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A Meta-analysis of the Association Between SLC6A3 Gene Polymorphisms and Schizophrenia

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Abstract

The dopamine transporter is coded by the *SLC6A3* gene and plays an important role in regulation of the neurotransmitter dopamine. To detect the association between the *SLC6A3* gene and the risk of schizophrenia, 31 case-control articles were included in this meta-analysis. There were 23 studies with 40 bp VNTR (3246 cases and 3639 controls), 4 studies with rs40184 (2020 cases and 1674 controls), rs6347 (1317 cases and 1917 controls), rs403636 (2045 cases and 1704 controls), and rs2975226 (849 cases and 904 controls); and 3 studies with rs12516948 (1920 cases and 1569 controls), rs27072 (984 cases and 1015 controls), rs6869645 (1142 cases and 1082 controls), rs37022 (1168 cases and 1091 controls), rs464049 (1169cases and 1096 controls), rs2652511 (707 cases and 714 controls), and rs3756450 (1176 cases and 1096 controls). Pooled, subgroup, and sensitivity analyses were performed, and the results were visualized by forest and funnel plots. In the dominant genetic model, the genotype AA+AT of rs2975226 in the Indian population ($P_z = 0$, odds ratio [OR] = 3.245, 95% confidence interval [CI] = 1.806–5.831), TT of rs464049 ($P_z = 0.002$, OR = 1.389, 95% CI = 1.129–1.708), and TT of rs3756450 ($P_z = 0.014$, OR = 1.251, 95% CI = 1.047–1.495) might be risk factors for schizophrenia. Additionally, no other single nucleotide polymorphisms were observed. These results indicate that more functional studies are warranted.

Keywords *SLC6A3* · Schizophrenia · Meta-analysis · Pooled analysis

Introduction

Schizophrenia is a complex chronic brain dysfunction, with an unclear pathogenesis (Wray and Visscher 2010). Investigations of twins and adoptees have reported that schizophrenia is caused by both genetic and environmental factors (Sullivan 2005). Epidemiological genetic studies suggest that genetic factors contribute significantly to the etiology of schizophrenia (Cardno and Gottesman 2000; Cordeiro et al. 2004). Many antipsychotic drugs are very effective for blocking dopamine receptors in the brain, indicating that dysfunction of the dopaminergic system is involved in the pathogenesis of schizophrenia (Creese et al. 1976). Imaging studies have also revealed that dopamine synthesis increases in the striatum of patients with schizophrenia (Fusar-Poli and Meyer-Lindenberg 2013; Howes et al. 2012). Therefore, dysfunction of the dopamine system has been considered to be the ultimate common pathway for the pathophysiology of schizophrenia (Howes and Kapur 2009; Laruelle et al. 1999; Lewis and Lieberman 2000). The dopamine transporter (DAT) plays an important role in dopamine neurotransmission by mediating the active re-uptake of synaptic dopamine into neurons (Carvelli et al. 2008; Srivastava et al. 2006). The DAT has been implicated in schizophrenia (Wiers et al. 2015) and a

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number of other psychiatric dopamine-related disorders, including clinical depression (Bahi and Dreyer 2019), attention-deficit hyperactivity disorder, bipolar disorder (Thal et al. 2019), and alcoholism (Wiers et al. 2015). DAT mRNA levels in the midbrain tissues of patients with schizophrenia are significantly lower than those in normal subjects (Purves-Tyson et al. 2017). Thus, the *SLC6A3* gene is a candidate gene for the pathogenesis of schizophrenia.

The DAT is coded by the *SLC6A3* gene, which is located on human chromosome 5q15 and consists of 15 coding exons over 64 kb long. Polymorphisms in the *SLC6A3* gene can affect the structure and function of the transporter. Variations in the 40-base-pair variable number of tandem repeats (40 bp VNTR) have been described in the 3′ untranslated region (3′ UTR) of the *SLC6A3* gene. Moreover, there are many single nucleotide polymorphisms (SNPs) in the *SLC6A3* gene, such as rs12516948 and rs27072 located at the 3′ UTR; rs6347 located in the exon region; rs40184, rs6869645, rs37022, rs464049, and rs403636 located in the intron region; and rs3756450, rs2652511 (− 839 A > T), and rs2975226 (− 67 T > A) located at the 5′ untranslated region (5′ UTR). Studies indicate that 40 bp VNTR might affect expression of the *SLC6A3* gene (Miller and Madras 2002; VanNess et al. 2005), thereby disordering the dopamine system and causing schizophrenia. One study showed that the 40 bp VNTR polymorphism of the *SLC6A3* gene is related to performance on the Wisconsin Card Sorting Test on which deficits have long been recognized as an enduring and core feature of patients with schizophrenia (Rybakowski et al. 2006). However, other reports have noted that 40 bp VNTR is not associated with schizophrenia. Associations between other SNPs in the *SLC6A3* gene and schizophrenia remain controversial.

