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RESEARCH ARTICLE

HTR1A Polymorphisms and Clinical Efficacy of Antipsychotic Drug Treatment in Schizophrenia: A Meta-Analysis

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Abstract

Background: This meta-analysis was conducted to evaluate whether HTR1A gene polymorphisms impact the efficacy of antipsychotic drugs in patients with schizophrenia.
Methods: Candidate gene studies that were published in English up to August 6, 2015 were identified by a literature search of PubMed, Web of Science, and Google scholar. Data were pooled from individual clinical trials considering overall symptoms, positive symptoms and negative symptoms, and standard mean differences were calculated by applying a random-effects model.
Results: The present meta-analysis included a total of 1281 patients from 10 studies. Three polymorphisms of HTR1A (rs6295, rs878567, and rs1423691) were selected for the analysis. In the pooled data from all studies, none of these HTR1A polymorphisms correlated significantly with either overall symptoms or positive symptoms. However, C allele carriers of the rs6295 polymorphism showed a significantly greater negative symptoms improvement than G allele carriers ($P = .04$, standardized mean difference = -0.14, 95%CI = 0.01 to 0.28).
Conclusions: The results of our present analysis indicate that the HTR1A rs6295 polymorphism may impact negative symptoms improvement but not on either overall symptoms or positive symptoms improvement. However, this meta-analysis was based on a small number of studies and patients, and the effect size on negative symptoms was small. Given this limitation, the results should be confirmed by further investigations.

Keywords: HTR1A, polymorphism, schizophrenia, antipsychotics, efficacy

Introduction

The effects of antipsychotic medications in schizophrenia are mediated by their interactions with several receptors expressed in the brain. Currently, the dopamine D2 and the serotonin 2A receptor are assumed to be representative target receptors of antipsychotic drugs. The serotonin 1A receptor (5-HT1AR) is another important receptor, since it has been implicated in

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both schizophrenia pathogenesis and antipsychotic mechanisms of action. 5-HT1AR is expressed in various sites throughout the brain such as the hippocampus (Barnes and Sharp, 1999; Aznar et al., 2003; Varnas et al., 2004), amygdala, and hypothalamus. A postmortem study including patients with schizophrenia demonstrated elevated 5-HT1AR density in the cortex of the frontal lobe (Hashimoto et al., 1991; Burnet et al., 1996; Sumiyoshi et al., 1996; Tauscher et al., 2002). This might be explained as an effect of serotonergic hypo-activation and glutamatergic hypo-transmission in this region (Wedzony et al., 1997; Newman-Tancredi and Kleven, 2011). In addition, second-generation antipsychotics, including aripiprazole, bifeprunox, clozapine, lurasidone, perospirone, quetiapine, and ziprasidone, are hypothesized to exhibit partial agonistic actions on the 5-HT1AR, and molecules directly targeting the 5-HT1AR ameliorate psychiatric symptoms (Jordan et al., 2002; Odagaki and Toyoshima, 2007; Murasaki et al., 2008; Fagiolini et al., 2010; Lerond et al., 2013). Furthermore, adjunctive therapy with anxiolytic agents exerting a partial agonistic action on the 5-HT1AR, such as buspirone and tandospirone, is known to improve psychiatric symptoms in schizophrenic patients (Kishi et al., 2013a). Based on these observations, the action of antipsychotics on the 5-HT1AR is supposed to play an important role in the treatment of psychiatric disorders.

The HTR1A gene encoding 5-HT1AR, mapped on chromosome 5q11.2–13, is an intronless gene approximately 2200 bp in size, including an approximately 1200-bp coding sequence known to code for 422 amino acids (http://www.ncbi.nlm.nih.gov/nuccore). A number of single nucleotide polymorphisms (SNPs) have been identified for HTR1A; a particularly important SNP is rs6295 (C-1019G), which is located in the promoter region and is known to be a functional polymorphism that regulates HTR1A transcription and region-specific modification of HTR1A expression (Wu and Comings, 1999; Lemonde et al., 2003; Albert and Lemonde, 2004). Thus, pharmacogenetic candidate gene studies were mainly focused on rs6295, and they investigated the relationship between psychiatric drug efficacy in mental disorders and rs6295, with the aim of developing personalized treatments. Several meta-analyses investigated data from studies focused on antidepressant efficacy and the rs6295 polymorphism, but none documented a statistically significant relationship on all populations or on Caucasian/Asian populations (Kato and Serretti, 2010; Zhao et al., 2012; Niitsu et al., 2013). Previous studies identified an association between the rs6295 polymorphism and symptomatic improvement in schizophrenia during treatment with antipsychotics, taking into consideration overall improvement of symptoms (Reynolds et al., 2006), amelioration of negative symptoms (Reynolds et al., 2006; Wang et al., 2008; Mossner et al., 2009), and improved attention (Sumiyoshi et al., 2010). On the other hand, negative findings exist (Ikeda et al., 2008; Crisafulli et al., 2012; Tang et al., 2014; Takekita et al., 2015); thus, no clear conclusion can be traced about the effect of this SNP on antipsychotic efficacy. Other HTR1A gene polymorphisms (in particular rs878567 and rs1423691) were investigated in regard to antipsychotic response, even if no functional effect is known for them. Some studies suggested that they may be associated with antipsychotic efficacy (Crisafulli et al., 2012; Gupta et al., 2012; Drago et al., 2013; Takekita et al., 2015).

