Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

A meta-analysis of data associating *DRD4* gene polymorphisms with schizophrenia

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

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Abstract: To explore the association between *DRD4* polymorphisms and schizophrenia risk, a meta-analysis was carried out with 41 case–control articles. Specifically, we included 28 articles (5,735 cases and 5,278 controls) that pertained to the 48 bp variable number tandem repeat (VNTR) polymorphism, nine articles (1,517 cases and 1,746 controls) that corresponded to the 12 bp tandem repeat (TR), six articles (1,912 cases and 1,836 controls) that addressed the 120 bp TR, 10 articles (2,927 cases and 2,938 controls) that entailed the −521 C>T polymorphism, six articles (1,735 cases and 1,724 controls) that pertained to the −616 C>G polymorphism, and four articles (1,191 cases and 1,215 controls) that involved the −376 C>T polymorphism. Pooled analysis, subgroup analysis, and sensitivity analysis were performed, and the data were visualized by means of forest and funnel plots. Results of pooled analysis indicated that the −521 CC variant (P_z=0.009, odds ratio [OR] =1.218, 95% confidence interval [CI] =1.050–1.413) and genotype L/L (ie, long allele) of the 120 bp TR were risk factors of schizophrenia (P_z=0.004, OR =1.275, 95% CI =1.081–1.504). The 48 bp VNTR, the 12 bp TR, the −616 C>G polymorphism, and the −376 C>T polymorphism were not associated with schizophrenia. Additional research is warranted to explore the association between polymorphisms of *DRD4* and schizophrenia risk.

Keywords: *DRD4*, schizophrenia, meta-analysis, polymorphism

Introduction

Schizophrenia is a chronic, severe mental disorder with a tremendously variable clinical presentation. Results of studies in which schizophrenia occurrence was evaluated among twins or children who were adopted have shown that this disease results from an interaction of genetics and environmental factors.[1] Specifically, schizophrenia is a multigene disease with a heritability of 60%–70%.[2] Although the pathogenesis and etiology of schizophrenia are not understood fully,[3] a large body of evidence has indicated that dopamine dysfunction is involved in the occurrence of this disease.[4–6]

Dopamine is an endogenous neurotransmitter that primarily functions by binding to dopamine receptors, which have five types. The D4 receptor has attracted attention in the field of schizophrenia research. In postmortem brain striatum of patients with schizophrenia, the density of D4 receptor was significantly higher than in brain tissues of unaffected patients; in contrast, the density of D2 and D3 receptors remained modest.[7] This upregulation of D4 receptor has been shown to be related to the disease rather than to pharmacological effects of treatment.[8] The pharmacological characteristics of D4 resemble those of D2 and D3, but the affinity of D4 for clozapine is an order of magnitude higher.[9] Hence, *DRD4* (chromosome 11p15.5) is a potential susceptibility gene for schizophrenia.[10]

The SZGene database is a viable resource for ascertaining the risk of schizophrenia.[11,12] Other investigators have determined that the −521 C>T and 120 bp tandem repeat

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http://dx.doi.org/10.2147/NDT.S156479

(TR) polymorphisms in *DRD4* are associated with nominally significant summary odds ratios (ORs) as risk factors for schizophrenia (P=0.003 and 0.005, respectively).[11] However, despite a great deal of research, an association between *DRD4* polymorphisms and schizophrenia risk remains debatable.

TRs in *DRD4* include a 48 bp variable number TR (VNTR), a 12 bp TR, and a 120 bp TR. The 48 bp VNTR is located in the third exon of *DRD4* and encodes a sequence of 16 amino acids in the region of the third cytoplasmic loop. Polymorphisms in the 48 bp VNTR were found to differ in the recruitment of cellular cAMP.[13] The 12 bp TR (rs4646983) is located in the first exon of *DRD4*, which corresponds to the N terminus of the gene product. Variants of the 12 bp TR modify an N-terminal glycosylation site, which affects expression levels of the membrane protein.[14] The 120 bp TR is located 1.2 kb upstream from the initiation codon, and polymorphisms at this site affect transcriptional efficiency.[15] Some researchers noted that the 120 bp TR was associated with attention-deficit hyperactivity disorder (ADHD)[16,17] and schizophrenia.[18] However, Tsutsumi et al[19] demonstrated that the 120 bp TR was not related to the risk of schizophrenia.

The −521 C>T polymorphism (rs1800955), located in the promoter region of *DRD4*, has been shown to be associated with novelty seeking[20,21] and schizophrenia.[22] Mitsuyasu et al suggested that the −521C variant could be a risk factor for schizophrenia among female patients.[23] However, other investigators found no relationship between −521 C>T and schizophrenia.[24] The −616 C>G (rs747302) and the −376 C>T (rs916455) polymorphisms are located in the promoter region of *DRD4*; these variants have not been associated conclusively with schizophrenia risk. A pooled analysis of data regarding polymorphisms in *DRD4* and schizophrenia risk is warranted.

Meta-analyses are proven tools for ascertaining associations of gene polymorphisms with disease.[25–27] Several meta-analyses previously have addressed the potential associations between *DRD4* polymorphisms and schizophrenia risk.[28–31] However, the authors of these studies examined just one polymorphic locus[28] or did not include the latest data.[31] Herein, we describe the results of our meta-analysis of the association between *DRD4* and schizophrenia risk.

Materials and methods

Literature searches

The SZGene, PubMed, and China National Knowledge Infrastructure (CNKI) databases were searched with the keywords "schizophrenia" and "*DRD4*". Reference lists from relevant articles also were screened to identify additional studies.

Inclusion criteria and exclusion criteria

Studies with the following features were included in the meta-analysis: 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 1, 2017. Studies were excluded for the following reasons: 1) no control group; 2) no usable genotype frequency data (attempts were made to contact authors via email for these data); and 3) duplicate reported sample data.

