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

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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 = 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 = 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. Specifically, schizophrenia is a multigene disease with a heritability of 60%–70%. Although the pathogenesis and etiology of schizophrenia are not understood fully, a large body of evidence has indicated that dopamine dysfunction is involved in the occurrence of this disease.

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. This upregulation of D4 receptor has been shown to be related to the disease rather than to pharmacological effects of treatment. The pharmacological characteristics of D4 resemble those of D2 and D3, but the affinity of D4 for clozapine is an order of magnitude higher. Hence, DRD4 (chromosome 11p15.5) is a potential susceptibility gene for schizophrenia.

The SZGene database is a viable resource for ascertaining the risk of schizophrenia. Other investigators have determined that the −521 C>T and 120 bp tandem repeat...
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 al19 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 seeking20,21 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 locus29 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.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_x, P_y, and P_z, 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
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   | 1997 | Israel  | Israeli   | Hospital based  | –                         | –                   | –                      |
| Kohn et al 43   | 1997 | Israel  | Israeli   | Hospital based  | –                         | –                   | –                      |
| Serretti et al 44-48 | 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                | 1.00                   |
| Mitsuysu et al 51 | 2007 | Japan   | East Asian| Hospital based  | 50.20                     | 0.81                | 0.76                   |
| Daniels et al 52 | 1994 | UK      | Caucasian | Hospital based  | 49.60                     | 0.80                | 0.68                   |
| Sommer et al 53 | 1993 | Minnesota | Caucasian | Population based | 65.00                     | 0.44                | 1.61                   |
| Rao et al 54    | 1994 | USA     | Caucasian | Population based | –                         | –                   | –                      |
| Hong et al 55   | 1997 | Taiwan  | East Asian| Hospital based  | 28.70                     | 0.68                | 0.62                   |
| Jonsson et al 56 | 1996 | Sweden  | Caucasian | Population based | 38.70                     | 0.573               | 0.73                   |
| Riznatt et al 57 | 2001 | Mexico  | Mestizos  | Hospital based  | –                         | –                   | –                      |
| Fujiiwara et al 58 | 1997 | Japan   | East Asian| Population based | –                         | –                   | –                      |
| Lung et al 59   | 2006 | Taiwan  | East Asian| Population based | –                         | –                   | –                      |
| Nakamura et al 59 | 1995 | Japan   | East Asian| Population based | –                         | –                   | –                      |
| Lung et al 59   | 2009 | Taiwan  | East Asian| Population based | –                         | –                   | –                      |
| Frosen et al 60 | 2007 | Mexico  | Caucasian | Population based | 34.60                     | 0.45                | 94.23                  |
| Zhang et al 61  | 2003 | China   | East Asian| Population based | 42.00                     | 0.43                | –                      |
| Tang et al 62   | 2001 | China   | East Asian| Population based | 33.00                     | 0.44                | 0.40                   |

(Continued)
unable to obtain specific data regarding the number of 7-repeat (7R) alleles in the 48 bp VNTR, 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 ($P = 0.349, OR = 1.071, 95\% \text{ CI} = 0.928–1.236$) under a random effects model with a

Table 2 Allele frequency of 48 bp VNTR polymorphism

| Author               | Year | Ethnicity | Controls source | Mean age of control group | Gender index (case) | Gender index (control) |
|----------------------|------|-----------|----------------|---------------------------|--------------------|-----------------------|
| Liang et al[64]      | 2005 | China     | East Asian     | Population based          | 26.00              | 0.98                  | 0.98                 |
| Zhao et al[65]       | 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[66]       | 2016 | China     | East Asian     | Population based          | 39.19              | 0.81                  | 0.89                 |
| Lu et al[64]         | 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          | 51.50              | 50.50                 | 0.75                 |
| Okuyama et al[73]    | 1999 | Japan     | East Asian     | Population based          | 44.80              | 42.60                 | 0.89                 |
| Mitsuysau et al[74,4] | 2001 | Japan     | East Asian     | Hospital based            | 41.20              | 41.80                 | –                    |
| Jonsson et al[64]    | 2001 | Sweden    | Caucasian      | Population based          | 78                 | –                     | –                    |
| Pai et al[75]        | 2015 | India     | Indian         | Population based          | 40.60              | 43.20                 | 1.00                 |
| Xing et al[76]       | 2003 | China     | East Asian     | Hospital based            | 47.20              | 42.10                 | 0.50                 |
| Lai et al[77]        | 2010 | China     | East Asian     | Hospital based            | –                  | –                     | –                    |
| Zhong et al[78]      | 2010 | China     | East Asian     | Hospital based            | 39.20              | 37.50                 | 1.00                 |
| Tsutsurni et al[79]  | 2011 | Japan     | East Asian     | Hospital based            | 47.20              | 42.10                 | 0.50                 |