However, the results obtained to date have not been comprehensively assessed in a meta-analysis. Thus, the present meta-analysis aimed to analyze the cumulative knowledge provided by candidate gene studies focused on the association between HTR1A gene polymorphisms and antipsychotic efficacy in schizophrenia.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009).

Search

We conducted a literature search using PubMed, Web of Science, and Google scholar to identify articles published in English until August 6, 2015. Search queries used were combinations of the following phrases: “schizophrenia or psychosis,” “serotonin 1A receptor or 5-HT 1A, HTR1A,” “antipsychotics or antipsychotic agents,” “response or efficacy,” and “gene or polymorphism.” In this search, the generic name of each antipsychotic was also used in place of “antipsychotics or antipsychotic agents.”

Furthermore, we also manually searched related journals published in English to complement the electronic search. Two independent investigators (Y.T., Y.K.) conducted the literature search.

Inclusion Criteria, Data Extraction, and Outcomes

The following inclusion criteria were applied to select includible studies: (1) They investigated the association between HTR1A polymorphisms and antipsychotic clinical efficacy; (2) The majority of patients had a diagnosis of schizophrenia or schizoaffective disorder based on DSM or ICD criteria (not applicable to patients with first psychotic episode); (3) Drug response was assessed using a standardized rating scale, such as the Positive and Negative Syndrome Scale or the Clinical Global Impression, at baseline and follow-up evaluations; (4) Genotype distribution was in Hardy–Weinberg equilibrium; (5) The study was conducted using the candidate gene approach; (6) The study was published in English and in a peer-reviewed journal; and (7) The study was based on an independent sample (nonoverlapping with other studies). When outcome data were not available in the article, we requested data from the author or we extracted the data from the published figures by the GSYS 2.4 program (Japan Charged-Particle Nuclear Reaction Data Group, http://www.jcprg.org/gsys/2.4/index-j.html, Sapporo, Japan). Based on the data obtained from articles that met the above criteria, we selected HTR1A SNPs with at least 3 includible studies. Two authors (Y.T. and Y.K.) independently extracted and checked the data. Any disagreement was resolved by discussion until consensus was reached.

The purposes of the present meta-analysis were to identify possible associations between HTR1A SNPs and baseline to endpoint changes in: overall symptoms, positive symptoms, negative symptoms.

Data Analysis

Data were analyzed using a random-effects model as defined by DerSimonian and Laird (1986), because clinical heterogeneity among the populations and interventions included was expected. The standardized mean difference (SMD) and its 95% CI were calculated for continuous outcomes. Missing SDs were imputed according to the method described in Section 16.1.3 of the Cochrane Handbook for Systematic Reviews of Interventions (The Cochrane Collaboration, 2011). Study heterogeneity was measured using the chi-squared and I-squared statistics, with chi-squared values of $P < .05$ and I^2 values of >50% indicating relevant heterogeneity (Higgins et al., 2003). In addition to the main

analysis, we performed a subgroup analysis defined a priory by race, that is, Asians vs Caucasians.

Furthermore, we performed a meta-regression using age (mean age for each sample), sex (percentage of males in each study), and study duration as the moderator variables. Publication bias was assessed by constructing funnel plots and conducting an Egger's test (Egger et al., 1997).

Data were analyzed using Review Manager 5.3.5 (Cochrane Informatics & Knowledge Management Department, http://tech.cochrane.org/revman). Stata/IC 14.0 (Stata Corporation, College Station, TX, USA) was used to perform the Egger's test and meta-regression analyses.

Results

Included Studies

The electronic search yielded a total of 948 potential studies. In addition, we found 5 studies when conducting the manual search. Among the 953 identified hits, 850 articles were found to be duplicated between the databases. Of the 103 unique studies, we excluded 84 articles based on title and abstract reviews. Based on full-text inspection, we excluded 9 other references for the following reasons: the HTR1A polymorphism investigated in the sample was not in Hardy-Weinberg equilibrium (2 articles: Bosia et al., 2015 and Mossner et al., 2009); all the investigated samples had the same genotype (1 article: Masellis et al., 2001); therapeutic response was not evaluated (3 articles: Kim and Yoon, 2011; Gu et al., 2013; Terzic et al., 2015); the study did not include a polymorphism investigated by at least 2 other articles (2 articles: Lane et al., 2006; Wang et al., 2015); overlapping samples (1 article: Chiesa et al., 2013).