Statistical analysis

A meta-analysis was carried out using Stata Version 10.0 (StataCorp LP, College Station, TX, USA). The P-value of Hardy–Weinberg equilibrium (P_{HWE}) was calculated for the control groups. ORs and 95% confidence intervals (CIs) were calculated to evaluate the strength of the associations. Under a random model,[32,33] associations between *DRD4* and the risk of schizophrenia were analyzed. A random model took into account population differences and heterogeneity among studies.[25,34] Pairwise differences between genotypes (AA vs aa, Aa vs aa, and AA vs Aa [A being the risk factor]) were used to determine a suitable genetic model.[35]

The heterogeneity of the studies was determined by Cochran's chi-square-based Q-statistic test.[36] The degree of heterogeneity was expressed as I^2 and was divided into low (I^2<25%), medium (I^2~50%), and high (I^2>75%) heterogeneity groups.[37] I^2>50% was regarded as indicating substantial heterogeneity.[38] Publication bias was calculated using Egger's test and was represented as a funnel plot in which the standard error of log(OR) of each study was plotted against its log(OR). A sensitivity analysis was conducted to test the impact of removing each single study on the pooled result. Statistical power was calculated by means of the PS program, as described previously.[39,40] P-values corresponding to association, heterogeneity, and publication bias tests were represented as P_z, P_h, and P_e, respectively. Statistical significance was defined as P<0.05 for all analyses.[41]

Results

Description of studies

A total of 211 English-language articles were obtained from SZGene and PubMed, and 14 Chinese-language articles were obtained from CNKI. After removing duplicate studies and those that did not meet our inclusion criteria, 41 articles were used in the meta-analysis (Figure 1). Specifically, 28 articles addressed the 48 bp VNTR,[23,42–68] nine articles involved the 12 bp

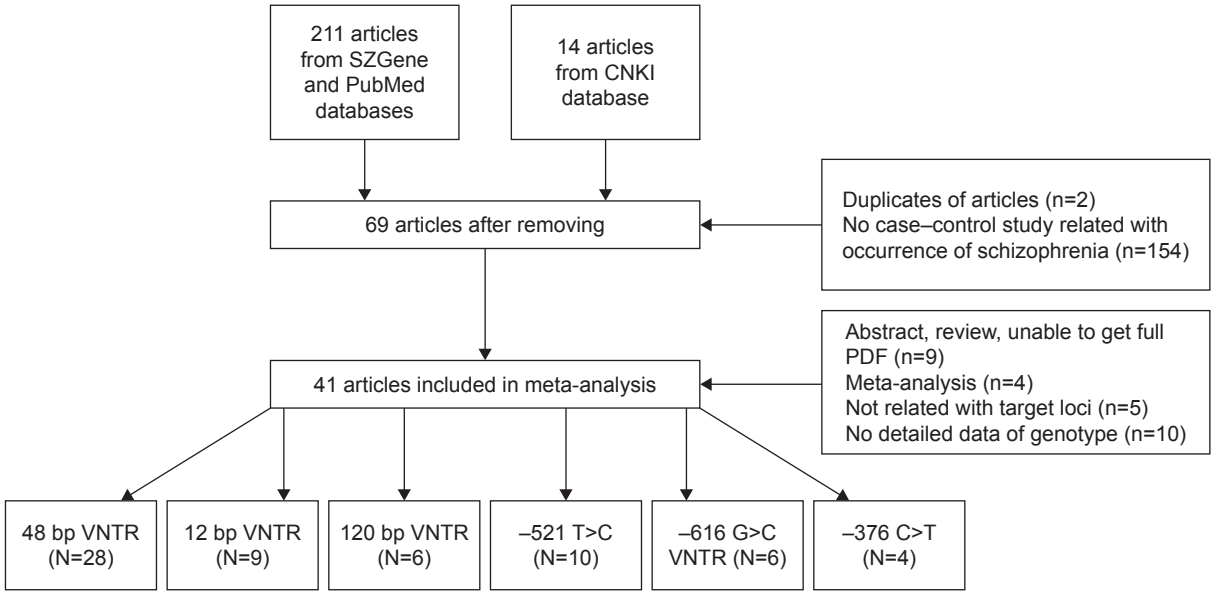

Figure 1 Study selection process in this meta-analysis.
Abbreviations: CNKI, China National Knowledge Infrastructure; VNTR, variable number tandem repeat.

TR,[23,43,48–50,69–72] six articles pertained to the 120 bp TR,[18,19,65,72–74] 10 articles addressed the –521 C>T polymorphism,[18,22–24,58,72–76] six articles referred to –616 C>G,[18,23,72,74–76] and four articles entailed –376 C>T.[18,23,72,75] Details of these studies are listed in Table 1. We omitted loci from our meta-analysis that were not represented in at least four articles.

Results of data analysis

No association between the 48 bp VNTR and schizophrenia risk

Allele frequencies of the 48 bp VNTR are listed in Table 2. Results of pooled analyses are summarized in Table 3, and data from subgroup analyses are depicted in Table 4. We were

Table 1 Characteristics of studies that qualified to be included in the meta-analysis

Author	Year	Country	Ethnicity	Controls source	Mean age of control group	Gender index (case)	Gender index (control)
Kaiser et al[42]	2000	German	Caucasian	Hospital based	43.53	0.83	0.34
Kohn et al[43,a]	1997	Israel	Israeli	Hospital based	–	–	–
Kohn et al[43,b]	1997	Israel	Israeli	Hospital based	–	–	–
Serretti et al[44,69]	1999, 2001	Italy	Caucasian	Hospital based	47.45	–	1.27
Hattori et al[45]	2009	Japan	East Asian	Population based	46.70	1.00	1.00
Tanaka et al[46]	1995	Japan	East Asian	Population based	45.80	0.84	0.56
Nanko et al[47]	1993	Japan	East Asian	Population based	–	–	–
Petronis et al[48]	1995	USA, Canada	Caucasian	Hospital based	–	–	–
Ohara et al[49]	1996	Japan	East Asian	Population based	34.40	0.99	1.37
Aguirre et al[50]	2007	Mexico	Indian	Population based	40.00		0.97
Mitsuyasu et al[23,c]	2007	Japan	East Asian	Hospital based	50.20	0.81	0.76
Daniels et al[51]	1994	UK	Caucasian	Hospital based	49.60	0.80	0.68
Sommer et al[52]	1993	Minnesota	Caucasian	Population based	65.00	0.44	1.61
Rao et al[53]	1994	USA	Caucasian	Population based	–	–	–
Hong et al[54]	1997	Taiwan	East Asian	Hospital based	28.70	0.68	0.62
Jonsson et al[55]	1996	Sweden	Caucasian	Population based	38.70	0.573	0.73
Rinetti et al[56]	2001	Mexico	Mestizos	Hospital based	–	–	–
Fujiwara et al[57]	1997	Japan	East Asian	Population based	–	–	–
Lung et al[58]	2006	Taiwan	East Asian	Population based	45.37	–	–
Nakamura et al[59]	1995	Japan	East Asian	Population based	–	–	–
Lung et al[60]	2009	Taiwan	East Asian	Population based	–	–	–
Fresan et al[61]	2007	Mexico	Caucasian	Population based	34.60	0.45	94.23
Zhang et al[62]	2003	China	East Asian	Population based	42.00	0.43	–
Tang et al[68]	2001	China	East Asian	Population based	33.00	0.44	0.40