Meta-analysis is a useful method to explore disease-gene associations (Barendregt et al. 2013; Munafo and Flint 2004). Only one meta-analysis of association research has been reported between the 40 bp VNTR in the *SLC6A3* gene and the risk of schizophrenia (Gamma et al. 2005). There are several newly published studies on its association with schizophrenia. Therefore, we performed a meta-analysis to further explore the association between the *SLC6A3* gene and the risk of schizophrenia.

Materials and Methods

Literature Search

To identify studies eligible for inclusion in this meta-analysis, English databases (PubMed and SZGene) and Chinese databases (CNKI, Wanfang, and Weipu) were searched with the keywords: "dopamine transporter gene," "DAT1," "SLC6A3," and "schizophrenia." References in the searched articles were also reviewed to identify additional studies.

Inclusion and Exclusion Criteria

The studies included in this meta-analysis met the following features: (1) case-control design; (2) involved patients with schizophrenia; (3) presented relevant data for case and control groups (e.g., allele/genotype frequencies, sample size, ethnicity, schizophrenia diagnostic criteria, and control group source); (4) removed duplicate sample data; and (5) published before August 1, 2018. If there were no detailed data in the article, we tried to obtain the data by emailing the authors. 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 email for these data); and (4) duplicate sample data.

Statistical Analyses

The meta-analysis was conducted using Stata version 10.0 (Stata Corp., College Station, TX, USA). The *P* value of the Hardy–Weinberg equilibrium (PHWE) was calculated for the control groups. The associations between *SLC6A3* and the risk of schizophrenia were detected under a random model (Munafo and Flint 2004; Myung and Park 2018). A suitable genetic model was selected according to previous studies (Thakkinstian et al. 2005; Xu et al. 2018). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the pooled and subgroup analyses.

Heterogeneity of the studies was determined by Cochran's chi-square-based *Q*-statistic test (Zintzaras and Ioannidis 2005). The degree of heterogeneity was expressed as I^2, which was divided into low ($I^2 < 25\%$), medium ($I^2 \sim 50\%$), and high ($I^2 > 75\%$) heterogeneity (Higgins et al. 2003; Naing et al. 2017). Publication bias was calculated using Egger's test and was visualized with a funnel plot, in which the standard error of the log (OR) of each study was plotted against its log (OR). A sensitivity analysis was conducted by removing one single study in turn to test the impact of each study on the pooled result. *P* values of the association, heterogeneity, and publication bias tests were represented by P_z, P_h, and P_e, respectively. A P value < 0.05 was considered significant for all statistical tests (Sedgwick and Marston 2015).

Results

Description of the Studies

A total of 212 English and 20 Chinese articles were searched, and 31 articles were analyzed in this study after applying the exclusion criteria (Fig. 1). The genotype data of the studies (Mas et al. 2009; Meda et al. 2010; Simons et al. 2013; Wonodi et al. 2009) were still unavailable after sending emails to the authors, so they were removed from

