No association between dopamine D3 receptor gene Ser9Gly polymorphism (rs6280) and risk of schizophrenia: an updated meta-analysis

Xing-ling Qi
Jin-feng Xuan
Jia-xin Xing
Bao-jie Wang
Jun Yao
School of Forensic Medicine, China Medical University, Shenyang, People's Republic of China

Objective: Ser9Gly (rs6280) is a functional single-nucleotide polymorphism (SNP) in the dopamine receptor D3 (DRD3) gene that may be associated with schizophrenia. We performed a meta-analysis to determine whether Ser9Gly influences the risk of schizophrenia and examined the relationship between the Ser9Gly SNP and the etiology of schizophrenia.

Methods: Case–control studies were retrieved from literature databases in accordance with established inclusion criteria. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the association between Ser9Gly and schizophrenia. Subgroup analysis and sensitivity analysis were also performed.

Results: Seventy-three studies comprising 10,634 patients with schizophrenia (cases) and 11,258 controls were included in this meta-analysis. Summary results indicated no association between Ser9Gly and risk of schizophrenia. In the dominant genetic model, the pooled OR using a random effects model was 0.950 (95% CI, 0.847–1.064; \( P = 0.374 \)).

Conclusion: Results of this meta-analysis suggest that the Ser9Gly SNP is not associated with schizophrenia. These data provide possible avenues for future case–control studies related to schizophrenia.

Keywords: dopamine receptor D3, schizophrenia, meta-analysis, gene polymorphism

Introduction

Schizophrenia is a common mental disorder caused by synergic effects of multiple genetic and environmental factors.\(^1\) Heritability of up to 80% has been reported for schizophrenia;\(^4\) however, the precise etiology of this disease remains inconclusive.\(^2,3\) Results of several genome-wide linkage and association studies have indicated genes and chromosomal regions associated with susceptibility to schizophrenia.\(^5,6\) Several investigators have suggested that dysregulated dopaminergic neurotransmission has a role in the pathogenesis of schizophrenia.\(^7,10\) Dopamine functions as a neurotransmitter by binding to dopamine receptors on the postsynaptic membrane and autoreceptors on the presynaptic membrane.

Dopamine receptor D3 (DRD3) is a candidate gene for evaluating an association between dopaminergic neurotransmission and schizophrenia risk. DRD3 is located on chromosome 3 in the q13.3 band and has 52% global homology with the D2 receptor band. DRD3 is primarily expressed in the limbic areas of the human brain\(^11\) and contributes emotional, cognitive, and endocrine functions.\(^12\) A single-nucleotide polymorphism (SNP) in the first exon of DRD3 corresponds to a serine-to-glycine substitution at position 9 in the extracellular N-terminal domain of the polypeptide
Ser9Gly is a functional SNP that yields a protein with altered dopamine-binding affinity. The substitution of serine with glycine is thought to yield D3 autoreceptors with a higher affinity for dopamine and more robust intracellular signaling. Other authors have associated Ser9Gly with acute pain in sickle cell disease, bipolar disorder, Parkinson’s disease, and suicidal behaviors.

In recent years, numerous molecular epidemiological studies have addressed the association between Ser9Gly and schizophrenia risk. However, some investigators determined that Ser9Gly was associated with the disease, whereas others found no association. These inconclusive and discordant findings have been attributed to small sample size, inclusion of various genetic backgrounds, and potential confounding bias.

Meta-analysis has been applied widely as a statistical method in medical studies, particularly for topics that are studied extensively yet yield controversial results. Utsunomiya et al conducted a meta-analysis in 2008 to evaluate the association between Ser9Gly and schizophrenia. Their pooled results of 9 case–control studies indicated that Ser9Gly was unlikely to confer susceptibility to schizophrenia in the Japanese population. In a second meta-analysis conducted in 2008, results involving 51 case–control studies indicated no association of Ser9Gly with schizophrenia. In the years since these meta-analyses were completed, additional molecular epidemiological studies have addressed the roles of Ser9Gly in the occurrence of schizophrenia in various populations. Herein, we describe an updated meta-analysis of studies involving associations between DRD3 polymorphisms and schizophrenia.