(*Continued*)

Table 1 (*Continued*)

Author	Year	Country	Ethnicity	Controls source	Mean age of control group	Gender index (case)	Gender index (control)
Liang[67]	2005	China	East Asian	Population based	26.00	0.98	0.98
Zhao et al[63]	2005	China	East Asian	Population based	34.00	0.88	0.88
Zhao et al[64]	2006	China	East Asian	Population based	29.40	0.84	1.00
Chen et al[65]	2016	China	East Asian	Hospital based	39.19	0.81	0.89
Lu et al[66]	2003	China	East Asian	Population based	65.00	0.74	1.22
Serretti et al[69]	1999	Italy	Caucasian	Population based	–	–	–
Hong et al[70]	1998	Taiwan	East Asian	Hospital based	30.20	28.70	0.62
Catalano et al[71]	1993	Italy	Caucasian	Hospital based	46.90	30.00	1.34
Nakajima et al[72]	2007	Japan	East Asian	Population based	47.00	46.70	1.00
Okuyama et al[22]	1999	Japan	East Asian	Population based	47.10	47.90	0.63
Mitsuyasu et al[75,d]	2001	Japan	East Asian	Hospital based	51.50	50.50	0.75
Jonsson et al[24]	2001	Sweden	Caucasian	Population based	44.80	42.60	0.80
Pai et al[73]	2015	India	Indian	Population based	–	–	–
Xing et al[18]	2003	China	East Asian	Hospital based	41.20	41.80	–
Lai et al[74]	2010	China	East Asian	Hospital based	40.60	43.20	1.00
Zhong et al[76]	2010	China	East Asian	Population based	39.20	37.50	1.00
Tsutsumi et al[19]	2011	Japan	East Asian	Hospital based	47.20	42.10	0.50

Notes: Gender index = female/male. [a]Ethnicity is Ashkenazi which included Jews whose origin (or whose parents' origin), was in European countries, apart from the Balkans; [b]ethnicity is non-Ashkenazi which included Jews whose origin was in North Africa or Asia. [c]Included 48 bp VNTR, 12 bp TR, and 120 bp TR; [d]did not include 48 bp VNTR, 12 bp TR, and 120 bp TR.

unable to obtain specific data regarding the number of 7-repeat (7R) alleles in the 48 bp VNTR,[44] despite multiple attempts to contact the corresponding author. Thus, this study was omitted from our analysis of an association between 7R and schizophrenia risk. When we conducted a pooled analysis of the remaining 5,316 cases and 4,677 controls, we found that 7R was not associated with schizophrenia risk (P_z=0.349, OR =1.071, 95% CI =0.928–1.236) under a random effects model with a

Table 2 Allele frequency of 48 bp VNTR polymorphism

Author	Allele distribution				Allele frequency			
	Cases (n)		Controls (n)		Cases (n)		Controls (n)	
	Short (≤4)	Long (≥5)	Short (≤4)	Long (≥5)	7R	Others	7R	Others
Kaiser et al[42]	1,006	270	1,182	322	232	1,044	282	1,222
Kohn et al[43,a]	–	–	–	–	22	76	52	238
Kohn et al[43,b]	–	–	–	–	13	85	17	101
Serretti et al[44,69]	709	129	990	212	–	–	–	–
Hattori et al[45]	1,066	54	1,076	60	2	1,118	6	1,130
Tanaka et al[46]	134	6	133	7	0	140	2	138
Nanko et al[47]	148	12	152	10	2	158	0	162
Petronis et al[48]	77	23	154	46	21	79	32	168
Ohara et al[49]	286	20	227	15	18	288	10	232
Aguirre et al[50]	120	72	224	114	46	146	98	240
Mitsuyasu et al[23,c]	406	18	447	27	1	423	3	471
Daniels et al[51]	159	53	193	45	52	160	45	193
Sommer et al[52]	182	48	171	59	43	187	54	176
Rao et al[53]	39	17	31	9	17	39	8	32
Hong et al[54]	172	6	78	6	0	178	0	84
Jonsson et al[55]	187	49	124	28	42	194	23	129
Rinetti et al[56]	36	38	48	26	31	43	25	49
Fujiwara et al[57]	34	0	22	0	0	34	0	22
Lung et al[58]	1,216	44	846	10	3	1,257	0	856
Nakamura et al[59]	189	13	98	6	0	202	0	104
Lung et al[60]	1,774	54	838	8	0	1,828	0	846
Fresan et al[61]	88	54	285	119	47	95	104	300
Zhang et al[62]	131	3	145	7	0	134	0	152
Tang et al[68]	980	40	332	10	1	1,019	0	342
Liang[67]	176	26	185	25	4	198	2	208
Zhao et al[63]	78	246	75	249	3	321	6	318
Zhao et al[64]	41	121	40	136	0	162	3	173
Chen et al[65]	219	49	299	37	0	268	0	336
Lu et al[66]	155	5	157	3	1	159	0	160

Notes: [a]Ethnicity is Ashkenazi which included Jews whose origin (or whose parents' origin), was in European countries, apart from the Balkans; [b]ethnicity is non-Ashkenazi which included Jews whose origin was in North Africa or Asia. [c]Included 48 bp VNTR, 12 bp TR, and 120 bp TR.
Abbreviations: 7R, 7 repeat; VNTR, variable number tandem repeat.