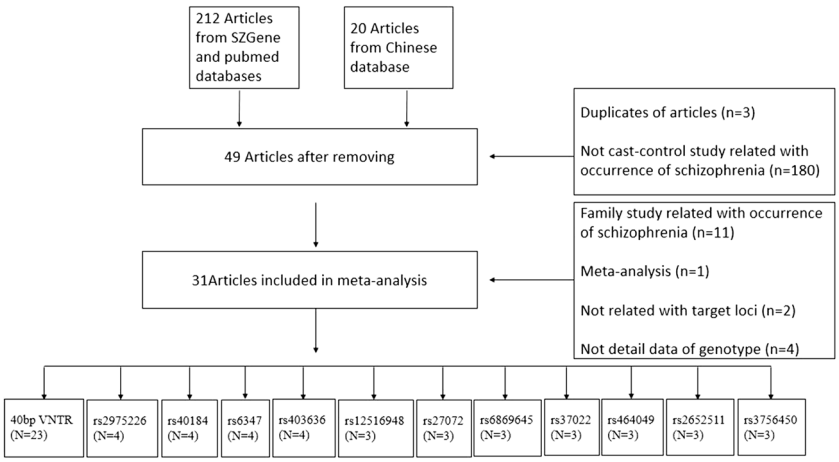

Fig. 1 Article selection process in this meta-analysis

the present meta-analysis. The baseline characteristics of the 31 qualified studies in this meta-analysis are described in Table 1. There were 23 articles about 48 bp VNTR (Alvarez et al. 2010; Bodeau-Pean et al. 1995; Cordeiro et al. 2004; Daniels et al. 1995; Fujiwara et al. 1997; Huang et al. 2010; Inada et al. 1996; Jeong et al. 2004; Joober et al. 2000; Krelling et al. 2008; Li et al. 1994; Lin Sicui et al. 2000; Liu et al. 2004; Martinez et al. 2001; Peitl et al. 2017; Persico and Macciardi 1997; Prata et al. 2009; Saiz et al. 2010; Semwal et al. 2002; Szekeres et al. 2004; Tybura et al. 2011; Zhang et al. 2003; Zilles et al. 2012), 4 articles about rs40184 (Kukshal et al. 2013; Pal et al. 2009; Talkowski et al. 2008; Yang et al. 2014), rs6347 (Cordeiro et al. 2010; Huang et al. 2010; Jeong et al. 2004; Talkowski et al. 2008), rs403636 (Kukshal et al. 2013; Pal et al. 2009; Talkowski et al. 2008; Yang et al. 2014), and rs2975226 (Alvarez et al. 2010; Fan Miao 2014; Huang et al. 2010; Khodayari et al. 2004); 3 articles about rs12516948 (Kukshal et al. 2013; Talkowski et al. 2008; Yang et al. 2014), rs27072 (Fan Miao 2014; Huang et al. 2010; Talkowski et al. 2008), rs6869645, rs37022, rs464049, rs3756450 (Kukshal et al. 2013; Pal et al. 2009; Talkowski et al. 2008), and rs2652511 (Fan Miao 2014; Galehdari et al. 2009; Huang et al. 2010). There were fewer than three articles about rs2963253, rs6345, rs6350, rs27048, rs2042449, rs463379, rs456082, rs2617605, rs2078247, G-660C, rs3863145, rs2550956, rs2975223, and rs2455391, so these SNPs were not analyzed.

Results of the Data Analysis

No Association Between 40 bp VNTR and the Risk of Schizophrenia

The common alleles were 9 repeat (R) and 10R of the 40 bp VNTR. Associations between the risk of schizophrenia and 9R and 10R were analyzed. The genotype data were not obtained after sending emails to the authors of an article (Zilles et al. 2012), in which there were only 9R carrier and 10R/10R genotype data. So, the article was omitted from the analysis. A pooled analysis of 3214 cases and 3619 controls was performed (Table 2). The results of the pooled analyses are summarized in Table 3, and data from the subgroup analyses are depicted in Table 4. No association was found between the risk for schizophrenia and 9R ($P_z = 0.15$, OR = 0.935, 95% CI = 0.852–1.025), or 10R ($P_z = 0.414$, OR = 1.037, 95% CI = 0.951–1.131), under a random effects model (Figs. S1–S2) (Arj-Ong et al. 2010; Thakkinstian et al. 2005). No association was found in the subgroup analysis by ethnicity or by source of the controls (Table 4). No significant heterogeneity was observed in the pooled or subgroup analyses.

The *SLC6A3* 10R/10R genotype has been associated with higher DAT1 mRNA expression in schizophrenic donors of frontal eye field tissue (Wonodi et al. 2009). The relationship between the 10R/10R genotype and the risk of schizophrenia was analyzed to better understand the association between 40 bp VNTR and schizophrenia. We conducted a pooled analysis, including 2939 cases and 3050 controls (Fig. S3), after omitting samples from an article in which the 10R/10R genotype data could not be obtained (Semwal et al. 2002). No association was observed in the pooled analysis ($P_z = 0.184$, OR = 1.285, 95% CI = 0.888–1.859) or in the subgroup analysis. Significant heterogeneity was detected in the pooled ($P_h = 0$, $I_2 = 89.2\%$), East Asian subgroup ($P_h = 0$, $I_2 = 95.7\%$), and population-based subgroup ($P_h = 0$, $I_2 = 92.1\%$) analyses (Table 4).

No Association Between rs40184 and the Risk of Schizophrenia

To include more data in the pooled allele analysis, 2020 cases and 1674 controls were analyzed, although details of the genotypes were not available for one article (Pal et al. 2009). The dominant model (Xu et al. 2018) was selected