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

Abbreviations: 7R, 7 repeat; VNTR, variable number tandem repeat.
power of 0.271 (Table 3 and Figure S1).35 No association was found in subgroup analysis by ethnicity (ie, Caucasian \(P_e=0.238\), OR =1.127, 95% CI =0.924–1.375], East Asian \([P_e=0.901,\) OR =0.966, 95% CI =0.560–1.667], Indian \([P_e=0.211,\) OR =0.772, 95% CI =0.514–1.158], Mestizos \([P_e=0.310,\) OR =1.413, 95% CI =0.725–2.754], and Israeli \([P_e=0.512,\) 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,41 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 \((P_e=0.073,\) 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 \((P_e=0.048,\) OR =1.949, 95% CI =1.007–3.77). Significant heterogeneity was found in the pooled analysis \((P_e=0.009,\) \(F=44\% \)) and in the subgroup analysis by ethnicity in the East Asian subgroup \((P_e=0.014,\) \(F=49.1\% \)) and by source of control in the hospital-based subgroup \((P_e=0.016,\) \(F=59.2\% \)).

### Table 3 Pooled associations of DRD4 polymorphisms and schizophrenia

| Loci | Genetic model | Studies (n) | OR | 95% CI | \(P_e\) | \(F\) | \(P_h\) | \(P_s\) |
|------|---------------|-------------|----|--------|--------|------|--------|--------|
| 48 bp VNTR | Allele contrast (7R and others) | 27 | Random | 1.071 | 0.928–1.236 | 0.349 | 8.1 | 0.352 | 0.727 |
| 48 bp VNTR | 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 |
| 12 bp TR | Homozygous codominant | 9 | Random | 0.756 | 0.434–1.317 | 0.323 | 0.0 | 0.729 | 0.214 |
| 12 bp TR | Heterozygous codominant | 9 | Random | 1.117 | 0.930–1.341 | 0.236 | 0.0 | 0.644 | 0.077 |
| 12 bp TR | Dominant | 9 | Random | 1.083 | 0.907–1.293 | 0.377 | 0.0 | 0.834 | 0.192 |
| 12 bp TR | 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 |
| 120 bp TR | Homozygous codominant | 6 | Random | 1.291 | 0.892–1.868 | 0.176 | 47.2 | 0.092 | 0.213 |
| 120 bp TR | Heterozygous codominant | 6 | Random | 1.010 | 0.744–1.372 | 0.949 | 22.9 | 0.262 | 0.223 |
| 120 bp TR | Dominant | 6 | Random | 1.152 | 0.837–1.584 | 0.386 | 34.3 | 0.179 | 0.176 |
| 120 bp TR | 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 |
| 521 T>C | Homozygous codominant | 10 | Random | 1.240 | 1.041–1.477 | 0.016 | 18.7 | 0.271 | 0.765 |
| 521 T>C | Heterozygous codominant | 10 | Random | 1.105 | 0.971–1.256 | 0.129 | 13.8 | 0.316 | 0.751 |
| 521 T>C | Dominant | 10 | Random | 1.136 | 1.004–1.289 | 0.043 | 19.2 | 0.266 | 0.620 |
| 521 T>C | 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 |
| 616 G>C | Homozygous codominant | 6 | Random | 0.637 | 0.469–0.866 | 0.004 | 46.4 | 0.096 | 0.488 |
| 616 G>C | Heterozygous codominant | 6 | Random | 1.123 | 0.974–1.296 | 0.110 | 0.0 | 0.986 | 0.169 |
| 616 G>C | Dominant | 6 | Random | 1.133 | 0.991–1.295 | 0.068 | 0.0 | 0.889 | 0.965 |
| 616 G>C | 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 |
| 376 C>T | Homozygous codominant | 4 | Random | 0.854 | 0.416–1.749 | 0.665 | 0.0 | 0.996 | 0.456 |
| 376 C>T | Heterozygous codominant | 4 | Random | 0.730 | 0.351–1.520 | 0.401 | 0.0 | 0.993 | 0.911 |
| 376 C>T | Dominant | 4 | Random | 0.820 | 0.401–1.676 | 0.586 | 0.0 | 0.994 | 0.583 |
| 376 C>T | 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.