Table 3 Pooled associations of *DRD4* polymorphisms and schizophrenia

Loci	Genetic model	Studies (n)	Statistical model	OR	95% CI	P_z	I^2	P_h	P_e
48 bp VNTR	Allele contrast (7R and others)	27	Random	1.071	0.928–1.236	0.349	8.1	0.352	0.727
	Allele contrast (S and L)	27	Random	1.135	0.988–1.303	0.073	44.0	0.009	0.151
12 bp TR	Allele contrast	9	Random	1.037	0.885–1.215	0.659	0.0	0.931	0.584
	Homozygous codominant	9	Random	0.756	0.434–1.317	0.323	0.0	0.729	0.214
	Heterozygous codominant	9	Random	1.117	0.930–1.341	0.236	0.0	0.644	0.077
	Dominant	9	Random	1.083	0.907–1.293	0.377	0.0	0.834	0.192
	Recessive	9	Random	0.724	0.417–1.259	0.253	0.0	0.681	0.180
120 bp TR	Allele contrast	6	Random	1.189	1.040–1.358	0.011	37.1	0.159	0.701
	Homozygous codominant	6	Random	1.291	0.892–1.868	0.176	47.2	0.092	0.213
	Heterozygous codominant	6	Random	1.010	0.744–1.372	0.949	22.9	0.262	0.223
	Dominant	6	Random	1.152	0.837–1.584	0.386	34.3	0.179	0.176
	Recessive	6	Random	1.275	1.081–1.504	0.004	33.1	0.187	0.756
–521 T>C	Allele contrast	10	Random	1.113	1.024–1.209	0.011	16.2	0.294	0.628
	Homozygous codominant	10	Random	1.240	1.041–1.477	0.016	18.7	0.271	0.765
	Heterozygous codominant	10	Random	1.105	0.971–1.256	0.129	13.8	0.316	0.751
	Dominant	10	Random	1.136	1.004–1.289	0.043	19.2	0.266	0.620
	Recessive	10	Random	1.177	1.024–1.353	0.021	0.0	0.467	0.812
–616 G>C	Allele contrast	6	Random	1.103	0.991–1.226	0.071	6.7	0.373	0.604
	Homozygous codominant	6	Random	0.637	0.469–0.866	0.004	46.4	0.096	0.488
	Heterozygous codominant	6	Random	1.123	0.974–1.296	0.110	0.0	0.986	0.169
	Dominant	6	Random	1.133	0.991–1.295	0.068	0.0	0.889	0.965
	Recessive	6	Random	1.140	0.840–1.548	0.400	48.3	0.085	0.338
–376 C>T	Allele contrast	4	Random	1.124	0.940–1.344	0.198	0.0	0.707	0.200
	Homozygous codominant	4	Random	0.854	0.416–1.749	0.665	0.0	0.996	0.456
	Heterozygous codominant	4	Random	0.730	0.351–1.520	0.401	0.0	0.993	0.911
	Dominant	4	Random	0.820	0.401–1.676	0.586	0.0	0.994	0.583
	Recessive	4	Random	1.171	0.962–1.425	0.117	0.0	0.707	0.214

Notes: L, long allele; S, short allele.
Abbreviations: CI, confidence interval; OR, odds ratio; 7R, 7 repeat; TR, tandem repeat; VNTR, variable number TR.

power of 0.271 (Table 3 and Figure S1).[35] No association was found in subgroup analysis by ethnicity (ie, Caucasian [P_z=0.238, OR =1.127, 95% CI =0.924–1.375], East Asian [P_z=0.901, OR =0.966, 95% CI =0.560–1.667], Indian [P_z=0.211, OR =0.772, 95% CI =0.514–1.158], Mestizos [P_z=0.310, OR =1.413, 95% CI =0.725–2.754], and Israeli [P_z=0.512, OR =1.164, 95% CI =0.739–1.835]). Moreover, no association of 7R with the risk of schizophrenia was ascertained in subgroup analysis by source of controls. No significant heterogeneity was found in the pooled or subgroup analyses.

To incorporate data from the study of Serretti et al,[44] the 48 bp VNTR was classified into S (short allele, ≤4 TRs) and L (long allele, ≥5 TRs) groups. In the study by Kohn et al,[43] the 48 bp VNTR data could not be categorized into S and L groups, so this study was omitted from the analysis. The remaining data comprised 5,637 cases and 5,074 controls (Table 3 and Figure S2). Results of a pooled analysis indicated no relationship between this polymorphism and schizophrenia risk (P_z=0.073, OR =1.135, 95% CI =0.988–1.303) with a power of 0.909. No association was found in the subgroup analysis by source of control or by ethnicity, except for Mestizos (P_z=0.048, OR =1.949, 95% CI =1.007–3.77). Significant heterogeneity was found in the pooled analysis (P_e=0.009, I^2=44%) and in the subgroup analysis by ethnicity in the East Asian subgroup (P_e=0.014, I^2=49.1%) and by source of control in the hospital-based subgroup (P_e=0.016, I^2=59.2%).

No association between the 12 bp TR and schizophrenia risk

To evaluate the relationship between the 12 bp TR and the risk of schizophrenia, 1,517 cases and 1,746 controls were included (Table 5 and Figures S3–S7). Allele groups were defined as in (ie, inserted) and de (ie, deleted). In the dominant model,[34,35] the pooled OR using a random effects model was 1.083 (P_z=0.377, 95% CI =0.907–1.293) with a power of 0.154 (Table 3). No association was found in subgroup analysis by ethnicity or by source of controls (Table 4). No significant heterogeneity was observed in the pooled or subgroup analyses.