Table 1 Baseline characteristics of qualified studies in this meta-analysis

Author	Year	Country	Ethnicity	Controls source	Mean age of control group	Diagnostic criteria	Gender index (case)	Gender index (control)
Alvarez	2009	Spain	Caucasians	Hospital-based	61.7	DSM-IV	0.830	1.610
Antonio	1997	Italy	Caucasians	Population-based	–	DSM-IIIR	0.598	–
Szekeres	2004	–	Caucasians	Population-based	–	DSM-IV	1.210	1.65
Daniels	1995	UK	Caucasians	Hospital-based	52.0	DSMIII-R	0.640	0.710
Tybura	2011	Poland	Caucasians	Hospital-based	31.9	ICD–10	1.040	1.050
Sylvie	1995	France	Caucasians	Population-based	48.0	DSM-III	0.470	0.820
Peitl	2017	Croatia	Caucasians	Population-based	37.6	DSM-IV-TR	0.376	0.865
Martinez	2001	–	Caucasians	Population-based	39.9	DSM-IV	–	–
Inada	1996	Japan	East Asia	Hospital-based	46.0	DSM-111-R	1.185	1.127
Sáiz	2010	Spanish	Caucasians	Population-based	40.6	DSM-IV	0.664	0.949
Cordeiro	2004	Brazil	Caucasians	Hospital-based	–	DSM-IV	–	–
Huang	2010	China	East Asia	Population-based	38.0	DSM-IV	0.607	0.547
Krelling	2008	Brazil	Caucasians	Population-based	–		–	–
Jeong	2004	Korea	East Asia	Population-based	22.4	DSM-IV	0.658	0.683
Prata	2009	UK	Caucasians	Population-based	–	DSM-IV	–	–
Fujiwara	1997	Japan	East Asia	Population-based	–	DSM-111-R	–	–
Joober	2000	Canada	Caucasians	Population-based	–	DSM-IV	–	–
Liu	2004	China	East Asia	Hospital-based	29.6	DSM-IV	0.068	0.090
Li	1993	China	East Asia	Population-based	25.1	DSM-IV	0.500	0.556
Semwal	2002	India	Indians	Hospital-based	–	DSM-IV	–	–
Lin	2000	China	East Asia	Population-based	35 .3	CCMD-2-R	0.664	0.976
Zhang	2003	China	East Asia	Population-based	42.0	CCMD-2-R	0.426	0.872
Zilles	2012	Germany	Caucasians	Population-based	–	ICD-10	0.882	2.330
Khodayari	2004	Iran	Iranian	Population-based	45.0	DSM-IV	0.000	0.000
Fan	2014	China	East Asia	Population-based	–	DSM-IV	0.938	1.859
Talkowski	2008	USA	Caucasian	Hospital-based	–	DSM-IV	–	–
Yang	2014	China	East Asia	Population-based	42.0	DSM-IV	0.772	0.835
Kukshal	2013	India	Indian	Population-based	–	DSM-IV	–	–
Pal	2009	Croatia	Caucasian	Population-based	50.3	ICD-10	0.705	–
Cordeiro	2010	Brazil	Caucasian	Hospital-based	–	DSM-IV	0.546	0.604
Galehdari	2009	Iran	East Asia	Population-based	39.4	DSM-IV	0.709	–

under a random effects model (Pan et al. 2014), and no association was detected ($P_z = 0.089$, OR = 1.131, 95% CI = 0.981–1.305) (Fig. S4). No association was found in the subgroup analysis by the source of the controls (Table 4). No significant heterogeneity was observed in pooled or subgroup analyses.

No Association Between rs6347 and the Risk of Schizophrenia

Pooled and subgroup analyses were performed in a random model with 1317 cases and 1917 controls. No association was noted between rs6347 and the risk of schizophrenia in the recessive model ($P_z = 0.89$, OR = 1.021, 95% CI = 0.764–1.363), or in the forest plot shown in Fig. S5. No relationship was found in the subgroup analysis by ethnicity or by the source of controls (Table 4). Significant heterogeneity was observed in the pooled analysis ($P_h = 0.026$, $I_2 = 67.7\%$).

No Association Between rs403636 and the Risk of Schizophrenia

In the dominant model and under a random model, no association was detected among 2045 cases and 1704 controls ($P_z = 0.536$, OR = 1.322, 95% CI = 0.546–3.203) (Fig. S6). No association was observed in the subgroup analysis by ethnicity or by source of the controls. Significant heterogeneity was noted in the pooled ($P_h = 0.012$, $I_2 = 77.2\%$) and population-based subgroup ($P_h = 0.006$, $I_2 = 86.7\%$) analyses.

Table 2 Distribution of genotype and allele frequencies of the 40 bp VNTR

		Allele frequency						Genotype distribution							
		Cases, *n*			Control, *n*			Cases, *n*			Control, *n*				
Author	Year	9R	10R	Other	9R	10R	Other	9/9	9/10	101/0	Other	9/9	9/10	10/10	Other
Alvarez	2009	88	222	8	180	390	10	12	62	77	8	28	121	131	10
Antonio	1997	99	187	8	56	111	1	25	48	69	5	7	41	35	1
Szekeres	2004	41	109	0	24	66	0	5	31	39	0	3	18	24	0
Daniels	1995	44	147	5	43	128	3	5	33	55	5	5	32	47	3
Tybura	2011	73	131	0	166	300	0	7	59	36	0	12	142	79	0
Sylvie	1995	50	129	3	61	118	3	6	38	44	3	9	41	38	3
Peitl	2017	161	439	0	170	412	0	15	131	154	0	24	122	145	0
Martinez	2001	13	42	1	13	49	0	2	8	17	1	1	11	19	0
Inada	1996	8	221	7	18	211	5	0	8	103	7	1	16	95	5
Sáiz	2010	162	377	7	281	544	15	22	117	129	5	51	175	180	14
Cordeiro	2004	109	314	17	111	328	13	15	78	112	15	19	70	124	13
Huang	2010	36	629	19	39	562	21	3	30	290	19	2	35	253	21
Krelling	2008	45	124	1	23	79	2	5	35	44	1	3	16	31	2
Jeong	2004	18	455	31	14	497	31	0	18	203	31	0	228	14	29
Prata	2009	20	62	0	20	68	0	2	16	23	0	2	16	26	0
Fujiwara	1997	5	76	1	3	43	0	0	5	35	1	0	3	20	0
Joober	2000	61	151	0	45	133	0	7	47	52	0	4	37	48	0
Liu	2004	11	144	3	12	128	4	0	11	65	3	0	12	56	4
Li	1993	13	187	10	11	182	3	0	12	84	9	1	9	85	3
Semwal	2002	72	520	22	139	986	35	–	–	–	–	–	–	–	–
Lin	2000	13	333	10	7	153	6	0	14	160	4	1	5	72	5
Zhang	2003	9	115	10	7	151	4	0	8	53	6	1	5	71	4
Zilles	2012	–	–	–	–	–	–	0	0	21	11	0	0	9	11