Methods
Identification of relevant studies
To identify studies eligible for inclusion in this meta-analysis, 3 online electronic English databases (PubMed, Embase, and Web of Science) and 1 online Chinese database (CNKI) were searched. The most recent search was conducted in July 2017. The following key words were used for study identification: DRD3, dopamine receptor 3, dopamine D3 receptor, dopamine receptor D3, schizophrenia, polymorphism, and Ser9Gly. Reference lists of the accessed articles and of potentially relevant review articles were screened to identify additional studies.

The following inclusion criteria were applied: 1) case–control design; 2) inclusion of patients with schizophrenia; and 3) statement of allele or genotype frequencies. For studies in which the same or overlapping data were reported by the same authors, the most recent article was selected. Excluded from the meta-analysis were studies 1) without a control population, 2) that duplicated an earlier publication, and 3) that lacked data regarding genotype frequency. Study authors were queried via e-mail for additional study details, such as allele or genotype frequencies or sample characteristics, when these data were not provided in the article.

Data extraction
Two reviewers independently extracted information from all eligible publications. Disagreements were resolved by discussion until the 2 reviewers reached consensus. The following details of each article were recorded: first author’s last name, publication year, sample size, region, and number of genotypes for cases and controls. To detect potentially moderating influences on the effects findings reported in the case–control studies, we also included the following variables: 1) ethnicity of the sample population; 2) source of controls; 3) mean age of the control group; 4) diagnostic criteria; and 5) gender index.

Statistical analysis
Stata version 10.0 (Stata Corp., College Station, TX, USA) was applied for statistical analysis. Hardy–Weinberg equilibrium (HWE) was determined for the genotype distribution of controls, and the chi-square goodness-of-fit test was performed to ascertain deviations from HWE. The Thakkinstian method was applied for pooled frequency analysis, as described previously. All statistical tests were 2-tailed, and significance was defined as \( P < 0.05 \).

Odds ratios (ORs) with accompanying 95% confidence intervals (CIs) were calculated to assess the strength of the association of Ser9Gly and schizophrenia. Pooled effect sizes among the included articles were examined with a random effects model, which accounts for heterogeneity among the studies and yields the likely effect size across populations. We did not apply a fixed effects model because we wanted to avoid the assumption that patients were being sampled from a single population. In the fixed effects model, the effect size could be biased by heterogeneity among studies.

Three genetic models were applied to determine overall pooled ORs: the allele contrast model, the dominant model, and the recessive model. As previously described, OR\(_1\) (AA vs aa), OR\(_2\) (Aa vs aa), and OR\(_3\) (AA vs Aa) were compared, with A defined as the risk allele. The most suitable genetic model was ascertained from these pairwise differences. Specifically, for OR\(_1\) = OR\(_2\) ≠1 and OR\(_3\) =1, the recessive model was selected (OR =1 means \( P > 0.05 \);
OR \#1 means \(P<0.05\). For \(OR_0 = OR_1 \neq 1\) and \(OR_1 = 1\), the dominant model was considered. For \(OR_0 = 1 \neq 1\) and \(OR_1 = 1\), the complete-oddominant model was presumed. Lastly, for \(OR_0 > OR_1 > 1\) and \(OR_0 > OR_1 > 1\) (or \(OR_0 < OR_1 < 1\) and \(OR_1 < OR_1 < 1\), the data were evaluated in the context of the codominant model.\(^{29}\)

The degree of heterogeneity between studies was determined by means of the \(Q\) statistic.\(^{30,31}\) Specifically, \(P>0.05\) by the \(Q\) test indicated the absence of heterogeneity, and \(P<0.05\) indicated heterogeneity. \(F\) was defined as the proportion of observed variance in effect sizes attributable to true differences among studies. Conventional interpretations of \(F\) include limits for low (<25%), moderate (approximately 50%), and high (>75%) heterogeneity.\(^{32}\) Subgroup analysis was carried out by ethnicity (ie, East Asian, Caucasian, and other populations) and by source of controls (ie, hospital-based and population-based).

