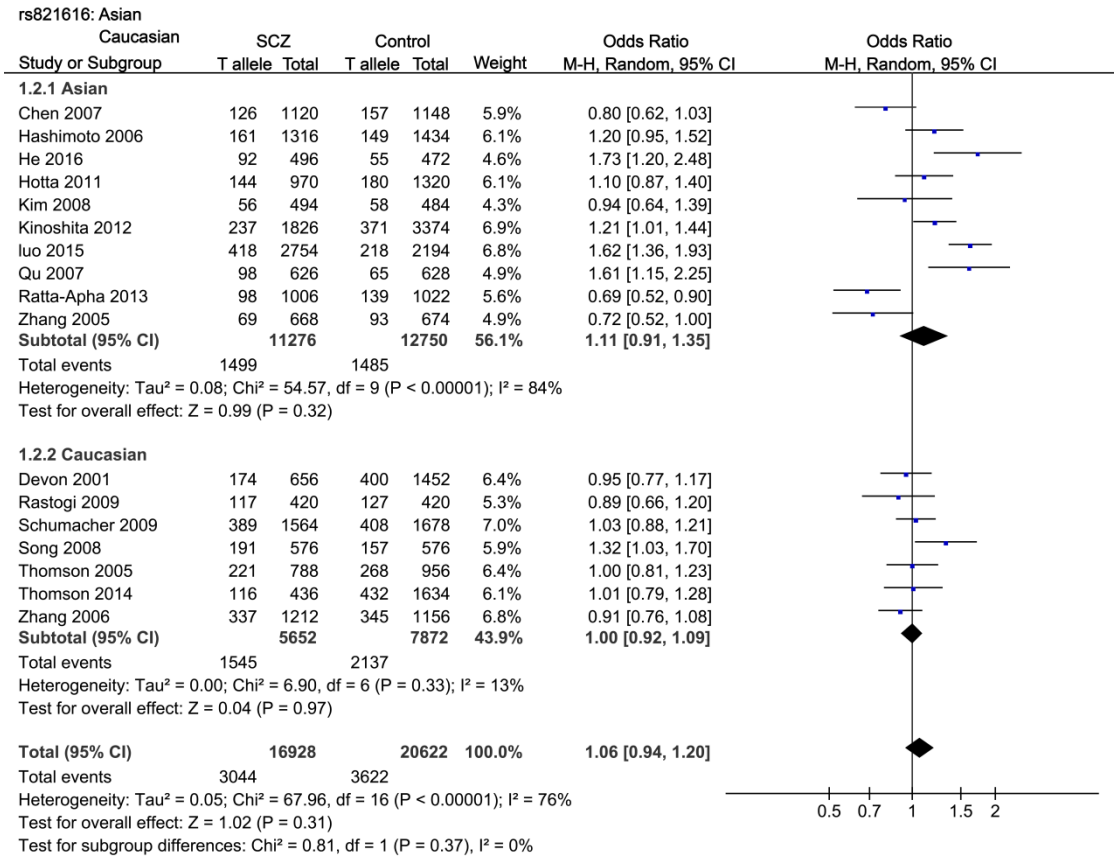
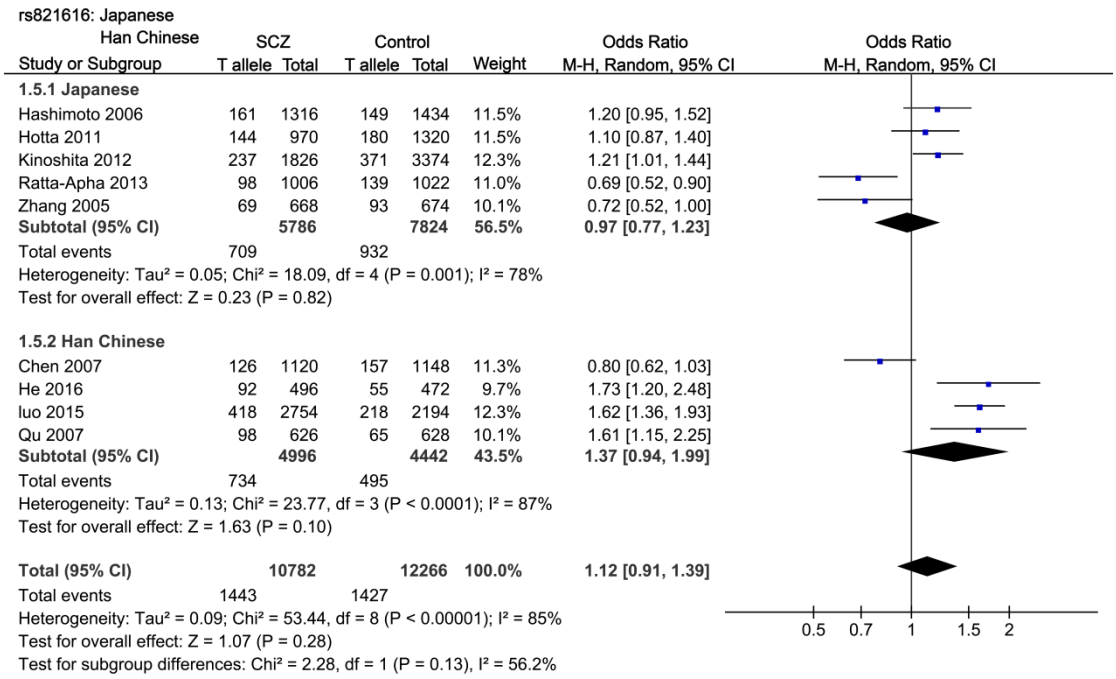


Fig. 6 Meta-analysis of *DISC1* rs3738401 in Japanese and Han Chinese populations.



Highlights:

Meta-analysis reveals not association of two *DISC1* SNPs, rs3738401 and rs821616 with schizophrenia either in Caucasian or Asian subjects.

Both rs3738401 and rs821616 showed not significantly association with schizophrenia in the Japanese or Han Chinese populations.

Abbreviation list

CI: confidence interval

DISC1: disrupted in schizophrenia 1

OR: odds ratio

SNP: single nucleotide polymorphism