Ultimately, 10 studies including 1281 patients were included in the present meta-analysis (Reynolds et al., 2006; Ikeda et al., 2008; Wang et al., 2008; Mossner et al., 2009; Sumiyoshi et al., 2010; Crisafulli et al., 2012; Gupta et al., 2012; Drago et al., 2013; Tang et al., 2014; Takekita et al., 2015). Three HTR1A polymorphisms were included in the analysis (rs6295 investigated by 10 studies, rs878567 by 4 studies, and rs1423691 by 3 studies). Figure 1 shows the flowchart of study selection and inclusion. Table 1 summarizes the characteristics of the included studies. Each study included 30 to 398 patients (median: 98) with a mean age of 32.4 years and a study duration of 4 weeks to 3 months. Male patients constituted 53.9% of the sample population, with Asians, Caucasians, and South Indians accounting for 53.3%, 17.7%, and 29.0%, respectively. Eight studies included only patients who had been diagnosed with schizophrenia; 3 of these studies were conducted in patients experiencing first-episode schizophrenia. Three studies used a single antipsychotic agent; in 2 of these studies that agent was risperidone. Eight studies used the Positive and Negative Syndrome Scale score as a parameter for assessing psychiatric symptoms, while the others used the Clinical Global Impression-I, SAPS, or SANS score. In all studies, genotype distributions of rs6295, rs878567, and rs1423691 were in Hardy–Weinberg equilibrium. No subgroup analysis or meta-regression was performed for polymorphisms other than rs6295, due to the limited number of studies evaluating these polymorphisms.

rs6295 and Antipsychotic Drug Response

In the total population, no significant correlation was observed between the rs6295 polymorphism and overall symptoms change from baseline to endpoint in the comparison between CC and G carriers (9 studies, SMD = 0.08, CI = -0.09 to 0.25, $P = .37$), the comparison between C and GG carriers (9 studies, SMD = 0.11, CI = -0.06 to 0.27, $P = .20$), or the comparison between the C allele and the G allele (9 studies, SMD = 0.07, CI = -0.04 to 0.17, $P = .21$; Figure 2; Table 2). Similarly, no significant correlation was found between the rs6295 polymorphism and positive symptoms change in the comparison CC vs G carriers (9 studies, SMD = 0.02, CI = -0.12 to 0.16, $P = .76$), C vs GG carriers (8 studies, SMD = -0.04, CI = -0.26 to 0.18, $P = .73$), or C vs G allele (8 studies, SMD = -0.01, CI = -0.12 to 0.09, $P = .84$; Figure 3; Table 2). Similarly,

