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ORIGINAL RESEARCH

Association between the *SLC6A4* gene and schizophrenia: an updated meta-analysis

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Background: In order to explore the association between the *SLC6A4* gene and the risk of schizophrenia, an updated meta-analysis was conducted using a total of 46 scientific articles.

Methods: Through a literature search, papers studied included 35 articles on serotonin-transporter-linked polymorphic region (5-HTTLPR) with 8,752 cases and 10,610 controls, 17 articles on second intron variable number of tandem repeats with 7,284 cases and 8,544 controls, four studies on rs1042173 with 1,351 cases and 2,101 controls, and four studies on rs140700 with 1,770 cases and 2,386 controls. Pooled, subgroup, and sensitivity analyses were performed, and the results were visualized by forest and funnel plots.

Results: An association between 5-HTTLPR and the risk of schizophrenia was not found, except for an Indian subgroup analysis (P_z=0.014, OR =1.749, 95% CI =1.120–2.731). A 10 repeats/12 repeats (10R/12R) genotype was a protective factor against schizophrenia (P_z=0.020, OR =0.789, 95% CI =0.646–0.963), but a 12R/12R genotype was a risk factor for schizophrenia (P_z=0.004, OR =1.936, 95% CI =1.238–3.029) in the pooled analyses. In Caucasians, a GG genotype of rs1042173 may be a risk factor for schizophrenia (P_z=0.006, OR =1.299, 95% CI =1.079–1.565). No association was found between rs140700 and the risk for schizophrenia.

Conclusion: Through meta-analysis, we were able to gain insight into previously reported associations between SLC6A4 polymorphism and schizophrenia.

Keywords: *SLC6A4*, gene, schizophrenia, meta-analysis, polymorphism

Introduction

Schizophrenia is a complex chronic brain dysfunction that has an elusive pathogenesis and is highly heritable.[1] Investigations into twins and adoptees have shown that schizophrenia was caused by both genetic and environmental factors.[2,3] Epidemiological genetic studies suggested that genetic factors contributed significantly to the etiology of schizophrenia.[4] Pathological mechanisms are based on various neurotransmitter and neurodevelopmental hypotheses, and the hypothesis of a 5-hydroxytryptamine (5-HT) system defect is an important one. The serotoninergic pathway has been implicated, for several reasons, as having a major role in the pathophysiology of schizophrenia. By binding with receptors, 5-HT negatively regulates cAMP-dependent signal transduction and inhibits neuronal activity by opening G-protein–gated inwardly rectifying potassium channels.[5] The serotonin transporter (5-HTT) has a crucial function in the regulation of 5-HT reuptake in presynaptic neurons. It has been noted that levels of 5-HTT change in schizophrenic patients.[6,7] Significant differences in mRNA levels of the serotonin transporter gene (*SLC6A4*)[8] and serotonin transporter protein levels[9] were observed in schizophrenic patients compared with healthy controls. Pharmacological evidence indicated that 5-HTT was a site of action for several drugs with central nervous system effects[10,11] and that 5-HTT was involved in the pathogenesis of schizophrenia.[12,13]

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Therefore, the *SLC6A4* gene is a candidate gene for the pathogenesis of schizophrenia.

The most studied polymorphisms in the *SLC6A4* gene are a 44-base pair (bp) insertion–deletion (serotonin-transporter-linked polymorphic region [5-HTTLPR]) in the promoter region, generating major L and S alleles, and a 17-bp variable number of tandem repeats (VNTR) in the second intron (STin2).[14] The STin2 consists of 17-bp VNTR elements existing in 9, 10, and 12 repeats (9R, 10R, and 12R), although other rare types, such as seven-repeat units, have also been reported. The single-nucleotide polymorphisms (SNPs), rs1042173 and rs140700, are located in the three prime untranslated region and intron 5 of the *SLC6A4* gene, respectively. Associations between the *SLC6A4* gene and schizophrenia are controversial.[15,16] Ambiguous results from different studies may possibly reflect sample sizes insufficient for obtaining adequate statistical power.

A meta-analysis is a useful method for interpreting controversial study results.[17,18] Four meta-analyses of the association between the *SLC6A4* gene and schizophrenia have been conducted;[19–22] however, the results are still controversial. In addition, a meta-analysis of the association between schizophrenia and rs1042173 and rs140700 does not exist. Thus, we intended to perform an updated meta-analysis to better analyze the association of *SLC6A4* with schizophrenia.

Materials and methods

Literature searches

To identify studies eligible for inclusion in this meta-analysis, English (PubMed and SchizophreniaGene [SzGene]) and Chinese language (China National Knowledge Infrastructure, Wanfang, and Weipu) databases were searched using the following keywords: "serotonin transporter," "SERTPR," "SERT-in2," "5-HTTLPR," "STin2 VNTR," "*SLC6A4*," and "schizophrenia." References of the searched articles were also reviewed to uncover more data.

Inclusion and exclusion criteria

Studies included in the meta-analysis met the following criteria: 1) case–control design; 2) involved patients with schizophrenia; 3) presented relevant data for case and control groups (eg, allele/genotype frequencies, sample size, ethnicity, schizophrenia diagnostic criteria, and control group source); 4) removed duplicate sample data; and 5) published before September 2018. If the article did not contain detailed data, we e-mailed the authors for further information. Studies were excluded for the following reasons: 1) family-based studies; 2) no control group; 3) no usable genotype frequency data (attempts were made to contact authors via e-mail for such data); and 4) duplicate reported sample data.