The AA+AT Genotype of rs2975226 Could Be a Risk Factor for Schizophrenia in the Indian Population

The allele frequencies of 849 cases and 904 controls were included in a pooled allele analysis. We could not obtain the genotype data of 242 cases and 290 controls for an article (Alvarez et al. 2010), so we conducted the pooled genotype and subgroup analyses after removing the article. In the dominant model (Fig. S7), the pooled OR using a random effects model was 1.669 ($P_z = 0.078$, 95% CI = 0.944–2.950). The genotype AA+AT of rs2975226 could be a risk factor for schizophrenia in the Indian population ($P_z = 0$, OR = 3.245, 95% CI = 1.806–5.831). Significant heterogeneity was noted in the pooled analysis ($P_h = 0.011$, $I_2 = 77.8\%$).

No Association Between rs12516948 and the Risk of Schizophrenia

A total of 1920 cases and 1569 controls were included to evaluate the relationship between rs12516948 and the risk of schizophrenia. In the recessive model (Fig. S8), the pooled OR using a random effects model was 1.165 ($P_z = 0.378$, 95% CI = 0.829–1.638). An association was detected in the hospital-based subgroup analysis ($P_z = 0.047$, OR = 1.462, 95% CI = 1.005–2.127). No significant heterogeneity was observed in the pooled or subgroup analyses.

No Association Between rs27072 and the Risk of Schizophrenia

Pooled and subgroup analyses were conducted in a random model with 984 cases and 1015 controls. No relationship was observed between rs27072 and the risk of schizophrenia in the pooled analysis ($P_z = 0.335$, OR = 1.112, 95% CI = 0.896–1.379) with a recessive model (Fig. S9). No association was detected in the subgroup analysis by ethnicity or by source of the controls. No significant heterogeneity was found in pooled or subgroup analyses.

Table 3 Pooled associations of SLC6A3 polymorphisms and schizophrenia

Loci	Genetic model	Studies (*n*)	Statistical	OR	95% CI	P_z	I_2	P_h	P_e
40 bp VNTR (9 VS others)	Allele contrast	22	Random	0.935	0.852–1.025	0.150	0.0	0.942	0.307
(10 vs others)	Allele contrast	22	Random	1.037	0.951–1.131	0.414	0.0	0.701	0.112
(10/10 vs others)	Genotype	22	Random	1.285	0.888–1.859	0.184	89.2	0.000	0.742
rs40184	Allele contrast	4	Random	1.097	0.995–1.210	0.063	0.0	0.791	0.104
	Homozygous codominant	3	Random	1.147	0.9151.438	0.233	0.0	0.807	0.069
	Heterozygous codominant	3	Random	1.131	0.974–1.314	0.105	0.0	0.687	0.808
	Dominant	3	Random	1.072	0.877–1.310	0.496	0.0	0.781	0.370
	Recessive	3	Random	1.131	0.981–1.305	0.089	00	0.728	0.611
rs6347	Allele contrast	4	Random	1.021	0.801–1.301	0.867	66.9	0.026	0.161
	Homozygous codominant	4	Random	1.270	0.746–2.165	0.379	36.5	0.193	0.076
	Heterozygous codominant	4	Random	1.012	0.760–1.346	0.936	64.5	0.038	0.530
	Dominant	4	Random	0.788	0.553–1.123	0.188	0.0	0.434	0.119
	Recessive	4	Random	1.021	0.764–1.363	0.89	67.7	0.026	0.341
rs403636	Allele contrast	4	Random	1.005	0.767–1.290	0.967	71.7	0.014	0.429
	Homozygous codominant	4	Random	1.267	0.496–3.239	0.621	79.3	0.008	0.623
	Heterozygous codominant	4	Random	0.917	0.732–1.149	0.451	47.9	0.124	0.227
	Dominant	4	Random	1.322	0.546–3.203	0.536	77.2	0.012	0.641
	Recessive	4	Random	0.956	0.733–1.248	0.742	63.6	0.041	0.343
rs2975226	Allele contrast	4	Random	1.360	1.000–1.850	0.050	69.3	0.021	0.577
	Homozygous codominant	3	Random	2.194	0.946–5.092	0.067	33.1	0.224	0.814
	Heterozygous codominant	3	Random	1.237	0.637–2.401	0.529	00	0.852	0.669
	Dominant	3	Random	1.669	0.944–2.950	0.078	77.8	0.011	0.741
	Recessive	3	Random	1.735	0.916–3.289	0.091	0.0	0.566	0.661
rs12516948	Allele contrast	3	Random	1.09	0.779–1.063	0.236	50.1	0.135	0.560
	Homozygous codominant	3	Random	1.204	0.806–1.797	0.364	49.7	0.137	0.050
	Heterozygous codominant	3	Random	1.125	0.850–1.489	0.411	0.8	0.365	0.130
	Dominant	3	Random	1.111	0.951–1.297	0.185	21.9	0.278	0.862
	Recessive	3	Random	1.165	0.829–1.638	0.378	35.2	0.214	0.120
rs27072	Allele contrast	3	Random	1.089	0.920–1.288	0.323	16.3	0.303	0.800
	Homozygous codominant	3	Random	1.110	0.730–1.688	0.626	0.0	0.500	0.879
	Heterozygous codominant	3	Random	1.108	0.885–1.388	0.372	25.4	0.262	0.683
	Dominant	3	Random	1.089	0.721–1.643	0.686	0.0	0.539	0.986
	Recessive	3	Random	1.112	0.896–1.379	0.335	25.0	0.263	0.777
rs6869645	Allele contrast	3	Random	1.078	0.783–1.485	0.646	39.0	0.194	0.409
	Homozygous codominant	3	Random	1.778	0.416–7.593	0.437	28.8	0.246	0.546
	Heterozygous codominant	3	Random	0.989	0.756–1.295	0.938	7.6	0.339	0.187
	Dominant	3	Random	1.761	0.421–7.360	0.438	27.1	0.254	0.563
	Recessive	3	Random	1.036	0.766–1.400	0.820	25.7	0.260	0.309
rs37022	Allele contrast	3	Random	1.047	0.790–1.150	0.617	37.9	0.200	0.801
	Homozygous codominant	3	Random	1.112	0.776–1.594	0.562	00	0.386	0.947
	Heterozygous codominant	3	Random	1.037	0.866–1.241	0.694	1.7	0.362	0.769
	Dominant	3	Random	1.116	0.786–1.586	0.538	0.0	0.496	0.940
	Recessive	3	Random	1.048	0.850–1.292	0.662	27.2	0.253	0.739
rs464049	Allele contrast	3	Random	1.188	0.710–0.929	0.002	15.8	0.305	0.332
	Homozygous codominant	3	Random	1.485	1.138–1.937	0.004	9.6	0.331	0.334
	Heterozygous codominant	3	Random	1.324	1.064–1.649	0.012	00	0.589	0.989
	Dominant	3	Random	1.237	1.029–1.487	0.023	0.5	0.366	0.103
	Recessive	3	Random	1.389	1.129–1.708	0.002	0.0	0.497	0.716
rs2652511	Allele contrast	3	Random	1.218	0.973–1.524	0.085	29.6	0.242	0.473