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 \((P_e=0.377,\) 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.
In the recessive model, genotype L/L was found to be a potential risk factor for schizophrenia \((P_z = 0.004, \text{OR} = 1.275, \text{95\% CI} = 1.081–1.504)\) with a power of 0.959 (Table 3). Findings from subgroup analysis indicated significant associations in East Asian \((P_z = 0.002, \text{OR} = 1.317, \text{95\% CI} = 1.108–1.565)\) and hospital-based subgroups \((P_z = 0.002, \text{OR} = 1.319, \text{95\% CI} = 1.134–1.708)\) (Table 4). No association was found for the other subgroups, and no significant heterogeneity was ascertained in the pooled or subgroup analyses.

### 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 analysis | 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 analysis | 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 | 0.772 | 0.514–1.158 | 0.211 | – | – |
| | Mestizos | 1 | 1.949 | 1.007–3.770 | 0.048 | – | – |
| | Israeli | 1 | 1.164 | 0.739–1.835 | 0.512 | 0.441 | 0.0 |
| 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 analysis | 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 analysis | 6 | 1.275 | 1.081–1.504 | 0.044 | 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 analysis | 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 analysis | 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 analysis | 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.
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 ($P = 0.021$, 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 ($P = 0.009$, 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 |             |           |           |
|                | in/in    | in/de      | de/de       | in/in    | in/de      | de/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$^{44,49}$    | 184  | 28          | 0           | 225      | 37         | 1           | 0.689      | 93.00     | 0.93      | 0.93      | 0.07       |
| Uguerre et al$^{50}$        | 48   | 34          | 1           | 75       | 55         | 4           | 0.102      | 78.31     | 21.69     | 76.49     | 23.51      |
| Mitsuyasu et al$^{51}$      | 136  | 56          | 5           | 176      | 53         | 10          | 0.027      | 83.20     | 16.79     | 84.70     | 15.30      |
| Kohn et al$^{51}$           | 40   | 9           | 0           | 126      | 19         | 0           | 0.311      | 94.00     | 6.00      | 91.00     | 9.00       |
| Kohn et al$^{51}$           | 44   | 4           | 1           | 53       | 6          | 0           | 0.416      | 94.00     | 6.00      | 94.00     | 6.00       |
| Catalano et al$^{52}$       | 76   | 3           | 0           | 69       | 6          | 0           | 0.718      | 98.10     | 1.90      | 96.00     | 4.00       |
| Nakajima et al$^{52}$       | 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. *included 48 bp VNTR, 12 bp TR, and 120 bp TR. Ethnicity is Ashkenazi which included Jews whose origin (or whose parents’ origin), was in European countries, apart from the Balkans; 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 |             |           |           |
|                | S/S     | S/L         | L/L         | S/S     | S/L         | L/L         |           |           |
| Mitsuys au et al$^{53}$ | 10   | 75          | 129         | 13      | 87          | 139         | 0.898      | 77.80     | 22.20     | 76.40     | 23.60      |
| Pai et al$^{54}$          | 23   | 77          | 87          | 11      | 61          | 64          | 0.501      | 32.90     | 67.10     | 30.50     | 69.50      |
| Xing et al$^{55}$         | 20   | 77          | 113         | 28      | 98          | 80          | 0.816      | 27.90     | 72.10     | 37.40     | 62.60      |
| Nakajima et al$^{52}$     | 24   | 183         | 362         | 33      | 192         | 345         | 0.363      | 20.00     | 80.00     | 23.00     | 77.00      |
| Tsutsumi et al$^{56}$     | 24   | 138         | 248         | 16      | 158         | 211         | 0.041      | 22.68     | 77.32     | 24.68     | 75.32      |
| Lai et al$^{57}$           | 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. *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 |             |           |           |
|                | CC      | CT          | TT          | CC      | CT          | TT          |           |           |
| Okuyama et al$^{58}$ | 58   | 125         | 69          | 38      | 142         | 89          | 0.119      | 48.00     | 52.00     | 41.00     | 59.00      |
| Mitsuys au et al$^{53}$ | 33   | 106         | 67          | 31      | 115         | 93          | 0.623      | 41.75     | 58.25     | 37.05     | 62.95      |
| Mitsuys au et al$^{53}$ | 25   | 122         | 61          | 25      | 110         | 75          | 0.109      | 41.30     | 58.70     | 38.10     | 61.90      |
| Lung et al$^{59}$       | 80   | 320         | 230         | 48      | 204         | 173         | 0.294      | 38.10     | 61.90     | 35.30     | 64.70      |
| Jonsson et al$^{54}$    | 23   | 74          | 35          | 60      | 205         | 118         | 0.061      | 45.50     | 54.50     | 42.00     | 58.00      |
| Pai et al$^{54}$         | 27   | 92          | 62          | 26      | 77          | 29          | 0.055      | 40.30     | 59.70     | 48.90     | 51.10      |
| Xing et al$^{54}$        | 37   | 103         | 70          | 25      | 111         | 70          | 0.059      | 42.10     | 57.90     | 39.10     | 60.90      |
| Nakajima et al$^{52}$    | 106  | 270         | 190         | 89      | 285         | 195         | 0.368      | 43.00     | 58.00     | 41.00     | 59.00      |
| Lai et al$^{54}$         | 87   | 115         | 120         | 81      | 95          | 124         | –          | 44.88     | 55.12     | 42.83     | 57.17      |
| Zhong et al$^{54}$       | 62   | 78          | 60          | 53      | 64          | 83          | –          | 45.91     | 54.09     | 42.50     | 57.50      |