Statistical analyses

The meta-analysis was conducted using Stata Version 10.0 (Stata Corp., College Station, TX, USA). A *P*-value of Hardy–Weinberg equilibrium (P_{HWE}) was calculated for control groups. Associations between *SLC6A4* and the risk of schizophrenia were detected under the random model.[23,24] A suitable genetic model was selected according to the previous articles.[25] ORs and 95% CIs were calculated in the pooled and subgroup analyses.

The heterogeneity of studies was determined by using Cochran's chi-squared *Q*-statistic test.[26] The degree of heterogeneity was expressed as I^2,which was divided into low ($I^2<25\%$), medium ($I^2\sim50\%$), and high ($I^2>75\%$) heterogeneity.[27,28] Publication bias was calculated by using Egger's test and was visualized in a funnel plot, in which the SE of the log OR of each study was plotted against its log OR. Sensitivity analysis, by removing one single study in turn, was conducted to test the impact of each study on pooled results. *P*-values of association, heterogeneity, and publication bias tests were represented by P_z, P_h, and P_e, respectively. In this study, $P<0.05$ was regarded as statistically significant in all statistical tests.[29] Statistical power was calculated by a PS program (Adobe Systems Incorporated, San Jose, CA, USA).[25]

Results

Description of studies

A total of 380 English and 16 Chinese published research articles were searched, and 46 articles were analyzed in this study after exclusion according to a PRISMA flow program (Figure 1).[30] Detailed data on five articles could not be obtained after sending e-mails to the authors;[31–35] therefore, they were removed in the present meta-analysis. Table 1 describes the baseline characteristics of 46 studies that were included in this meta-analysis. The studies included 35 articles about 5-HTTLPR,[16,36–68] 17 studies about Stin2,[16,37,39–41,44,47,53,59,65,69–75] four articles about rs1042173,[40,47,76,77] and four articles about rs140700.[71,76,78,79]

No association between 5-HTTLPR and the risk of schizophrenia

In a random model,[80,81] the pooled and subgroup analyses of 8,752 cases and 10,610 controls were performed (Table 2). Table 3 summarizes the results of the pooled analyses

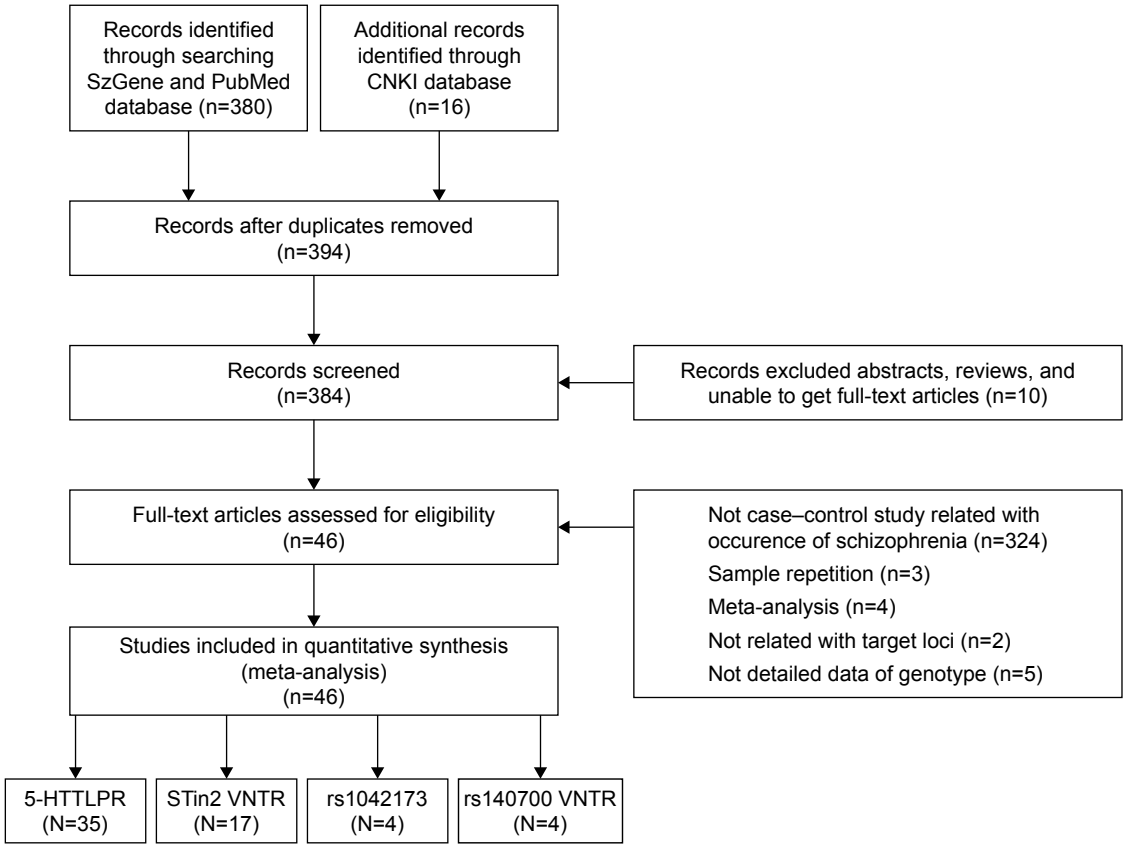

Figure 1 Study selection process in this meta-analysis.
Abbreviations: CNKI, China National Knowledge Infrastructure; 5-HTTLPR, serotonin-transporter-linked polymorphic region; STin2 VNTR, second intron variable number of tandem repeats.

and Table 4 depicts the data from the subgroup analyses. No association was found between 5-HTTLPR and the risk of schizophrenia with P_z=0.054 (OR =1.085, 95% CI =0.999–1.178) with a power of 0.935 in the dominant model.[82] No associations were found in the subgroup analyses, except in an Indian group (P_z=0.014, OR =1.749, 95% CI =1.120–2.731). No significant heterogeneity was observed in the pooled analysis (P_h=0.294, I^2=10.4%).