Publication bias was evaluated by visual inspection of a funnel plot in which the standard error of log(OR) of each study was plotted against its log(OR). An asymmetric plot implied possible publication bias, and the degree of asymmetry was calculated by means of Egger's test. \(P<0.05\) indicated significant publication bias.\(^{33}\)

Sensitivity analysis was performed to assess the potential influence of a single study on the pooled effect size. Specifically, each study was omitted singly from the meta-analysis, and significant alterations to the pooled effect size were ascertained.

**Results**

A total of 155 articles were identified by database searches. After removing duplicate or overlapping articles and those that did not fulfill the inclusion criteria, 60 publications were included in the meta-analysis.\(^{12,19-23,26,34-45}\) These articles included 73 individual studies that comprised 10,634 patients with schizophrenia (ie, cases) and 11,258 unaffected participants (ie, controls). Patients of diverse races and ethnicities were included (eg, East Asian, Caucasian, Latino, and Indian). The mean age of the controls ranged from 25.0 to 53.0 years. The key characteristics of the studies are summarized in Table 1. Genotype and allele frequencies, and details regarding HWE are presented in Table 2. For Ser9Gly, the total numbers of Ser/Ser, Ser/Gly, and Gly/Gly genotypes were 5,532, 5,117, and 1,900 for cases and 5,173, 5,066, and 1,022 for controls, respectively. Of the 73 studies, 4 studies deviated significantly from HWE.

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

| References           | Year | Location    | Ethnicity | Controls source | Mean age of control group | Diagnostic criteria | Gender index (case) | Gender index (control) |
|----------------------|------|-------------|-----------|-----------------|---------------------------|---------------------|---------------------|-----------------------|
| Crocq et al\(^{19}\) | 1992 | France      | Caucasian | Hospital-based  | 33.9                      | DSM-III-R           | 0.38                | -                     |
| Crocq et al\(^{19}\) | 1992 | UK          | Caucasian | Population-based | 45.9                      | DSM-III-R           | 0.58                | 0.74                  |
| Yang et al\(^{20}\)  | 1993 | China       | East Asians | Population-based | 25.05                     | RDC                 | 0.49                | 0.56                  |
| Nanko et al\(^{21}\) | 1993 | Japan       | East Asians | Population-based | 27.5                      | DSM-III-R           | 0.82                | 0.91                  |
| Jonsson et al\(^{22}\) | 1993 | Sweden      | Caucasian | Population-based | 28.0                      | DSM-III-R           | 0.46                | 0.61                  |
| Nöthen et al\(^{23}\) | 1993 | Germany     | Caucasian | Population-based | 28.2                      | DSM-III-R           | 0.5                 | 0.88                  |
| Nöthen et al\(^{23}\) | 1993 | Germany     | Caucasian | Population-based | 48                        | DSM-III-R           | 0.38                | 0.72                  |
| Laurent et al\(^{24}\) | 1994 | France      | Caucasian | Population-based | 38                        | ICD-9               | -                   | -                     |
| Saha et al\(^{25}\)  | 1994 | Singapore   | East Asians | Population-based | 46.6                      | DSM-III-R           | 0.74                | 0.8                   |
| Mant et al\(^{26}\)  | 1994 | UK          | Caucasian | Population-based | 46.6                      | DSM-III-R           | 0.74                | 0.8                   |
| Kennedy et al\(^{27}\) | 1995 | North America | Caucasian | Hospital-based  | -                         | DSM-III-R           | -                   | -                     |
| Kennedy et al\(^{27}\) | 1995 | Italy       | Caucasian | Hospital-based  | -                         | DSM-III-R           | -                   | -                     |
| Inada et al\(^{28}\)  | 1995 | Japan       | East Asians | Population-based | 54                        | -                   | 1.09                | 1                     |
| Durany et al\(^{29}\) | 1996 | Spain       | Caucasian | Population-based | 53                        | ICD-10              | 1.38                | 1.44                  |
| Gaitonde et al\(^{30}\) | 1996 | UK          | Caucasian | Hospital-based  | 41.7                      | ND                  | 0.83                | 0.93                  |
| Ohara et al\(^{31}\)  | 1996 | Japan       | East Asians | Population-based | 34.4                      | DSM-IV              | -                   | 1.37                  |
| Rietschel et al\(^{32}\) | 1996 | Germany     | Caucasian | Population-based | 30.2                      | DSM-III-R           | 0.66                | 0.96                  |
| Shaikh et al\(^{33}\) | 1996 | UK          | Caucasian | Hospital-based  | -                         | DSM-III-R           | -                   | -                     |
| Tanaka et al\(^{34}\) | 1996 | Japan       | East Asians | Population-based | 42.7                      | DSM-III-R           | 0.92                | 0.41                  |
| Nimgaonkar et al\(^{35}\) | 1996 | USA         | African-American | Hospital-based  | -                         | DSM-III-R           | 1.24                | 1.33                  |
| Nimgaonkar et al\(^{35}\) | 1996 | USA         | Caucasian | Hospital-based  | -                         | DSM-III-R           | 0.67                | 1.1                   |
| Chen et al\(^{36}\)   | 1997 | China       | East Asians | Hospital-based  | 45                        | DSM-III-R           | 0.86                | 1.13                  |
| Ebstein et al\(^{37}\) | 1997 | Italy       | Caucasian | Population-based | 36.5                      | DSM-III-R           | 0.31                | 1.03                  |
| Ebstein et al\(^{37}\) | 1997 | Israel      | Ashkenazi  | Population-based | 32.9                      | DSM-III-R           | -                   | 0.94                  |