Genotype L/L of the 120 bp TR might be a risk factor for schizophrenia

In a random model, a pooled analysis was conducted (1,912 cases and 1,836 controls) to evaluate the relationship between genotype L/L of the 120 bp TR and schizophrenia

Table 4 Subgroup associations of *DRD4* polymorphisms with schizophrenia

Polymorphism	Subgroup analysis	Studies (n)	OR	95% CI	P_z	P_h	I^2
48 bp VNTR (7R and others)	Overall	22	1.095	0.953–1.259	0.349	0.352	8.1
	Ethnicity						
	Caucasian	7	1.127	0.924–1.375	0.238	0.195	30.6
	East Asian	11	0.966	0.560–1.667	0.901	0.413	3.1
	Indian	1	0.772	0.514–1.158	0.211	–	–
	Mestizos	1	1.413	0.725–2.754	0.310	–	–
	Israeli	2	1.164	0.739–1.835	0.512	0.441	0.0
	Source of controls						
	Population based	15	1.031	0.796–1.336	0.816	0.242	18.9
	Hospital based	7	1.070	0.917–1.248	0.393	0.490	0.0
48 bp VNTR (S and L)	Overall	26	1.147	1.003–1.312	0.073	0.009	44.0
	Ethnicity						
	Caucasian	8	1.037	0.882–1.219	0.662	0.173	32.0
	East Asian	16	1.165	0.919–1.475	0.206	0.014	49.1
	Indian	1	1.179	0.815–1.705	0.382	–	–
	Mestizos	1	1.949	1.007–3.770	0.048	–	–
	Israeli						
	Source of controls						
	Population based	18	1.165	0.977–1.390	0.089	0.069	35.4
	Hospital based	8	1.091	0.862–1.381	0.468	0.016	59.2
12 bp TR	Overall	10	1.083	0.907–1.293	0.377	0.834	0.0
	Ethnicity						
	Indian	1	0.927	0.533–1.612	0.788	–	–
	Caucasian	3	0.787	0.509–1.218	0.283	0.611	0.0
	East Asian	4	1.178	0.949–1.462	0.137	0.910	0.0
	Israeli	2	1.312	0.642–2.679	0.456	0.610	0.0
	Source of controls						
	Population based	4	1.133	0.908–1.413	0.270	0.710	0.0
	Hospital based	6	1.012	0.706–1.450	0.949	0.272	21.5
120 bp TR	Overall	6	1.275	1.081–1.504	0.004	0.187	33.1
	Ethnicity						
	East Asian	5	1.317	1.108–1.565	0.002	0.196	33.9
	Indian	1	0.979	0.629–1.524	0.924	–	–
	Source of controls						
	Population based	2	1.102	0.892–1.360	0.368	0.551	0.0
	Hospital based	4	1.319	1.134–1.708	0.002	0.225	31.2
–521 T>C	Overall	10	1.177	1.024–1.353	0.021	0.467	0.0
	Ethnicity						
	Caucasian	1	1.136	0.670–1.925	0.636	–	–
	East Asian	8	1.218	1.050–1.413	0.009	0.571	0.0
	Indian	1	0.715	0.395–1.293	0.267		
	Source of controls						
	Population based	6	1.188	0.972–1.451	0.092	0.258	23.5
	Hospital based	4	1.143	0.901–1.450	0.270	0.561	0.0
–616 G>C	Overall	6	1.133	0.991–1.295	0.068	0.889	0.0
	Source of controls						
	Population based	2	1.117	0.915–1.364	0.275	0.966	0.0
	Hospital based	4	1.146	0.956–1.317	0.140	0.645	0.0
–376 C>T	Overall	4	1.171	0.962–1.425	0.117	0.707	0.0
	Source of controls						
	Population based	1	1.079	0.805–1.447	0.611	–	–
	Hospital based	3	1.252	0.960–1.632	0.117	0.653	0.0

Notes: L, long allele; S, short allele.
Abbreviations: CI, confidence interval; OR, odds ratio; 7R, 7 repeat; TR, tandem repeat; VNTR, variable number TR.

risk (Table 6 and Figures S8–S12). In the recessive model,[34,35] genotype L/L was found to be a potential risk factor for schizophrenia (P_z=0.004, OR =1.275, 95% CI =1.081–1.504) with a power of 0.959 (Table 3). Findings from subgroup analysis indicated significant associations in East Asian (P_z=0.002, OR =1.317, 95% CI =1.108–1.565) and hospital-based subgroups (P_z=0.002, OR =1.319, 95% CI =1.134–1.708) (Table 4). No association was found for the other subgroups, and no significant heterogeneity was ascertained in the pooled or subgroup analyses.

The –521 CC variant might be a risk factor for schizophrenia

Pooled and subgroup analyses were performed in a random model with 2,927 cases and 2,938 controls (Table 7 and Figures S13–S17). In the recessive model, –521 CC was found to be a potential risk factor for schizophrenia in the pooled analysis (P_z=0.021, OR =1.177, 95% CI =1.024–1.353) with a power of 0.656 (Table 3). In subgroup analyses by ethnicity and source of controls, the association was only detected in the East Asian subgroup (P_z=0.009, OR =1.218, 95% CI =1.050–1.413) (Table 4). No significant heterogeneity was noted in the pooled or subgroup analyses.

Table 5 Genotype distribution and allele frequency of 12 bp TR

Author	Genotype distribution						P_{HWE}	Allele frequency			
	Cases, n			Controls, n				Case (%)		Controls (%)	
	in/in	in/de	de/de	in/in	in/de	de/de		in	de	in	de
Petronis et al[48]	43	6	1	80	20	0	0.267	92.00	8.00	90.00	10.00
Ohara et al[49]	144	9	0	116	5	0	0.816	97.06	2.94	97.93	2.07
Serretti et al[44,69]	184	28	0	225	37	1	0.689	0.93	0.07	0.93	0.07
Aguirre et al[50]	48	34	1	75	55	4	0.102	78.31	21.69	76.49	23.51
Mitsuyasu et al[23,a]	136	56	5	176	53	10	0.027	83.20	16.70	84.70	15.30
Kohn et al[43,b]	40	9	0	126	19	0	0.311	94.00	6.00	91.00	9.00
Kohn et al[43,c]	44	4	1	53	6	0	0.416	94.00	6.00	94.00	6.00
Hong et al[54]	68	10	2	35	7	0	0.556	91.25	8.75	91.70	8.30
Catalano et al[71]	76	3	0	69	6	0	0.718	98.10	1.90	96.00	4.00
Nakajima et al[72]	413	140	12	431	119	18	0.008	85.50	14.50	86.50	13.50

Notes: P_{HWE}, *P*-value of Hardy–Weinberg equilibrium. [a]Included 48 bp VNTR, 12 bp TR, and 120 bp TR. [b]Ethnicity is Ashkenazi which included Jews whose origin (or whose parents' origin), was in European countries, apart from the Balkans; [c]ethnicity is non-Ashkenazi which included Jews whose origin was in North Africa or Asia.
Abbreviations: de, deleted; in, inserted; TR, tandem repeat.