Genotypes 10R/12R and 12R/12R of STin2 VNTR may be associated with the risk of schizophrenia

The allele frequencies of 7,284 cases and 8,544 controls were included in the pooled and subgroup analyses, under a random model (Table 5); 10R and 12R are common alleles; therefore, alleles (10R and 12R) and genotypes (10R/10R, 10R/12R, and 12R/12R) were analyzed for an association with the risk of schizophrenia, respectively (Tables 3 and 4). A 10R/12R genotype was a protective factor against schizophrenia (P_z=0.020, OR =0.789, 95% CI =0.646–0.963), but a 12R/12R genotype was a risk factor for schizophrenia (P_z=0.004, OR =1.936, 95% CI =1.238–3.029) in the pooled analyses. The two pooled analyses had high powers of 1.000. In the subgroup analyses, 10R/12R was a protective factor against schizophrenia in East Asia (P_z=0.040, OR =0.617, 95% CI =0.389–0.978), India (P_z=0.014, OR =0.635, 95% CI =0.441–0.913) and in a population-based analysis (P_z=0.028, OR =0.794, 95% CI =0.646–0.976). A 12R/12R genotype was a risk factor for schizophrenia in East Asia (P_z=0.000, OR =4.482, 95% CI =2.312–8.689) and in population-based (P_z=0.013, OR =1.755, 95% CI =1.124–2.742) and hospital-based (P_z=0.000, OR =10.689, 95% CI =5.303–21.544) subgroup analyses. The significant heterogeneity was observed in these associated analyses.

Genotype GG of rs1042173 may be a risk factor for schizophrenia in Caucasians

In a recessive and a random model, no association was detected among 1,351 cases and 2,101 controls (P_z=0.057, OR =1.199, 95% CI =0.994–1.445; Table 6). Tables 3 and 4 shows the results. In Caucasians, a GG genotype may be a

Table 1 Characteristics of the qualified studies in this meta-analysis

Authors	Year	Country	Ethnicity	Controls source	Mean age of the control group	Cases, n	Controls, n	Diagnostic criteria	Gender index (case)	Gender index (control)
Li and Li[65]	2013	People's Republic of China	Han	Population-based	27.7±8.0	526	528	*DSM-IV*	1.000	1.000
Frtdtrique et al[69]	1997	France	Caucasians	Population-based	–	105	114	*DSM-III-R*	0.438	0.932
Pae et al[36]	2005	Korea	Korea	Hospital-based	–	111	172	*DSM-IV*	1.090	0.000
Saiz et al[37]	2007	Spain	Caucasians	Population-based	40.6±11.3	227	420	*DSM-IV*	0.667	0.961
Naylor et al[38]	1998	Australia	Caucasians	Population-based	–	58	62	*DSM-III-R*	–	–
Liu et al[70]	1999	People's Republic of China	Han	Population-based	42.0±10.0	260	362	*DSM-III-R*	0.709	0.813
Ikeda et al[39]	2006	Japan	Japanese	Population-based	33.6±12.9	287	288	*DSM-IV*	0.939	0.92
Lin et al[71]	2009	People's Republic of China	Han	Population-based	37.0±8.16	329	288	*DSM-IV*	0.621	0.811
Vijayan et al[40]	2009	Indian	Indian	Population-based	31.7±6.92	243	243	*DSM-IV*	–	–
Lee et al[41]	2009	Korea	Korea	Population-based	–	141	115	*DSM-IV*	–	–
Pae et al[42]	2003	Korea	Korea	Hospital-based	30.3±9.4	111	208	*DSM-IV*	1.096	0.818
Gu et al[43]	2013	People's Republic of China	Han	Population-based	22.4±6.6	404	385	ICD-10	0.515	0.629
Kaiser et al[16]	2001	Germany	Caucasians	Population-based	30.1±7.6	684	587	*DSM-IV*	0.887	0.289
Tsai et al[72]	2002	People's Republic of China	Han	Hospital-based	42.8±9.2	114	127	*DSM-III-R*	1.426	1.822
Herken et al[44]	2003	Turkey	Caucasians	Population-based	–	143	68	*DSM-IV*	1.860	–
Serretti et al[45]	2002	Raffaele	Caucasians	Hospital-based	46.0±15.5	261	457	*DSM-IV*	–	1.041
Tsai et al[67]	2000	People's Republic of China	Han	Population-based	49.6±0.8	90	104	*DSM-IV*	0.525	2.596
Han et al[46]	2004	Korea	Korean	Hospital-based	–	168	158	*DSM-IV*	–	–
Zaboli et al[47]	2008	European	Caucasians	Population-based	41.0±11.2	155	246	*DSM-III-R*	0.667	0.629
Golimbet et al[48]	2017	Russian	Russian	Population-based	34.3±18.1	1,285	1,061	ICD-10	1.633	2.333
Herken et al[73]	2002	Turkish	Turkish	Population-based	–	128	135	*DSM-IV*	–	–
Peitl et al[49]	2017	Croatia	Croatia	Population-based	37.6±11.5	300	291	*DSM-IV*	0.376	0.865
Carlstrom et al[76]	2012	Scandinavia	Caucasians	Population-based	–	837	1,473	*DSM-IV*	–	–
Terzic et al[50]	2015	Ljubljana	Slovenian	Population-based	–	138	94	*DSM-IV*	–	–
Lu et al[68]	2012	the Netherland and Germany	Caucasians	Population-based	–	2,030	1,288	*DSM-IV*	–	–
Golimbet et al[51]	2010	Russian	Russian	Population-based	55.6±20.5	58	62	ICD-10	0.277	0.824
Golimbet et al[52]	2003	Russian	Russian	Hospital-based	31.6±13.5	110	124	ICD-10	0.746	1.696
Stober et al[53]	1998	German	Caucasians	population-based	29.9±10.0	180	223	ICD-10	0.622	0.701