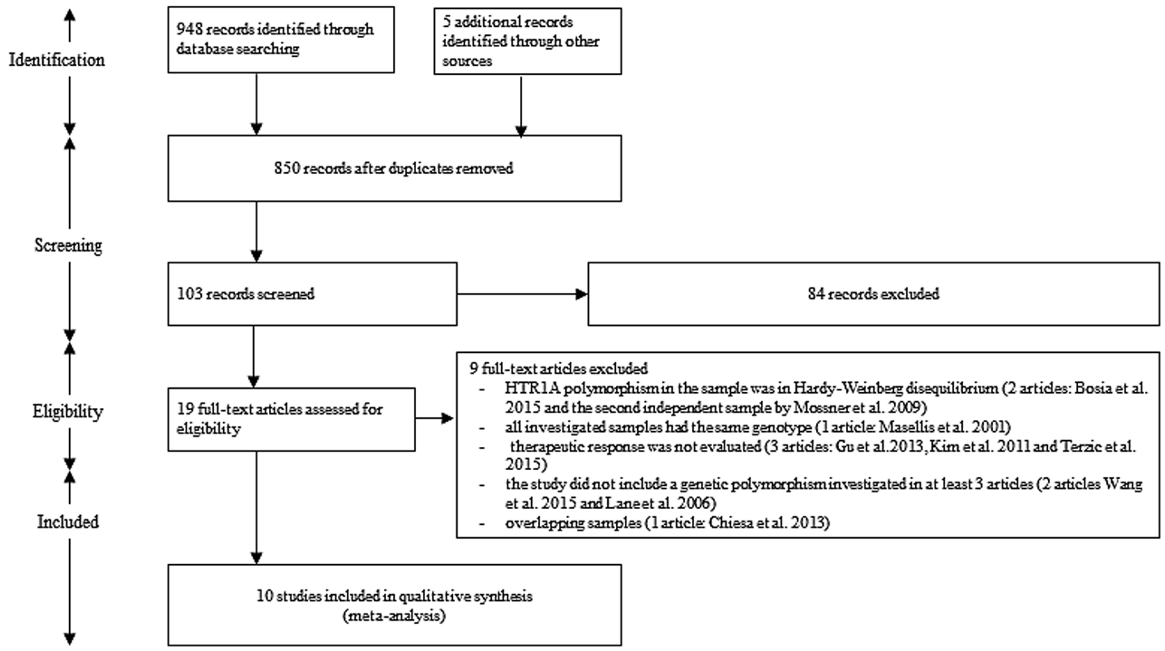

Figure 1. Study flow diagram.

Table 1. Description of the Included Studies

Study	Sample Size (male/female)	Country	Ethnicity	Age (SD)	Setting	Diagnostic Criteria	Patient Type	Medication	Duration of Treatment	Outcome Measure	HTR1A SNP
Crisafulli et al., 2012	221 (126/95)	Korea	Asian	38.01 (12.67)	In-patients	DSM-IV	Not any particular restriction	RIS, OLZ, QEP, AMI and others (All APDs are not identified)	37.64±1S6.76 days from admission to discharge	PANSS	rs10042486, rs6295, rs878567, rs1423691
Drago et al., 2013	96 (51/45)	German, Yugoslavia, Turkey, Other	Caucasian	34.28 (11.29)	In-patients	DSM-IV	Acute	HPD	4W	PANSS	rs6295, rs878567, rs1423691, rs10085024
Gupta et al., 2012	371 (224/147)	India	South Indian	29.63 (8.63)	In and out-patients	DSM-IV	Most of them are of chronic patients	RIS, OLZ, CLZ, ZIP, QEP, ARI, AMI	3M	CGI-I	rs6295, rs34118353, rs878567, rs1423691
Ikeda et al., 2008	120 (58/62)	Japan	Asian	31.2 (8.7)	In and out-patients	DSM-IV-TR	First-episode, neuroleptic-naïve DUP < 5 y	RIS	8W	PANSS	rs6295
Mossner et al., 2009	68 (44/24)	German	Caucasian	31.7	NR	ICD-10	First-episode	RIS, HPD	4W	PANSS	rs6295
Reynolds et al., 2006	63 (45/18)	Spain	Caucasian	25.1 (6.5)	In and out-patients	Drug-naive patients with first-episode psychosis	Drug-naive patients with first-episode psychosis	RIS, OLZ, QEP, HPD, ZIP, AMI	3M	PANSS	rs6295
Sumiyoshi et al., 2010	30 (11/19)	Japan	Asian	31.6 (11.0)	Out-patients	DSM-IV-TR	Acute	OLZ, PER	3M	SAPS, SANS	rs6295
Takekita et al., 2015	100 (43/57)	Japan	Asian	44.1 (16.2)	In and out-patients	DSM-IV-TR	Acute	PER, ARI	12W	PANSS	rs1364043, rs878567, rs6295, rs10042486
Tang et al., 2014	82 (45/37)	Chinese	Asian	25.8 (7.1)	In-patients	DSM-IV	First psychotic episode	Baseline : CPZ, RIS, CLZ, FLU endpoint : CLZ, CPZ, RIS	10W	PANSS and PANSS 5 factors	rs6295
Wang et al., 2008	130 (43/87)	China	Asian	30.35 (11.33)	NR	DSM-IV	- Not treatment resistance - SGAs-naïve - Not APDs administration for 4W	RIS	8W	PANSS	rs6295

Abbreviations: AMI, amisulpride; APD, antipsychotic drug; ARI, aripiprazole; CGI-I, clinical global impression of improvement; CLZ, clozapine; CPZ, chlorpromazine; DUP, duration of untreated psychosis; FLU, fluphenazine; HPD, haloperidol; NR, not reported; OLZ, olanzapine; PANSS, Positive and Negative Syndrome Scale; PER, perospirone; QEP, quetiapine; RCT, randomized clinical trial; RIS, risperidone; SAPS, scale for assessment of positive symptoms; SANS, scale for the assessment of negative symptoms; SGA, second-generation antipsychotic; SNP, single nucleotide polymorphism; ZIP, ziprasidone.