Table 3 (continued)

Loci	Genetic model	Studies (*n*)	Statistical	OR	95% CI	P_z	I_2	P_h	P_e
	Homozygous codominant	3	Random	1.378	0.886–2.141	0.155	0.0	0.842	0.635
	Heterozygous codominant	3	Random	1.333	0.872–2.037	0.184	0.0	0.755	0.257
	Dominant	3	Random	1.204	0.881–1.646	0.245	42.6	0.175	0.044
	Recessive	3	Random	1.387	0.937–2.051	0.102	0.0	0.874	0.359
rs3756450	Allele contrast	3	Random	0.872	0.755–1.009	0.065	0.0	0.697	0.737
	Homozygous codominant	3	Random	1.020	0.687–1.513	0.922	0.0	0.892	0.894
	Heterozygous codominant	3	Random	1.286	1.069–1.546	0.008	0.0	0.837	0.602
	Dominant	3	Random	0.919	0.629–1.343	0.662	0.0	0.877	0.967
	Recessive	3	Random	1.251	1.047–1.495	0.014	0.0	0.837	0.813

No Association Between rs6869645 and the Risk of Schizophrenia

Pooled and subgroups association studies were conducted with 1142 cases and 1082 controls and a random model. No associations were detected in the pooled analysis ($P_z = 0.438$, OR = 1.761, 95% CI = 0.421–7.360) with the dominant model (Fig. S10) or in subgroup analyses. No significant heterogeneity was found in the pooled or subgroup analyses.

No Association Between rs37022 and the Risk of Schizophrenia

We assessed the association between rs37022 and the risk of schizophrenia in pooled and subgroup analyses with 1168 cases and 1091 controls in a random model. In the recessive model (Fig. S11), no associations were detected in the pooled ($P_z = 0.662$, OR = 1.048, 95% CI = 0.850–1.292) or subgroup analyses. No significant heterogeneity was observed in the pooled or subgroup analyses.

TT of rs464049 Might Be a Risk Factor for Schizophrenia

The genotype data of 1169 cases and 1096 controls were used to evaluate the relationship between rs464049 and the risk of schizophrenia in a random model. In the recessive model (Fig. S12), TT of rs464049 could be a risk factor for schizophrenia in a pooled analysis ($P_z = 0.002$, OR = 1.389, 95% CI = 1.129–1.708) in the Caucasian subgroup ($P_z = 0.002$, OR = 1.504, 95% CI = 1.164–1.943) and in the hospital-based subgroup ($P_z = 0.007$, OR = 1.459, 95% CI = 1.107–1.923) analyses. No significant heterogeneity was observed in pooled or subgroup analyses.