Collier et al[74]	1996	European	Caucasians	Population-based	–	129	187	*DSM-III-R*	–	–
Kotler et al[54]	1999			Population-based	28.0±15.0	82	821	ICD-10	0.586	1.61
Rao et al[55]	1998	The USA	Caucasians	Population-based	30.0±10.0	80	127	*DSM-IV*	0.667	1.953
Rao et al[55]	1998	The USA	African American	Population-based	30.0±8.0	47	37	*DSM-IV*	0.741	1.313
Pakhomova et al[56]	2011	Russian	Russian	Population-based	18.9±6.7	65	111	ICD-10	0.444	0.609
Mendes de Oliveira et al[57]	1998	European	Caucasians	Hospital-based	–	39	89	*DSM-IV*	–	–
Bayle et al[58]	2003	French	Caucasians	Hospital-based	35.0±10.0	185	159	*DSM-IV*	0.434	0.529
Mata et al[59]	2004	Spain	Caucasians	Population-based	26.9±5.5	187	278	*DSM-IV*	0.680	0.887
Sanjuan et al[60]	2006	Spain	Caucasians	Population-based	–	158	138	*DSM-IV*	0.500	–
Pal et al[79]	2009	Croatian	Caucasians	Population-based	50.3±7.5	104	131	ICD-10	0.705	–
Chong et al[61]	2000		East Asia	Population-based	–	338	103	*DSM-IV*	0.565	–
Pae et al[62]	2006	Koreans	Koreans	Hospital-based	–	152	152	*DSM-IV*	–	–
Young et al[63]	2006	The USA	Caucasians	Population-based	–	12	15	*DSM-IV*	–	–
Jing et al[64]	2016	People's Republic of China	Han	Population-based	30.9±6.7	624	683	*DSM-IV*	0.830	0.882
Li et al[78]	2013	People's Republic of China	Han	Population-based	33.1±11.8	189	300	*DSM-IV*	2.316	2.297
Yang et al[75]	2001	People's Republic of China	Han	Population-based	–	260	362	*DSM-III-R*	–	–
Zuo et al[66]	2003	People's Republic of China	Han	Hospital-based	–	157	185	CCMD-II-R	0.622	0.312
Xuan et al[77]	2012	People's Republic of China	Han	Population-based	–	132	150	*DSM-IV*	1.000	1.000

Abbreviations: CCMD-II-R, Chinese Classification of Mental Disorders, Second Edition, Revised; *DSM-III-R*, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; ICD-10, International Classification of Diseases-10.

Table 2 Genotype distribution and allele frequency of 5-HTTLPR

Authors	Year	Genotype distribution						P_{HWE}	Allele frequency			
		Cases, n			Controls, n				Cases, %		Controls, %	
		LL	LS	SS	LL	LS	SS		L	S	L	S
Pae et al[36]	2005	4	35	72	10	49	113	0.143	43	179	69	275
Saiz	2007	64	104	59	124	203	93	0.566	232	222	451	389
Naylor et al[38]	1998	11	30	17	19	29	14	0.646	52	64	67	57
Ikeda et al[39]	2006	16	82	189	12	101	175	0.588	114	460	125	451
Vijayan et al[40]	2009	40	123	79	62	118	61	0.748	203	281	242	240
Lee et al[41]	2009	7	52	82	3	45	67	0.151	66	216	51	179
Pae et al[42]	2003	4	35	72	11	58	139	0.140	43	179	80	336
Gu et al[43]	2013	14	101	289	7	90	288	0.992	129	679	104	666
Kaiser et al[16]	2001	253	324	107	207	286	94	0.772	830	538	700	474
Herken et al[44]	2003	30	70	40	17	24	27	0.022	130	150	58	78
Serretti et al[45]	2002	89	121	51	165	217	75	0.800	299	223	547	367
Tsai et al[67]	1999	9	28	53	15	30	59	0.002	46	134	60	148
Han et al[46]	2004	7	52	109	8	54	96	0.910	66	270	70	246
Zaboli et al[47]	2008	56	73	26	75	126	45	0.532	185	125	276	216
Golimbet et al[48]	2017	486	595	204	413	503	145	0.677	1,567	1,003	1,329	793
Peitl et al[49]	2017	118	124	58	103	138	50	0.746	360	240	344	238
Terzic	2015	52	71	15	47	34	13	0.104	175	101	128	60
Lu et al[68]	2012	407	626	254	690	992	345	0.719	1,440	1,134	2,372	1,682
Golimbet et al[51]	2010	27	20	11	22	28	12	0.567	74	42	72	52
Golimbet et al[52]	2003	42	46	22	45	57	22	0.594	130	90	147	101
Stober	1998	58	90	32	79	112	42	0.834	206	154	270	196
Kotler et al[54]	1999	24	38	20	210	446	165	0.010	86	78	866	776
Rao et al[55]	1998	28	32	20	43	59	25	0.559	88	72	145	109
Rao et al[55]	1998	25	18	4	18	12	7	0.079	68	26	48	26
Pakhomova	2011	20	37	8	43	48	20	0.310	77	53	134	88
Mendes de Oliveira et al[57]	1998	12	21	6	39	43	16	0.480	45	33	121	75
Bayle et al[58]	2003	48	99	38	40	83	36	0.573	195	175	163	155
Mata et al[59]	2004	41	102	44	63	124	91	0.100	184	190	250	306
Sanjuan et al[60]	2006	33	78	47	44	68	26	0.976	144	172	156	120
Chong et al[61]	2000	33	130	175	13	32	58	0.019	196	480	58	148
Pae et al[62]	2006	5	46	101	9	47	96	0.322	56	248	65	239
Young	2006	2	5	5	6	7	2	0.985	9	15	19	11
Jing et al[64]	2016	51	267	306	66	248	369	0.012	369	879	380	986
Li et al[78]	2013	5	35	149	24	134	142	0.325	45	333	182	418
Zuo	2003	15	50	92	21	49	115	0.000	80	234	91	279