(Continued)
| References                           | Year | Location               | Ethnicity     | Controls source      | Mean age of control group | Diagnostic criteria | Gender index (case) | Gender index (control) |
|-------------------------------------|------|------------------------|---------------|----------------------|---------------------------|---------------------|---------------------|-----------------------|
| Ebstein et al^13^                   | 1997 | Israel                 | Non-Ashkenazi | Population-based     | 32.9                      | DSM-III-R            | –                   | 0.94                  |
| Maziade et al^18^                   | 1997 | Canada                 | Caucasian     | Population-based     | –                         | DSM-III-R            | 0.46                | –                     |
| Hawi et al^12^                      | 1998 | Ireland                | Caucasian     | Population-based     | –                         | DSM-III-R            | 0.47                | 0.79                  |
| Krebs et al^13^                     | 1998 | France                 | Caucasian     | Population-based     | 35.47                     | DSM-III-R            | 0.62                | 1                     |
| Spurlock et al^15^                  | 1998 | Ireland                | Caucasian     | Population-based     | –                         | DSM-III-R            | –                   | –                     |
| Spurlock et al^15^                  | 1998 | Northern Sweden        | Caucasian     | Population-based     | –                         | DSM-III-R            | –                   | –                     |
| Ishiguro et al^13^                  | 2000 | Japan                  | East Asians   | Population-based     | 47.2                      | DSM-III-R or ICD-10   | 0.74                | 1.07                  |
| Ishiguro et al^13^                  | 2000 | Japan                  | East Asians   | Population-based     | 48.5                      | DSM-III-R or ICD-11   | 0.9                 | 0.81                  |
| Joober et al^14^                    | 2001 | Canada                 | Hospital-based| –                    | DSM-IV                    | –                   | –                   | –                     |
| Meszaros et al^19^                  | 2000 | Austria                | Caucasian     | Population-based     | –                         | DSM-III-R            | –                   | –                     |
| Sivagnan sundaram et al^15^         | 2000 | UK                     | Caucasian     | Population-based     | –                         | DSM-III-R            | –                   | –                     |
| Hauser et al^17^                    | 2000 | Poland                 | Caucasian     | Population-based     | 28.76                     | DSM-IV              | –                   | –                     |
| Cordeiro et al^17^                  | 2001 | Brazil                 | Latinos       | Population-based     | –                         | ICD-10              | –                   | –                     |
| Levie et al^17^                     | 2001 | India                  | Indians       | Population-based     | 43                        | DSM-IV              | –                   | 0.83                  |
| Rybakowski et al^12^                | 2001 | Poland                 | Caucasian     | Population-based     | 27                        | DSM-IV or ICD-10     | 0.61                | 1.13                  |
| Anney et al^13^                     | 2002 | UK and Ireland         | Caucasian     | Population-based     | 43                        | DSM-IV              | 0.28                | 0.28                  |
| Ventriglia et al^16^                | 2002 | Italy                  | Caucasian     | Population-based     | –                         | DSM-IV              | –                   | –                     |
| Morimoto et al^12^                  | 2002 | Japan                  | East Asians   | Population-based     | –                         | ICD-10              | 1.14                | –                     |
| Zhao et al^13^                      | 2002 | China                  | East Asians   | Population-based     | 55.9                      | DSM-III-R            | 0.83                | 1.4                   |