Table 6 Genotype distribution and allele frequency of 120 bp TR

Author	Genotype distribution						P_{HWE}	Allele frequency			
	Cases, n			Controls, n				Cases (%)		Controls (%)	
	S/S	S/L	L/L	S/S	S/L	L/L		S	L	S	L
Mitsuyasu et al[23,a]	10	75	129	13	87	139	0.898	77.80	22.20	76.40	23.60
Pai et al[73]	23	77	87	11	61	64	0.501	32.90	67.10	30.50	69.50
Xing et al[18]	20	77	113	28	98	80	0.816	27.90	72.10	37.40	62.60
Nakajima et al[72]	24	183	362	33	192	345	0.363	20.00	80.00	23.00	78.00
Tsutsumi et al[19]	24	138	248	16	158	211	0.041	22.68	77.32	24.68	75.32
Lai et al[74]	28	161	133	40	166	94	0.013	33.70	66.30	41.00	59.00

Notes: L, long allele; P_{HWE}, *P*-value of Hardy–Weinberg equilibrium; S, short allele. [a]Included 48 bp VNTR, 12 bp TR, and 120 bp TR.
Abbreviation: TR, tandem repeat.

Table 7 Genotype distribution and allele frequency of –521 C>T

Author	Genotype distribution						P_{HWE}	Allele frequency			
	Cases, n			Controls, n				Cases (%)		Controls (%)	
	CC	CT	TT	CC	CT	TT		C	T	C	T
Okuyama et al[22]	58	125	69	38	142	89	0.119	48.00	52.00	41.00	59.00
Mitsuyasu et al[23,a]	33	106	67	31	115	93	0.623	41.75	58.25	37.05	62.95
Mitsuyasu et al[75,b]	25	122	61	25	110	75	0.109	41.30	58.70	38.10	61.90
Lung et al[58]	80	320	230	48	204	173	0.294	38.10	61.90	35.30	64.70
Jonsson et al[24]	23	74	35	60	205	118	0.061	45.50	54.50	42.00	58.00
Pai et al[73]	27	92	62	26	77	29	0.055	40.30	59.70	48.90	51.10
Xing et al[18]	37	103	70	25	111	70	0.059	42.10	57.90	39.10	60.90
Nakajima et al[72]	106	270	190	89	285	195	0.368	43.00	58.00	41.00	59.00
Lai et al[74]	87	115	120	81	95	124	–	44.88	55.12	42.83	57.17
Zhong et al[76]	62	78	60	53	64	83	–	45.91	54.09	42.50	57.50

Notes: P_{HWE}, *P*-value of Hardy–Weinberg equilibrium. [a]Included 48 bp VNTR, 12 bp TR, and 120 bp TR; [b]did not include 48 bp VNTR, 12 bp TR, and 120 bp TR.
Abbreviation: TR, tandem repeat.

Table 8 Genotype distribution and allele frequency of –616 C>G

Author	Genotype distribution						P_{HWE}	Allele frequency			
	Cases, n			Controls, n				Cases (%)		Controls (%)	
	GG	GC	CC	GG	GC	CC		G	C	G	C
Mitsuyasu et al[23,a]	102	89	19	112	98	30	0.243	69.80	30.20	67.10	32.90
Mitsuyasu et al[75,b]	89	89	30	100	85	25	0.296	64.20	35.80	67.90	32.10
Xing et al[18]	83	100	27	91	102	13	0.025	63.30	36.70	68.90	31.10
Nakajima et al[72]	267	248	49	285	224	59	0.134	69.00	31.00	69.50	29.50
Lai et al[74]	161	113	48	166	102	32	0.009	67.55	32.45	72.33	27.67
Zhong et al[76]	112	77	31	107	68	25	0.010	68.41	31.59	70.50	29.50

Notes: P_{HWE}, *P*-value of Hardy–Weinberg equilibrium. [a]Included 48 bp VNTR, 12 bp TR, and 120 bp TR; [b]did not include 48 bp VNTR, 12 bp TR, and 120 bp TR.
Abbreviation: TR, tandem repeat.

Table 9 Genotype distribution and allele frequency of –376 C>T

Author	Genotype distribution						P_{HWE}	Allele frequency			
	Cases, n			Controls, n				Cases (%)		Controls (%)	
	CC	CT	TT	CC	CT	TT		C	T	C	T
Mitsuyasu et al[23,a]	177	34	1	193	43	1	0.39	91.50	8.50	90.45	9.45
Mitsuyasu et al[75,b]	179	28	1	168	41	1	0.367	92.80	0.72	89.80	1.02
Xing et al[74]	137	66	7	127	74	5	0.126	81.00	19.00	79.60	20.40
Nakajima et al[72]	453	100	8	447	108	7	0.869	90.00	10.00	89.50	10.50

Notes: P_{HWE}, *P*-value of Hardy–Weinberg equilibrium. [a]Included 48 bp VNTR, 12 bp TR, and 120 bp TR; [b]did not include 48 bp VNTR, 12 bp TR, and 120 bp TR.
Abbreviation: TR, tandem repeat.

No association between –616 C>G and the risk of schizophrenia

In a random model, pooled (Table 3) and subgroup (Table 4) analyses were performed with 1,735 cases and 1,724 controls (Table 8 and Figures S18–S22). Using the dominant model, results of the pooled analysis indicated a lack of an association between –616 C>G and schizophrenia risk (P_z=0.068, OR =1.133, 95% CI =0.991–1.295) with a power of 0.45. All cases and controls in this analysis corresponded to the East Asian subgroup. Findings from a subgroup analysis of source of controls showed no association. There was no significant heterogeneity in the pooled or subgroup analyses.

No association of the –376 C>T variant with schizophrenia

We assessed the relationship between the –376 C>T polymorphism and schizophrenia risk in pooled and subgroup analyses of 1,191 cases and 1,215 controls in a random model (Tables 3, 4, and 9 and Figures S23–S27). In the recessive model, –376 C>T was not associated with the risk of schizophrenia in a pooled analysis (P_z=0.117, OR =1.171, 95% CI =0.962–1.425) with a power of 0.357 (Table 3). No association was detected in subgroup analyses by ethnicity or source of controls (Table 4). No significant heterogeneity was ascertained in the pooled or subgroup analyses.