Abbreviations: 5-HTTLPR, serotonin-transporter-linked polymorphic region; P_{HWE}, *P*-value of Hardy–Weinberg equilibrium.

risk factor for schizophrenia (P_z=0.006, OR =1.299, 95% CI =1.079–1.565), with a power of 0.893. No significant heterogeneity was observed in the pooled or subgroup analyses.

No association between rs140700 and the risk of schizophrenia

Under a random model, the allele frequencies of 1,770 cases and 2,386 controls were included in the pooled and subgroup analyses (Table 7). In a dominant model, no association was detected between rs140700 and the risk of schizophrenia in the pooled and subgroup analyses (Tables 3 and 4). Significant heterogeneity was observed in the pooled (P_h=0.000, I^2=93.2%) and East Asia subgroup (P_h=0.000, I^2=93.5%) analyses.

Sensitivity analysis

We conducted sensitivity analyses by omitting each study individually; the pooled ORs did not change significantly. Thus, the results were considered stable and reasonable.

Publication bias

Any publication bias was made visible by funnel plots, in which the SE of the log OR of each study was plotted against its log OR. No evidence of publication bias was found in the pooled analyses (Figures 2–7).

Table 3 Pooled association of *SLC6A4* polymorphisms with schizophrenia

Loci	Genetic model	Studies (n)	Statistical	OR	95% CI	P_z	I^2	P_h	P_e
5-HTTLPR	Allele contrast	35	Random	0.934	0.868–1.004	0.066	53.6	0.000	0.587
	Homozygous codominant	35	Random	1.142	0.782–0.980	0.021	15.6	0.206	0.912
	Heterozygous codominant	35	Random	1.066	0.980–1.161	0.138	7.7	0.340	0.165
	Dominant	35	Random	1.085	0.999–1.178	0.054	10.4	0.294	0.211
	Recessive	35	Random	1.082	0.961–1.218	0.195	57.8	0.000	0.846
STin2 VNTR	10R vs others	17	Random	0.884	0.725–1.077	0.221	82.8	0.000	0.951
	12R vs others	17	Random	1.134	0.931–1.381	0.21	82.8	0.000	0.936
	10R/10R vs others	17	Random	0.907	0.624–1.319	0.611	78.9	0.000	0.401
	10R/12R vs others	17	Random	0.789	0.646–0.963	0.020	71.1	0.000	0.748
	12R/12R vs others	17	Random	1.936	1.238–3.029	0.004	94.7	0.000	0.474
rs1042173	Contrast	4	Random	1.094	0.962–1.245	0.17	22.7	0.275	0.412
	Homozygous codominant	4	Random	1.214	0.921–1.600	0.169	26.4	0.253	0.336
	Heterozygous codominant	4	Random	1.011	0.812–1.260	0.920	18.0	0.301	0.941
	Dominant	4	Random	1.077	0.856–1.354	0.528	26.9	0.250	0.722
	Recessive	4	Random	1.199	0.994–1.445	0.057	14.5	0.320	0.155
rs140700	Allele contrast	4	Random	1.052	0.519–1.734	0.863	92.9	0.000	0.359
	Homozygous codominant	4	Random	0.809	0.236–2.774	0.736	63.7	0.041	0.223
	Heterozygous codominant	4	Random	0.971	0.500–1.884	0.931	91.9	0.000	0.685
	Dominant	4	Random	1.003	0.503–1.999	0.993	93.2	0.000	0.560
	Recessive	4	Random	0.830	0.284–2.422	0.733	53.5	0.092	0.333

Abbreviations: 5-HTTLPR, serotonin-transporter-linked polymorphic region; P_z, P_h, and P_e, *P*-values of association, heterogeneity, and publication bias tests, respectively; R, repeats; STin2 VNTR, second intron variable number of tandem repeats.

Table 4 Subgroup association of *SLC6A4* polymorphisms with schizophrenia

Loci	Subgroup analysis	Studies (n)	OR	95% CI	P_z	I^2	P_h
5HTTLPR	Caucasians	21	1.053	0.974–1.138	0.192	1.6	0.437
	East Asia	12	1.204	0.953–1.521	0.119	4.1	0.404
	African American	1	0.834	0.352–1.975	0.679	0.0	0.000
	Indians	1	1.749	1.120–2.731	0.014	0.0	0.000
	Population-based	26	1.089	0.982–1.209	0.131	28.3	0.090
	Hospital-based	9	1.094	0.897–1.335	0.273	0.0	0.939
STin2 VNTR 1010	Caucasians	9	0.883	0.645–1.207	0.435	63.7	0.005
	East Asia	7	0.857	0.310–2.374	0.767	75.5	0.00
	Indians	1	0.639	0.368–1.108	0.111	–	0.000
	Population-based	16	0.930	0.639–1.354	0.704	79.8	0.000
	Hospital-based	1	0.155	0.008–3.040	0.220	–	–
1012	Caucasians	9	0.944	0.832–1.072	0.374	0.0	0.706
	East Asia	7	0.617	0.389–0.978	0.040	80.8	0.000
	Indians	1	0.635	0.441–0.913	0.014	–	–
	Population-based	16	0.794	0.646–0.976	0.028	72.8	0.000
	Hospital-based	1	0.667	0.290–1.536	0.341	–	–
1212	Caucasians	9	1.042	0.916–1.186	0.531	0.0	0.885
	East Asia	7	4.482	2.312–8.689	0.000	92.1	0.000
	Indians	1	1.573	1.086–2.280	0.170	–	–
	Population-based	16	1.755	1.124–2.742	0.013	94.5	0.000
	Hospital-based	1	10.689	5.303–21.544	0.000	–	–
rs1042173	Caucasians	2	1.299	1.0791.565	0.006	0.0	0.421
	East Asia	1	0.834	0.5171.346	0.458	–	–
	Indians	1	1.213	0.7981.843	0.365	–	–
rs140700	Caucasians	2	1.253	0.8271.896	0.287	42.6	0.187
	East Asia	2	0.757	0.2152.670	0.665	93.5	0.000