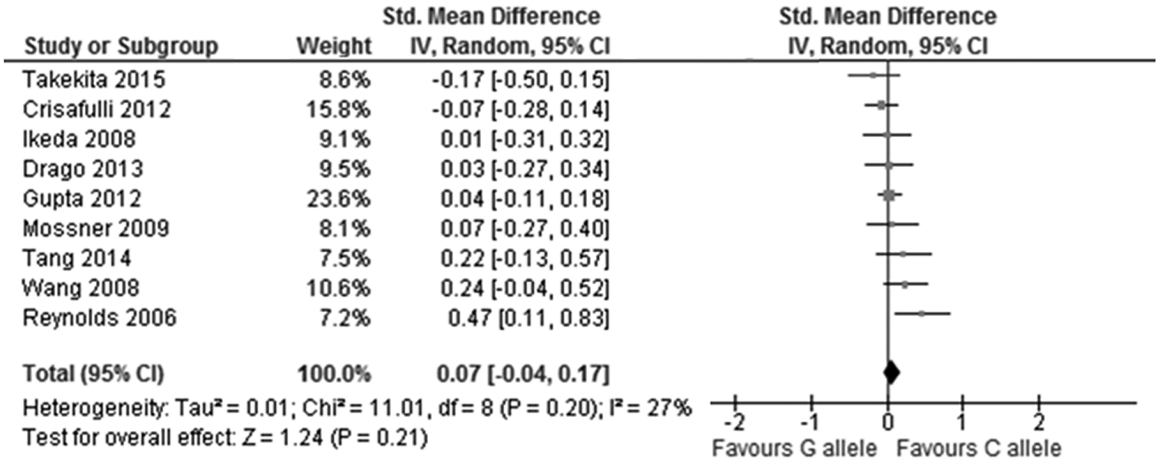

Figure 2. Forest plot for the association with rs6295 polymorphism (C alleles vs G alleles) and improvement of overall symptoms.

no significant correlation was found between the rs6295 polymorphism and negative symptoms change in the comparison CC vs G carriers (9 studies, SMD = 0.18, Cl = -0.04 to 0.39, *P* = .10) or the comparison C vs GG carriers (8 studies, SMD = 0.13, CI = -0.09 to 0.36, *P* = .24), but a significantly higher improvement in negative symptoms was observed in C allele carriers when comparing C vs G allele (8 studies, SMD = -0.14, CI = 0.01 to 0.28, *P* = .04) (Figure 4; Table 2).

In regard to heterogeneity, a significant inter-study heterogeneity was observed only for negative symptoms data in the comparison between CG and G carriers (*P* = .03, I^2 = 53%). No significant heterogeneity was detected in any of the other comparisons for rs6295 (Table 2).

rs878567 and Antipsychotic Drug Response

In the total population (4 studies, n = 743), none of the comparisons revealed a significant correlation between the rs878567 polymorphism and changes in all 3 types of psychotic symptoms (overall symptoms, positive symptoms, and negative symptoms) (Table 2). There was no significant heterogeneity in any of these comparisons.

rs1423691 and Antipsychotic Drug Response

In the total population (3 studies, n = 666), none of the comparisons revealed a significant correlation between the rs1423691polymorphism and changes in all 3 types of psychotic symptoms (overall symptoms, positive symptoms, and negative symptoms) (Table 2). There was no significant heterogeneity in any of these comparisons.

Subgroup Analysis, Meta-Regression, and Publication Bias

In the subgroup analyses by race (Caucasian, Asian, and South Indian), no significant correlation was detected between any phenotype (change in overall symptoms, positive symptoms, or negative symptoms) and the rs6295 polymorphism (supplementary Table 1). No significant heterogeneity was found between subgroups (supplementary Table 1).

Meta-regression analysis of the rs6295 polymorphism indicated higher improvement in negative symptoms in G carriers vs CC carriers as the mean age increased (coefficient = -0.04, SE = 0.012, *P* = .02) (Table 3). This result may represent a potential source of the significant inter-study heterogeneity detected in the comparison between rs6295 CC and G carriers for negative symptom improvement. However, no impact of other moderator variables on the association between the rs6295 polymorphism and symptom improvement was found (Table 3).

Visual inspection of funnel-plots for each distribution of the 3 HTR1A polymorphisms revealed no evidence of publication bias (supplementary Figure 1). Egger's test for publication bias did not suggest evidence of publication bias for any of the performed comparisons for the 3 HTR1A polymorphisms (supplementary Figure 1; Table 2).

Discussion

To our knowledge, this is the first meta-analysis investigating the impact of HTR1A polymorphisms (rs6295, rs1423691, rs878567) on the efficacy of antipsychotic medications in patients with schizophrenia. The analyses were performed employing 3 efficacy parameters, that is, improvement in overall symptoms, positive symptoms, and negative symptoms; 10 studies and 1281 patients were included. Our results indicate that the investigated HTR1A polymorphisms are unlikely to impact overall symptom or positive symptom change during antipsychotic treatment. However, the rs6295 polymorphism showed a small effect on negative symptom improvement in the comparison C vs G allele (*P* = .04, SMD = 0.14, CI = 0.01 to 0.28).