No Association Between rs2652511 and the Risk of Schizophrenia

Pooled and subgroup analyses were evaluated in a random model with 707 cases and 714 controls. In the recessive model (Fig. S13), no association was noted in the pooled analysis ($P_z = 0.102$, OR = 1.387, 95% CI = 0.937–2.051). A subgroup analysis could not be performed. No significant heterogeneity was detected in the pooled analysis.

TT of rs3756450 Might Be a Risk Factor for Schizophrenia

In the random model, we assessed the association between rs3756450 and the risk for schizophrenia with 1176 cases and 1096 controls. In the recessive model (Fig. S14), TT might be a risk factor for schizophrenia in the pooled analysis ($P_z = 0.014$, OR = 1.251, 95% CI = 1.047–1.495), but no association was detected in subgroup analyses. No significant heterogeneity was found in the pooled or subgroup analyses.

Sensitivity Analysis

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

Publication Bias

Publication bias was visualized with funnel plots, in which the standard error of the log (OR) of each study was plotted against its log (OR). No evidence of publication bias was found in pooled analyses (Figs. S15–S28).

Discussion

No association was detected between 40 bp VNTR and the risk of schizophrenia, which is consistent with a previous meta-analysis (Gamma et al. 2005). Moreover, 40 bp VNTR has been reported not to be related with striatal DAT availability in humans (Costa et al. 2011), tardive dyskinesia among patients with schizophrenia (Srivastava et al. 2006), and DAT gene expression or protein function (Lafuente et al. 2007). However, a possible interaction between the *DRD3* and

Table 4 Subgroup associations of SLC6A3 polymorphisms with schizophrenia

Loci	Subgroup analysis	Studies (*n*)	OR	95% CI	P_z	I_2	P_h
40 bp VNTR allele contrast (9 vs others)	Caucasians	13	0.933	0.842–1.035	0.190	0.0	0.933
	East Asia	8	0.911	0.693–1.198	0.505	0.0	0.523
	Indians	1	0.976	0.721–1.321	0.874	–	–
	Population-based	15	0.943	0.836–1.062	0.333	0.0	0.914
	Hospital-based	7	0.923	0.799–1.066	0.276	0.0	0.628
(10 vs others)	Caucasians	13	1.056	0.953–1.169	0.298	0.0	0.894
	East Asia	8	0.979	0.744–1.286	0.877	32.2	0.171
	Indians	1	0.976	0.743–1.282	0.863	–	–
	Population-based	15	1.032	0.920–1.157	0.595	1.9	0.430
	Hospital-based	7	1.040	0.907–1.192	0.574	0.0	0.821
(10/10 vs others)	Caucasians	14	1.059	0.928–1.208	0.393	0.0	0.910
	East Asia	8	1.762	0.516–6.015	0.366	95.7	0.000
	Population-based	16	1.285	0.888–1.859	0.280	92.1	0.000
	Hospital-based	6	1.067	0.872–1.305	0.531	0.0	0.701
rs40184	Population-based	2	1.136	0.964–1.338	0.129	0.0	0.429
	Hospital-based	1	1.118	0.840–1.490	0.445	–	–
rs6347	Caucasians	2	1.217	0.893–1.658	0.213	61.5	0.107
	East Asia	2	0.809	0.534–1.227	0.319	52.4	0.147
	Population-based	2	0.809	0.534–1.227	0.319	52.4	0.147
	Hospital-based	2	1.217	0.893–1.658	0.213	61.5	0.107
rs403636	Population-based	2	2.001	0.412–9.724	0.390	86.7	0.006
	Hospital-based	1	0.675	0.297–1.535	0.348	–	–
rs2975226	Caucasians	1	1.104	0.864–1.412	0.428	–	–
	East Asia	2	1.294	0.873–1.919	0.200	44.9	0.178
	Indians	1	3.245	1.806–5.831	0.000	–	–
rs12516948	Population-based	2	0.987	0.677–1.440	0.947	0.0	0.317
	Hospital-based	1	1.462	1.005–2.127	0.047	–	–
rs27072	Caucasians	1	1.196	0.915–1.563	0.191	–	–
	East Asia	2	1.074	0.736–1.568	0.711	52.3	0.148
	Population-based	2	1.074	0.736–1.568	0.711	52.3	0.148
	Hospital-based	1	1.196	0.915–1.563	0.191	–	–
rs6869645	Caucasians	2	0.891	0.228–3.472	0.867	0.0	0.507
	Indians	1	6.250	0.728–53.689	0.095	–	–
	Population-based	2	4.634	0.776–27.671	0.093	0.0	0.624
	Hospital-based	1	0.718	0.160–3.226	0.666	–	–
rs37022	Caucasians	2	1.100	0.773–1.565	0.598	40.0	0.197
	Indians	1	0.96	0.752–1.225	0.741	–	–
	Population-based	2	0.939	0.753–1.170	0.573	0.0	0.675
	Hospital-based	1	1.247	0.954–1.629	0.107	–	–
rs464049	Caucasians	2	1.504	1.164–1.943	0.002	0.0	0.560
	Indians	1	1.198	0.844–1.699	0.312	–	–
	Population-based	2	1.321	0.933–1.871	0.117	10.5	0.290
	Hospital-based	1	1.459	1.107–1.923	0.007	–	–
rs3756450	Caucasians	2	1.293	0.996–1.679	0.054	0.0	0.622
	Indians	1	1.216	0.953–1.552	0.116	–	–
	Population-based	2	1.204	0.965–1.503	0.101	0.0	0.850
	Hospital-based	1	1.341	0.994–1.809	0.054	–	–