Abbreviations: 5-HTTLPR, serotonin-transporter-linked polymorphic region; P_z and P_h, *P*-values of association and heterogeneity, respectively; STin2 VNTR, second intron variable number of tandem repeats.

Table 5 Genotype distribution and allele frequency of STin2 VNTR

Authors	Year	Genotype distribution						Allele frequency							
		Case			Control			Case					Control		
		10	12	Others	10	12	Others	1010	1012	1212	Others	1010	1012	1212	Others
Frtdtrique	1997	84	120	6	79	143	6	24	36	39	6	18	41	50	5
Saiz	2007	171	281	2	305	530	5	42	86	97	2	64	177	174	5
Liu et al[70]	1999	22	498	0	58	665	1	2	18	240	0	5	48	308	1
Ikeda et al[39]	2006	51	523	0	46	530	0	1	49	237	0	3	40	245	0
Lin et al[71]	2009	55	425	0	107	457	0	6	43	191	0	9	89	184	0
Vijayan et al[40]	2009	137	343	0	189	297	0	24	89	127	0	36	117	90	0
Lee et al[41]	2009	36	246	0	23	207	0	4	28	109	0	3	17	95	0
Kaiser et al[16]	2001	493	835	40	485	668	21	95	291	259	39	108	259	199	21
Tsai et al[72]	2002	10	218	0	22	232	0	0	10	104	0	3	16	108	0
Herken et al[44]	2003	82	204	0	31	59	0	12	58	73	0	8	15	22	0
Zaboli et al[47]	2008	122	184	0	176	302	0	30	62	61	0	29	118	92	0
Herken et al[73]	2002	72	184	0	71	198	1	9	54	65	0	7	57	70	1
Stober	1998	141	217	2	204	254	8	29	83	66	2	54	96	75	8
Collier et al[74]	1996	94	162	2	169	202	3	19	56	52	2	42	85	57	3
Mata et al[59]	2004	103	221	0	178	288	0	15	73	74	0	37	104	92	0
Li et al[78]	2013	333	45	0	418	182	0	149	35	5	0	142	134	24	0
Yang	2001	22	498	0	58	665	1	2	18	240	0	5	48	308	1

Abbreviation: STin2 VNTR, second intron variable number of tandem repeats.

Discussion

We found no association between 5-HTTLPR and the risk of schizophrenia, except in Indians. The scale for Indians was small and was found in only one article; therefore, the association may be a false-positive. A negative association between 5-HTTLPR and the risk of schizophrenia was consistent with the results of the previous meta-analyses,[19,21] but inconsistent with the results of Allen et al.[22] Differences may exist in results found because Allen et al only analyzed articles on the SzGene in their meta-analysis. An association between suicidal behavior and 5-HTTLPR was not detected in a recent meta-analysis,[83] which conflicts with previous evidence suggesting an association between 5-HTTLPR and violent suicidal behavior. The L allele of the 5-HTTLPR was reported as improving transcription of the *SLC6A4* gene.[84] A meta-analysis noted an association between the S allele of 5-HTTLPR and the risk of bipolar disorder.[85] Psychiatric disorders share genetic variants.[21] A haplotype, including 5-HTTLPR and rs16965628 markers, is thought to be associated with an obsessive–compulsive disorder.[86] Therefore, 5-HTTLPR may link with other SNPs to influence the serotoninergic pathway.

STin2 VNTR was associated with the risk of schizophrenia, but a significant difference was not detected in the allele analysis, inconsistent with other meta-analyses.[19,20] Gatt et al reviewed the relevant meta-analysis between STin2 VNTR and schizophrenia and found that the 12R genotype was associated with schizophrenia as a protective factor, while 9R and 10R genotypes were not associated with schizophrenia.[21] Our results showed that the 10R/12R genotype was a protective factor for schizophrenia, while the 12R/12R genotype was a risk factor for schizophrenia, in the pooled and several subgroup analyses. Genotypes with 12R may significantly increase relative *5-HTT* gene expression,[87] leading to increasing vulnerability to schizophrenia. STin2.12R has a superior enhancer-like property within the developing rostral hindbrain, which

Table 6 Genotype distribution and allele frequency of rs1042173

Authors	Year	Genotype distribution						P_{HWE}	Allele frequency			
		Cases, n			Controls, n				Cases, %		Controls, %	
		GG	GT	TT	GG	GT	TT		G	T	G	T
Vijayan et al[40]	2009	63	119	50	55	112	67	0.538	245	219	222	246
Zaboli et al[47]	2008	39	78	38	58	129	59	0.444	156	154	245	247
Carlstrom	2012	207	402	223	291	770	410	0.039	816	848	1,352	1,590
Xuan et al[77]	2012	77	43	12	94	48	8	0.568	197	67	236	64

Abbreviation: P_{HWE}, *P*-value of Hardy–Weinberg equilibrium.