5-HT1AR is considered to play an important role in antipsychotic mechanisms of action both directly and through indirect mechanisms (Meltzer and Massey, 2011; Newman-Tancredi and Kleven, 2011). As a "direct" mechanism, some antipsychotic drugs are known to improve psychiatric symptoms via a partial agonistic action exerted on 5-HT1AR (Jordan et al., 2002; Odagaki and Toyoshima, 2007; Murasaki et al., 2008; Fagiolini et al., 2010; Kishi et al., 2013a; Lerond et al., 2013). As an "indirect" effect, second-generation antipsychotics are known to indirectly cause dopamine release in the prefrontal cortex via postsynaptic 5-HT1AR and 5-HT1A autoreceptors present in the raphe nucleus (Di Matteo et al., 2000; Ichikawa et al., 2001; Diaz-Mataix et al., 2005; Bortolozzi et al., 2010; Celada et al., 2013; Huang et al., 2014). Functional SNPs in the HTR1A gene have a relevant impact on 5-HT1AR level/activity. Particularly, rs6295 in the promoter region of HTR1A is known to be a functional polymorphism (Jacobsen et al., 2008; Albert and Fiori, 2014). In raphe cells, the C-G change

Table 2. Association between the HTR1A polymorphisms and antipsychotic efficacy

					Test for Overall Effect		Heterogeneity		*P* Value of Egger's Test
	N	N	SMD	95 % CI	*P*	Z	*P*	I^2 (%)	
rs6295									
Overall symptoms									
CC vs G carriers	9	1226	0.08	-0.09 to 0.25	.37	0.90	.06	47	.243
C carriers vs GG	9	1226	0.11	-0.06 to 0.27	.20	1.28	.78	0	.823
C alleles vs G alleles	9	2452	0.07	-0.04 to 0.17	.21	1.24	.20	27	.352
Positive symptoms									
CC vs G carriers	9	894	0.02	-0.12 to 0.16	.76	0.30	.67	0	.112
C carriers vs GG	8	864	-0.04	-0.26 to 0.18	.73	0.35	.96	0	.309
C alleles vs G alleles	8	1728	-0.01	-0.12 to 0.09	.84	0.20	.87	0	.26
Negative symptoms									
CC vs G carriers	9	894	0.18	-0.04 to 0.39	.10	1.62	.03*	53	.292
C carriers vs GG	8	864	0.13	-0.09 to 0.36	.24	1.17	.55	0	.727
C alleles vs G alleles	8	1728	0.14	0.01 to 0.28	.04*	2.04	.12	38	.29
rs878567									
Overall symptoms									
CC vs G carriers	4	743	0.02	-0.14 to 0.17	.85	0.19	.81	0	.883
C carriers vs GG	4	743	0.04	-0.27 to 0.35	.79	0.27	.20	36	.616
C alleles vs G alleles	4	1486	0.02	-0.09 to 0.13	.75	0.33	.89	0	.626
Positive symptoms									
CC vs G carriers	3	378	-0.05	-0.27 to 0.16	.63	0.49	.51	0	.882
C carriers vs GG	3	378	-0.12	-0.48 to 0.24	.51	0.66	.79	0	.658
C alleles vs G alleles	3	756	-0.06	-0.22 to 0.11	.49	0.69	.59	0	.791
Negative symptoms									
CC vs G carriers	3	378	0.09	-0.13 to 0.31	.41	0.82	.65	0	.05
C carriers vs GG	3	378	0.08	-0.51 to 0.68	.78	0.28	.10	57	.931
C alleles vs G alleles	3	756	0.08	-0.09 to 0.24	.38	0.89	.93	0	.771
rs1423691									
Overall symptoms									
CC vs G carriers	3	666	-0.04	-0.21 to 0.13	.66	0.43	.69	0	.774
C carriers vs GG	3	666	-0.05	-0.46 to 0.36	.80	0.26	.07	62	.419
C alleles vs G alleles	3	1332	0.00	-0.11 to 0.12	.97	0.04	.86	0	.825
Positive symptoms									
CC vs G carriers	2	302	0.06	-0.30 to 0.18	.63	0.48	.44	0	NA
C carriers vs GG	2	302	-0.16	-0.55 to 0.23	.42	0.81	.62	0	NA
C alleles vs G alleles	2	604	-0.07	-0.26 to 0.11	.45	0.76	.49	0	NA
Negative symptoms									
CC vs G carriers	2	302	0.03	-0.22 to 0.27	.82	0.22	.98	0	NA
C carriers vs GG	2	302	-0.10	-0.77 to 0.56	.76	0.31	.09	65	NA
C alleles vs G alleles	2	604	0.00	-0.18 to 0.19	.98	0.02	.47	0	NA

Abbreviations: NA, not applicable; SMD, standardized mean difference.