Sensitivity analysis

The results of sensitivity analyses showed that the combined ORs did not change significantly for meta-analyses in which each study was omitted singly. Thus, the results were considered stable and reasonable.

Publication bias

Potential publication bias was found in funnel plots in which the standard error of log(OR) of each study was plotted against its log(OR). No evidence of publication bias was found in pooled analyses (Figures 2–8).

Discussion

Results of other studies have associated the 7R polymorphism with ADHD in a meta-analysis[77] and with increased brain

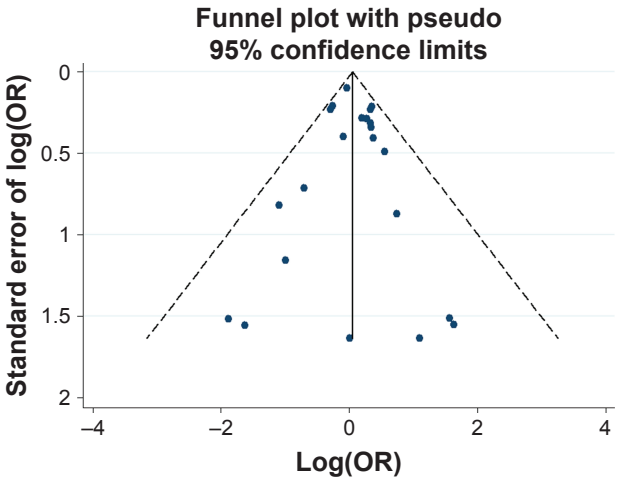

Figure 2 Funnel plot analysis for the detection of publication bias in the association between the 48 bp VNTR (7R vs others) and schizophrenia.
Abbreviations: OR, odds ratio; 7R, 7 repeat; VNTR, variable number tandem repeat.

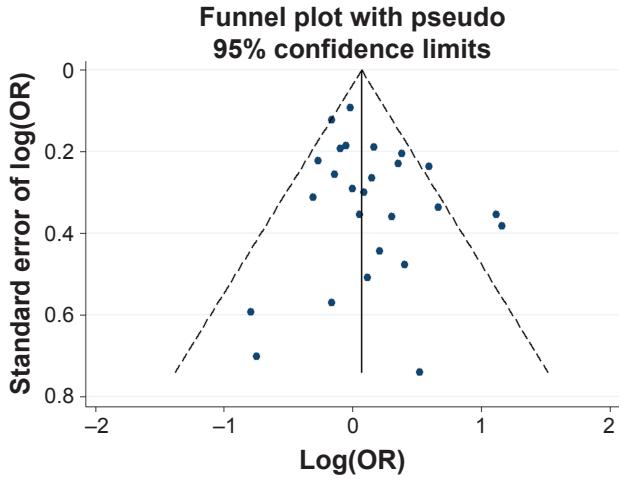

Figure 3 Funnel plot analysis for the detection of publication bias in the association between 48 bp VNTR (L vs S) and schizophrenia.
Notes: L, long allele; S, short allele.
Abbreviations: OR, odds ratio; VNTR, variable number tandem repeat.

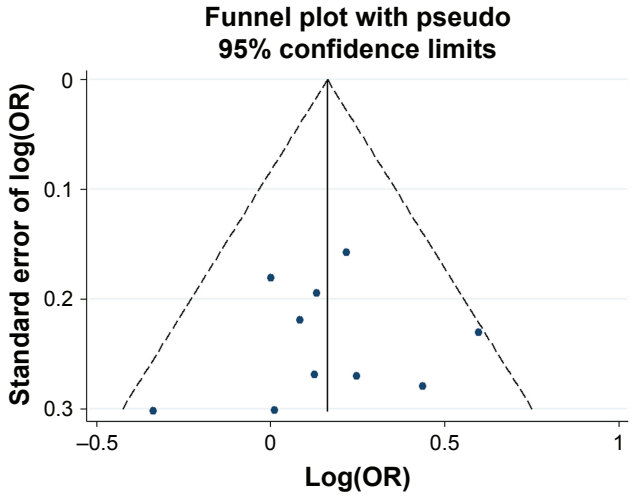

Figure 6 Funnel plot analysis for the detection of publication bias in the association between −521 C>T and schizophrenia.
Abbreviation: OR, odds ratio.

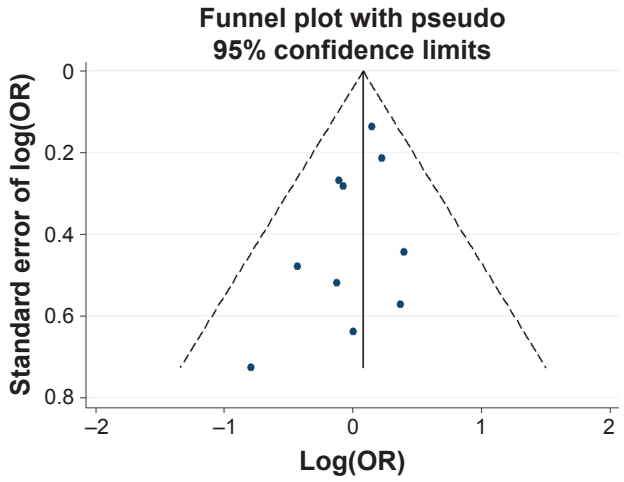

Figure 4 Funnel plot analysis for the detection of publication bias in the association between 12 bp TR and schizophrenia.
Abbreviations: OR, odds ratio; TR, tandem repeat.

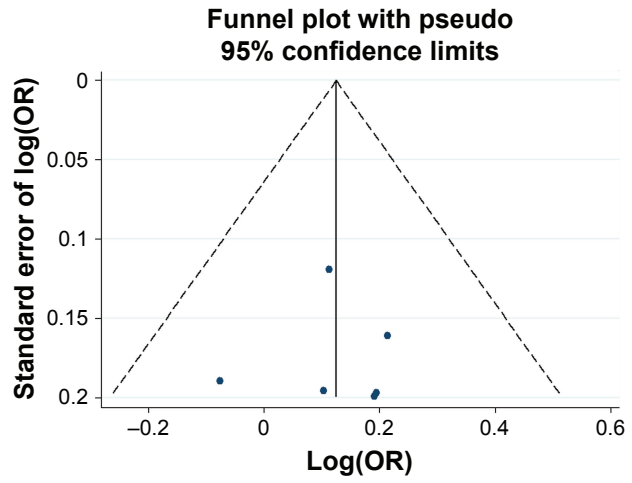

Figure 7 Funnel plot analysis for the detection of publication bias in the association between −616 C>G and schizophrenia.
Abbreviation: OR, odds ratio.