Table 7 Genotype distribution and allele frequency of rs140700

Authors	Year	Genotype distribution						P_{HWE}	Allele frequency			
		Cases, n			Controls, n				Cases, %		Controls, %	
		GG	GA	AA	GG	GA	AA		G	A	G	A
Li et al[78]	2013	369	127	30	259	212	57	0.173	865	187	730	326
Lin et al[71]	2009	277	30	2	244	18	1	0.295	584	34	506	20
Carlstrom	2012	689	140	2	1,233	221	10	0.977	1,518	144	2,687	241
Pal et al[79]	2009	80	19	5	112	18	1	0.769	179	29	242	20

Abbreviation: P_{HWE}, *P*-value of Hardy–Weinberg equilibrium.

may lead to aberrant serotonergic neuronal development.[40,88] In addition, STin2 acts as a transcriptional regulator in an allele-dependent manner in the developing mouse brain.[89] Haplotype analysis demonstrated that two STin2-containing haplotypes were associated with the risk of schizophrenia, but no association was found in the single locus.[71] No association was detected in Caucasians and Indians, which may be the result of different genetic backgrounds. Significant heterogeneity was assessed in the pooled analysis, and heterogeneity was found in all subgroups, except Caucasians. This was the first meta-analysis of the association between the risk of schizophrenia and rs1042173 and rs140700.

Gatt et al comprehensively reviewed a meta-analysis of the association between *SLC6A4* (5-HTTLPR and STin2 VNTR) and schizophrenia.[21] To some extent, it would seem that our meta-analysis is superfluous. However, it was an updated analysis, assessing the association of the *SLC6A4* gene with schizophrenia using high statistical powers. Our study also included seven studies published after 2013 and three studies in Chinese. Moreover, four variations (5-HTTLPR, STin2 VNTR, rs1042173, and rs140700) were analyzed in our meta-analysis. Genome-wide association studies (GWASs) can discover novel and unexpected candidate loci in an unbiased manner. Previous GWAS analyses found that the *SLC6A4* gene was not associated with schizophrenia.[90–93] A comparison of 12 single-disorder GWAS meta-analyses suggested no overlap in significant genetic variants identified from the different studies.[21] However, structural magnetic resonance imaging scans suggested that *SLC6A4* was related to deficits of brain structural networks in schizophrenia.[94] Our results are inconsistent with those of the previous meta-analysis. Several reasons for this may exist: First, many recently published studies were included in our analysis; therefore, the scale of samples used was larger than those used before. Second, the articles from both English and Chinese language databases were included. Third, geographical environment, culture, lifestyle, and genetic background and diseases may affect genetic polymorphisms.[95,96]

Significant heterogeneity was found in overall and subgroup analyses, especially for STin2 VNTR and rs140700. Although we performed subgroup analyses according to ethnicity to investigate potential sources of heterogeneity,

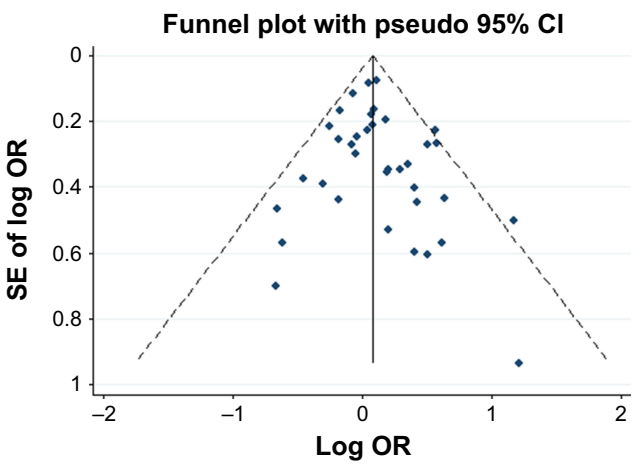

Figure 2 Funnel plot analysis on the detection of publication bias in the association between 5-HTTLPR (SS + LS vs LL) and schizophrenia.
Abbreviation: 5-HTTLPR, serotonin-transporter-linked polymorphic region.

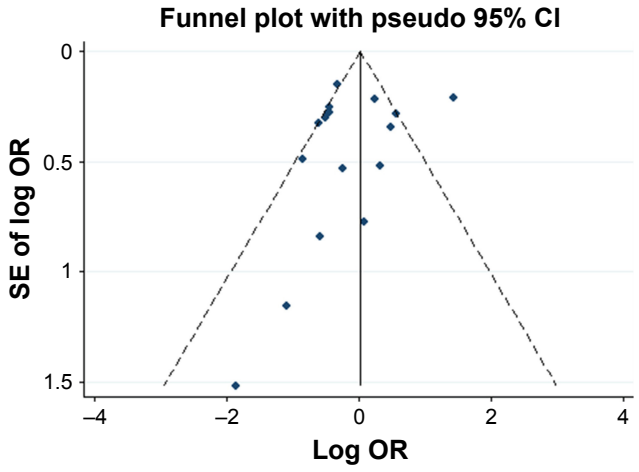

Figure 3 Funnel plot analysis on the detection of publication bias in the association between STin2 VNTR (10R/10R vs others) and schizophrenia.
Abbreviation: STin2 VNTR, second intron variable number of tandem repeats.