Notes: $P_{HWE}$, P-value of Hardy–Weinberg equilibrium. *included 48 bp VNTR, 12 bp TR, and 120 bp TR; †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<sub>HWE</sub> | Allele frequency |
|---------------|-----------------------|----------------|-----------------|
|               | Cases, n              | Controls, n    | Cases (%)       | Controls (%)    |
|               | GG   | GC   | CC   | GG   | GC   | CC   | GG   | GC   | CC   |
| Mitsuyasu et al<sup>a</sup> | 102 | 89  | 19  | 112 | 98  | 30  | 0.243 | 69.80 | 30.20 | 67.10 | 32.90 |
| Mitsuyasu et al<sup>b</sup> | 89  | 89  | 30  | 100 | 85  | 25  | 0.296 | 64.20 | 35.80 | 67.90 | 32.10 |
| Xing et al<sup>a</sup> | 83  | 100 | 27  | 91  | 102 | 13  | 0.025 | 63.30 | 36.70 | 68.90 | 31.10 |
| Nakajima et al<sup>a</sup> | 267 | 248 | 49  | 285 | 224 | 59  | 0.134 | 69.00 | 31.00 | 69.50 | 29.50 |
| Lai et al<sup>b</sup> | 161 | 113 | 48  | 166 | 102 | 32  | 0.009 | 67.55 | 32.45 | 72.33 | 27.67 |
| Zhong et al<sup>a</sup> | 112 | 77  | 31  | 107 | 68  | 25  | 0.010 | 68.41 | 31.59 | 70.50 | 29.50 |

Notes: P<sub>HWE</sub>, 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<sub>HWE</sub> | Allele frequency |
|---------------|-----------------------|----------------|-----------------|
|               | Cases, n              | Controls, n    | Cases (%)       | Controls (%)    |
|               | CC   | CT   | TT  | CC   | CT   | TT  | CC   | CT   | TT  |
| Mitsuyasu et al<sup>a</sup> | 177 | 34  | 1   | 193 | 43  | 1   | 0.39  | 91.50 | 8.50  | 90.45 | 9.45  |
| Mitsuyasu et al<sup>b</sup> | 179 | 28  | 1   | 168 | 41  | 1   | 0.367 | 92.80 | 0.72  | 89.80 | 1.02  |
| Xing et al<sup>a</sup> | 137 | 66  | 7   | 127 | 74  | 5   | 0.126 | 81.00 | 19.00 | 79.60 | 20.40 |
| Nakajima et al<sup>a</sup> | 453 | 100 | 8   | 447 | 108 | 7   | 0.869 | 90.00 | 10.00 | 89.50 | 10.50 |

Notes: P<sub>HWE</sub>, 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<sub>HWE</sub>=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<sub>HWE</sub>=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<sup>77</sup> and with increased brain...
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 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 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 6 Funnel plot analysis for the detection of publication bias in the association between −521 C>T and schizophrenia.
Abbreviation: OR, odds ratio.

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 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. 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.

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 demonstrated an association between the 48-bp VNTR and schizophrenia risk but noted that sample bias might have led to a false-positive result. 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, the authors found no LD between −521 T>C and 120 bp TR (r²=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. 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. 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.

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Disclosure
The authors report no conflicts of interest in this work.

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