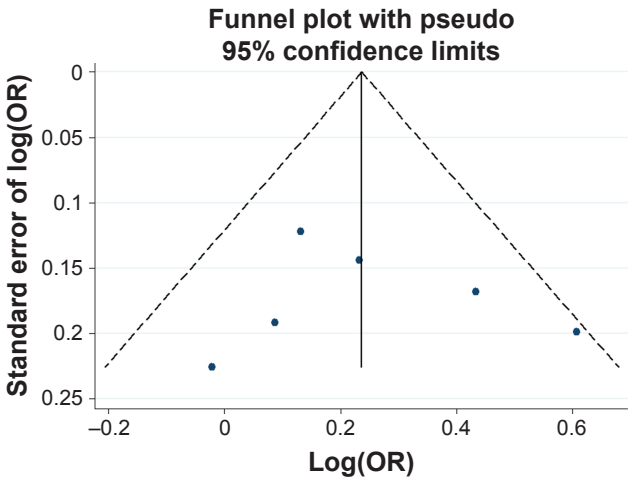

Figure 5 Funnel plot analysis for the detection of publication bias in the association between 120 bp TR and schizophrenia.
Abbreviations: OR, odds ratio; TR, tandem repeat.

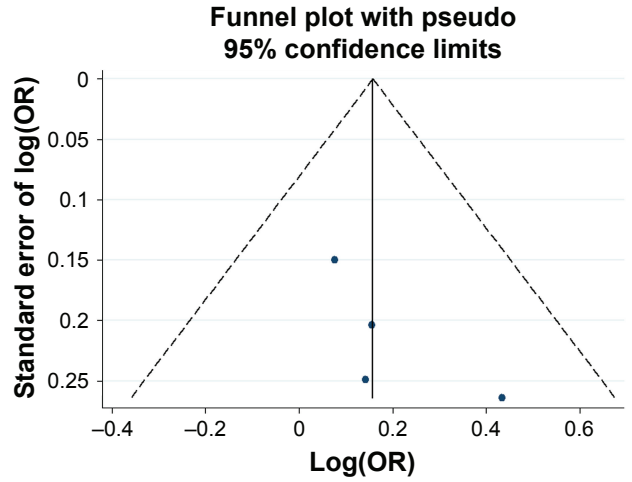

Figure 8 Funnel plot analysis for the detection of publication bias in the association between −376 C>T and schizophrenia.
Abbreviation: OR, odds ratio.

activity to unpleasant stimuli.[78] We sought to determine whether 7R was also associated with schizophrenia risk. Findings of our pooled and subgroup analyses indicated that 7R was not associated with the risk of schizophrenia. Similarly, we found that the 48 bp VNTR (classified into L and S groups) was not associated with schizophrenia risk in most of our pooled and subgroup analyses, which is consistent with previously published meta-analyses.[29,30] Only in the Mestizos subgroup, an association was detected. Our literature search yielded one article addressing Mestizos patients, and this article had an insufficient sample size to verify this association. Hence, the utility of the 48 bp VNTR as a means to assess schizophrenia risk in the Mestizo population warrants additional investigation. Lung et al[28] demonstrated an association between the 48-bp VNTR and schizophrenia risk but noted that sample bias might have led to a false-positive result.[29]

We determined that the L/L genotype of the 120 bp TR and the −521 CC variant might be risk factors for schizophrenia among East Asians; this relationship was not found in other populations. This discrepancy between East Asians and other populations might have resulted from the small sample sizes of the other ethnicity subgroups, the distinct genetic backgrounds, or different demographic or lifestyle factors within the subgroups. The statistical power for the pooled analysis of the 12 bp TR, the −616 C>G polymorphism, and the −376 C>T variant was low. Therefore, these results will need to be validated further. In a study of linkage disequilibrium (LD) of *DRD4* that included 17 polymorphisms,[23] the authors found no LD between −521 T>C and 120 bp TR (r^2=0.00). For all pairs of −616 C>G, −376 C>T, 12 bp TR, and 48 bp VNTR, no significant LD was observed.

Multiple meta-analyses have been conducted to date on the association between *DRD4* and schizophrenia. The current meta-analysis included some new studies, involved a large sample size, and had high statistical power. We addressed six loci in *DRD4*; no other meta-analysis involving four of these loci (12 bp TR, 120 bp TR, −616 C>G, and −376 C>T) has been carried out. Moreover, we conducted subgroup analysis by ethnicity and by source of controls and included data both from SZGene and the CNKI databases.

The results described herein should be interpreted with caution. The present study was limited by a lack of exact allele/genotype frequencies for some of the included articles, despite our efforts to acquire this information from the corresponding authors. Therefore, these articles were omitted from the meta-analysis. Second, controls in some of the articles did not conform to Hardy–Weinberg equilibrium because of sample bias. Third, case–control studies were included in this meta-analysis, but family-based studies were not.[77] The ability to exploit cosegregation of variants with disease within families helps distinguish causal from noncausal factors. Family-based studies are more powerful to detect risk factors of diseases.[79] Moreover, we did not address possible interactions between the six loci and epigenetic factors. An association between *DRD4* and schizophrenia risk was detected based on case–control studies rather than on functional ones. Our results will need to be validated on a functional level.

Conclusion

The −521 CC variant and the L/L genotype of the 120-bp TR might be risk factors for schizophrenia. No association with schizophrenia was detected for the 48 bp VNTR, the 12 bp TR, −616 C>G, or −376 C>T. Our results may provide an informative reference for subsequent genome-wide association studies.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (No 81601653) and the Doctoral Research Start Foundation of Liaoning Province (201601115) (both to Dr Jun Yao). The article was edited by native English-speaking experts of BioMed Proofreading, LLC.

Disclosure

The authors report no conflicts of interest in this work.

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