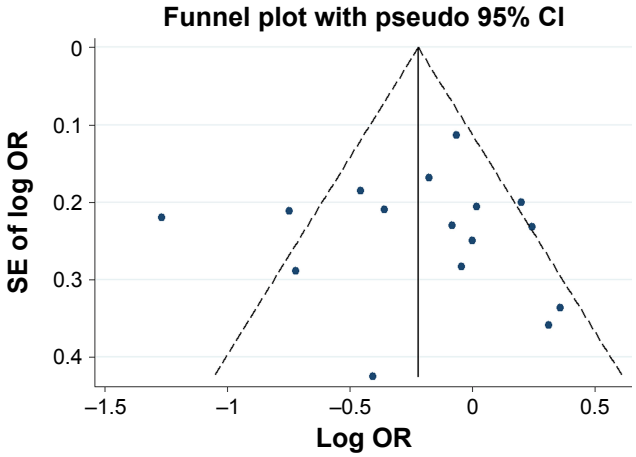

Figure 4 Funnel plot analysis on the detection of publication bias in the association between STin2 VNTR (10R/12R vs others) and schizophrenia.
Abbreviation: STin2 VNTR, second intron variable number of tandem repeats.

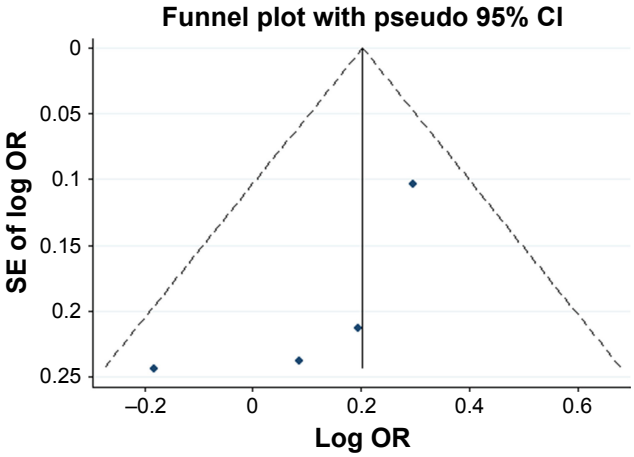

Figure 6 Funnel plot analysis on the detection of publication bias in the association between rs1042173 (GG vs GT + TT) and schizophrenia.

this did not completely account for the heterogeneity. These results suggest that other aspects may partially contribute to heterogeneity, such as distinct genetic backgrounds and the different habits and customs of the people sampled.[97]

Overall, however, the results described herein should be interpreted with caution. First, the small sample size for rs1042173 and rs140700 should be borne in mind. Several associations only appeared in the subgroup analyses, for which only one or two articles were used. Therefore, these samples may not be representative and comprehensive. In addition, it was hard to conduct subgroup analyses for some SNPs because of so few articles. Second, deviations in the P_{HWE} and significant heterogeneity were observed in this study because of sample bias. Third, family-based studies, which were more robust than case–control designs, were not included in this analysis.[98–101] Fourth, interactions between multiple genes and SNPs may affect the risk of schizophrenia,[21] meaning that genetic interactional and functional studies are needed.

Conclusion

Our meta-analysis showed a lack of association between 5-HTTLPR and the risk of schizophrenia, except in an Indian subgroup analysis. The 10R/12R genotype was a protective factor against schizophrenia, while the12R/12R genotype was a risk factor for schizophrenia in the pooled analyses. In Caucasians, the GG genotype of rs1042173 may be a risk factor for schizophrenia. No association was found between rs140700 and the risk of schizophrenia. Increased genetic interactional and functional studies are warranted to explore the association between polymorphisms of the *SLC6A4* gene and schizophrenia risk.

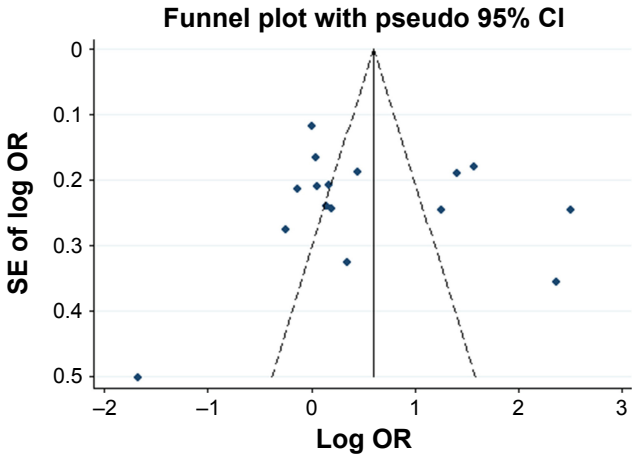

Figure 5 Funnel plot analysis on the detection of publication bias in the association between STin2 VNTR (12R/12R vs others) and schizophrenia.
Abbreviation: STin2 VNTR, second intron variable number of tandem repeats.

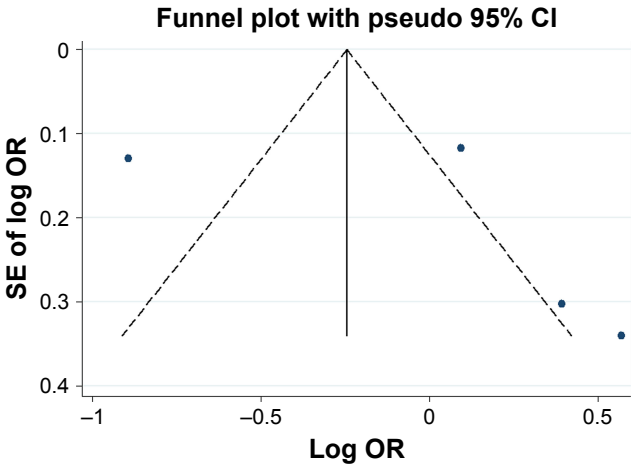

Figure 7 Funnel plot analysis on the detection of publication bias in the association between rs140700 (AA + AG vs GG) and schizophrenia.

Disclosure

The authors report no conflicts of interest in this work.

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