*Significant difference ($P < .05$).

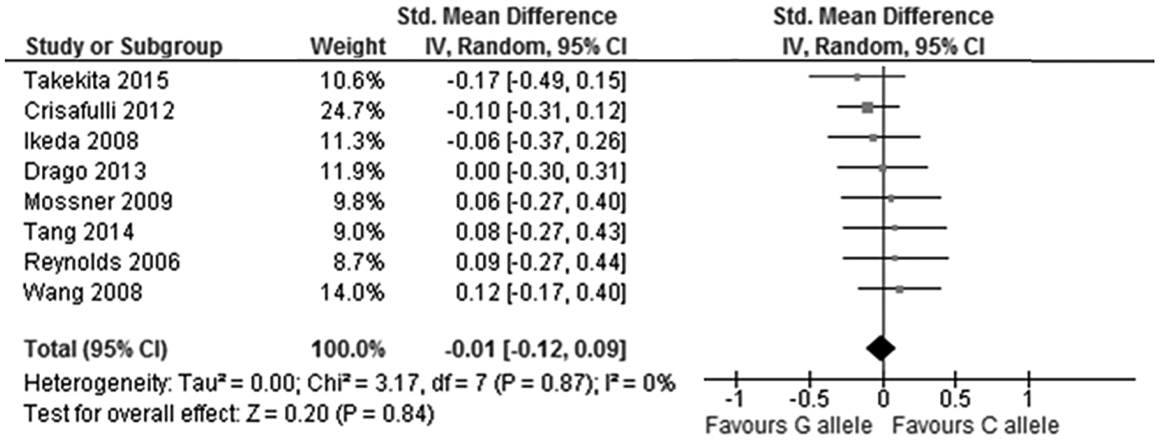

Figure 3. Forest plot for the association with rs6295 polymorphism (C alleles vs G alleles) and improvement of positive symptoms.

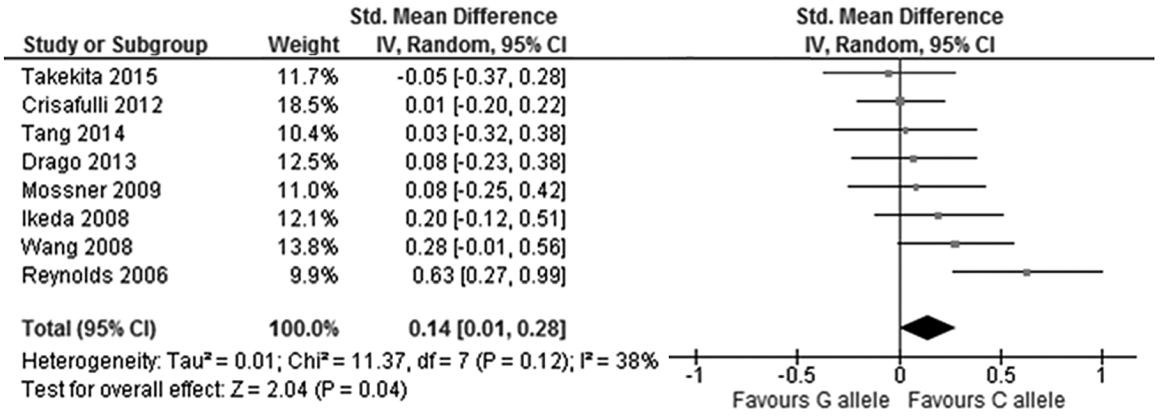

Figure 4. Forest plot for the association with rs6295 polymorphism (C alleles vs G alleles) and improvement of negative symptoms.