SLC6A3 genes might be involved in the risk of schizophrenia (Saiz et al. 2010). One study reported that 9R is associated with greater activation than 10R in patients with schizophrenia (Prata et al. 2009). Thus, further functional studies should try to determine the association between 40 bp VNTR and the risk of schizophrenia.

No association was detected between rs40184 and the risk for schizophrenia. This polymorphism is related to major depressive disorder (Pattarachotanant et al. 2010), harm avoidance in bipolar disorder (Huang et al. 2015), pediatric bipolar disorder (Mick et al. 2008), and migraine with aura (Todt et al. 2009). Significant differences have been noted in the allele frequencies of rs40184 among healthy subjects of different ancestries (Pattarachotanant et al. 2010). The present meta-analysis only included East Asian and Iranian population groups, so our results need to be interpreted carefully.

Rs6347, located in the exon, was a synonymous mutation. No association between rs6347 and the risk of schizophrenia was observed in our meta-analysis. Heterogeneity was detected in the pooled study but was not found in subgroup analyses. Therefore, there might be other factors affecting the heterogeneity. To some degree, the population-based subgroup was responsible for the heterogeneity in the pooled analysis.

The AA+AT genotype of rs2975226 was a risk factor for schizophrenia in the Indian subgroup analysis, but not in the pooled analysis. This difference may be due to two factors. First, cultural, lifestyle, environmental stress, and population differences may account for the differences in the genotype and allele frequencies of the rs2975226 gene (Huang et al. 2010). Second, there was only one article on the Indian population and it had a small sample size. Significant heterogeneity was detected in the pooled analysis but was not found in subgroup analyses, so other factors may be affecting the heterogeneity. Additionally, other studies have shown that rs2975226 is associated with bipolar disorder (Khodayari et al. 2004) and activity of the promoter (Bamne et al. 2010). Therefore, further studies are required to explore its function.

In the hospital-based subgroup analysis, rs12516948 was associated with the risk for schizophrenia, but only one article was included in this subgroup analysis. An association was found between the risk of schizophrenia and rs464049 in Caucasians and hospital-based subgroup analyses. This variation is involved in neurobehavioral recovery (Treble-Barna et al. 2017). The association between rs3756450 and the risk of schizophrenia was found in a pooled analysis, but not in subgroup analyses. Therefore, other factors may account for the association.

Our meta-analysis assessed the association between the *SLC6A3* gene and schizophrenia. It included not only the 40 bp VNTR as reported by previous meta-analyses but also the 11 other SNPs of which there are no meta-analyses. The data in our study were extracted from English (Pubmed and SZgene) and Chinese databases. Therefore, more relevant data were included than in previous studies. However, the geographical environment, culture, lifestyle, and genetic background may have affected the genetic polymorphisms (Frey 2014; Walton et al. 2014), and the hospital-based control population could have been affected by other diseases (Yao et al. 2015). This may explain the controversial relationship between *SLC6A3* and the risk of schizophrenia.

The results described herein should be interpreted with caution. First, in this study, there were not enough articles on the included SNPs, except for 40 bp VNTR. Some associations only appeared in subgroup analyses, in which there were only one or two articles. Therefore, the results are not representative or comprehensive. Additionally, it was difficult to conduct subgroup analyses for some SNPs, because of the limited number of articles. Second, deviation in the PHWE and significant heterogeneity were observed in this study because of sample bias. Third, family-based studies, which are more robust than a case-control design (Georgieva et al. 2002), were not included in this analysis (Greenwood et al. 2016; King et al. 1997; Maier et al. 1996). Fourth, interactions between multiple genes might affect the risk of schizophrenia (Talkowski et al. 2008).

Conclusion

In summary, our meta-analysis showed that the AA+AT genotype of rs2975226 in the Indian population, TT of rs464049, and TT of rs3756450 might be risk factors for schizophrenia under a dominant genetic model. No association was observed among other SNPs on the *SLC6A3* gene. More functional studies are warranted to explore the associations between *SLC6A3* gene polymorphisms and the risk of schizophrenia.

Authors' Contributions Bao-jie Wang and Mei Ding designed the study and wrote the protocol. Feng-ling Xu managed the literature search, and Xue Wu, Yong-ping Liu, and Xi Xia checked the literature. Feng-ling Xu performed the analyses. The first draft of the manuscript was written by Feng-ling Xu and revised by Jun Yao.

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