Table 3. Results of Meta-Regression Analyses for rs6295

				Test for Overall Effect	Heterogeneity
	Moderator Variable	Coefficient	Standard Error	*P* value	I^2 (%)
Overall symptoms					
CC vs G carriers	Study duration	0.005	0.039	.90	53
	Mean age	-0.028	0.014	.08	33.76
	Male ratio	0.009	0.009	.34	51.02
C carriers vs GG	Study duration	0.008	0.027	.77	0
	Mean age	-0.015	0.015	.37	0
	Male ratio	-0.006	0.009	.56	0
C alleles vs G alleles	Study duration	0.003	0.021	.91	36.44
	Mean age	-0.015	0.015	.37	0
	Male ratio	0.003	0.006	.62	35.5
Positive symptoms					
CC vs G carriers	Study duration	-0.022	0.030	.49	0
	Mean age	-0.026	0.012	.08	0
	Male ratio	0.003	0.007	.65	0
C carriers vs GG	Study duration	0.008	0.036	.84	0
	Mean age	-0.010	0.021	.65	0
	Male ratio	-0.008	0.010	.48	0
C alleles vs G alleles	Study duration	-0.010	0.020	.63	0
	Mean age	-0.015	0.010	.17	0
	Male ratio	0.000	0.005	.98	0
Negative symptoms					
CC vs G carriers	Study duration	0.031	0.043	.49	58.11
	Mean age	-0.040	0.012	.02*	0
	Male ratio	0.009	0.010	.40	57.72
C carriers vs GG	Study duration	-0.001	0.038	.98	0
	Mean age	-0.014	0.021	.54	0
	Male ratio	-0.002	0.010	.82	0
C alleles vs G alleles	Study duration	0.015	0.027	.60	45.44
	Mean age	-0.023	0.010	.06	0
	Male ratio	0.004	0.007	.54	45.69

*Significant difference ($P < .05$).

impairs the binding of nuclear proteins (eg, Deaf1) to a palindrome DNA element located at this polymorphism (Lemonde et al., 2003; Albert and Fiori, 2014). The rs6295 G allele is associated with a reduced efficiency of Deaf-1 binding, resulting in increased 5-HT1A autoreceptor expression in the raphe nucleus, where serotonin neurons originate (Albert, 2012). In contrast, 5-HT1AR expression is hypothesized to be decreased on the postsynaptic side, such as in the prefrontal cortex (Czesak et al., 2006). Consistently, Deaf1 -/- mice show a 50% increase in 5-HT1A RNA in the raphe, but a 30% decrease in the prefrontal cortex, confirming the role of Deaf1 in regulating HTR1A gene expression (Czesak et al., 2012). Basic study data suggested that lowered postsynaptic 5-HT1AR density may lead to reduced serotonergic signal transduction, which may in turn reduce dopamine release in the prefrontal cortex (Varrault et al., 1992; Bortolozzi et al., 2010). These findings are consistent with the results of the present meta-analysis that support the hypothesis of rs6295 selective impact on negative symptoms. However, this result should be interpreted with caution given that the effect was small (SMD = 0.14).

The other polymorphisms investigated by the present meta-analysis, that is, rs878567 and rs1423691, are located in the HTR1A downstream region, and they involve no amino acid substitutions (Gonzalez-Castro et al., 2013). It has been suggested that the rs878567 polymorphism might be related to mood disorders (particularly major depressive disorder) (Kishi et al., 2013b), methamphetamine-induced psychosis (Kishi et al., 2010), and attention deficit-hyperactivity disorder (Park et al., 2013) and that rs1423691 may also be associated with attention deficit-hyperactivity disorder (Park et al., 2013). However, there are no reports supporting a functional effect of these polymorphisms, and the present meta-analysis did not reveal significant correlations between these SNPs and clinical responses to antipsychotics. A limited number of studies was available for these 2 polymorphisms, and further data would be helpful in clarifying their role in antipsychotic response.

The limitations of the present meta-analysis should be considered. First, the number of studies included was small, particularly for rs878567 and rs1423691. Second, only candidate gene studies and not genome-wide association studies were included. Third, nongenetic stratification factors may have influenced the results. Indeed, studies using different antipsychotic drugs were included, and 5-HT1AR binding affinity is not the same for all antipsychotics. It was not possible to perform stratified analyses to account for this source of heterogeneity, since the antipsychotic drugs used varied greatly among the studies. Attention should also be paid to other sources of stratification among the included studies, such as ethnicity, diagnosis, and other clinical differences (eg, disease duration), duration of the study, and tools used to assess symptom improvement.

In conclusion, the present meta-analysis indicated that antipsychotic treatment may be more effective in improving negative symptoms in C allele than in G allele carriers of the HTR1A rs6295 polymorphism. This finding is consistent with data obtained from basic research on the importance of 5-HT1AR in antipsychotic mechanisms of action and the role of the HTR1A rs6295 polymorphism in regulating 5-HT1AR expression. However, this finding showed a small effect size, and relatively few studies and patients were included in the present meta-analysis; thus, the result should be confirmed in larger samples possibly including clinically homogeneous patients.

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Dr. Takekita had access to all study data and takes full responsibility for its integrity and accuracy of the analysis. Drs. Takekita, Fabbri, Koshikawa, and Tajika participated in study conception and design, data acquisition, and statistical analysis. The manuscript was written by Drs. Takekita and Fabbri. Drs. Kato, Kinoshita, and Serretti supervised the review.

Statement of Interest

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