| Tang et al^14^                      | 2002 | China                  | East Asians   | Population-based     | 33                        | CCMD-II-R            | 0.76                | 1.06                  |
| Jönsson et al^17^                   | 2003 | Sweden                 | Caucasian     | Population-based     | –                         | DSM-III-R            | –                   | –                     |
| Iwata et al^16^                     | 2003 | Japan                  | East Asians   | Population-based     | –                         | DSM-IV              | –                   | –                     |
| Baritaki et al^16^                  | 2004 | Greece                 | Caucasian     | Population-based     | 45.1                      | DSM-IV              | 0.7                 | 0.63                  |
| Jönsson et al^14^                   | 2004 | Germany                | Caucasian     | Population-based     | 30.2                      | DSM-IV              | 0.85                | 0.25                  |
| A et al^16^                         | 2004 | China                  | East Asians   | Population-based     | –                         | –                   | 0.63                | –                     |
| Staddon et al^17^                   | 2005 | Northern Spain         | Basque        | Population-based     | –                         | DSM-IV              | 0.54                | 1                     |
| Yang^17^                            | 2005 | China                  | East Asians   | Population-based     | 35.04                     | DSM-IV              | 1.12                | 1.09                  |
| Liang^17^                           | 2005 | China                  | East Asians   | Population-based     | 25                        | DSM-IV or CCMD-3     | 0.98                | 0.98                  |
| Talkowski et al^18^                 | 2006 | USA                    | Caucasian     | Population-based     | –                         | DSM-IV              | –                   | –                     |
| Yi et al^18^                        | 2006 | China                  | East Asians   | Population-based     | 35                        | DSM-IV              | 1.12                | 1.13                  |
| Ma et al^11^                        | 2008 | China                  | East Asians   | Hospital-based       | 35.02                     | DSM-IV              | 0.62                | 0.81                  |
| Lorenzo et al^16^                   | 2007 | Spain                  | Caucasian     | Population-based     | –                         | DSM-IV              | –                   | –                     |
| Chang et al^14^                     | 2007 | China                  | East Asians   | Population-based     | –                         | DSM-IV              | –                   | –                     |
| Güzey et al^14^                     | 2007 | Italy                  | Caucasian     | Population-based     | –                         | DSM-IV              | 0.2                 | 0.17                  |
| Fathalli et al^15^                  | 2008 | Canada, Tunisia, Hungary| Caucasian   | Hospital-based       | –                         | DSM-III-R or ICD-10   | 0.37                | 0.85                  |
| Utsunomiya et al^14^                | 2008 | Japan                  | East Asians   | Population-based     | 55                        | DSM-IV              | 0.92                | 0.92                  |
| Kreiling et al^18^                  | 2008 | Brazil                 | Latinos       | Population-based     | 40.27                     | –                   | –                   | –                     |
| Barlas et al^17^                    | 2009 | Turkey                 | Caucasian     | Population-based     | 31.7                      | DSM-IV              | 0.21                | 0.23                  |
| Zai et al^18^                       | 2010 | Europe                 | Caucasian     | Population-based     | –                         | DSM-IV              | 0.57                | 0.42                  |
| Sáiz et al^15^                      | 2010 | Asturias, Spain         | Basque        | Population-based     | 40.6                      | DSM-IV              | 0.66                | 0.95                  |
| Nuni kawa et al^10^                 | 2010 | Japan                  | East Asians   | Population-based     | 38.1                      | DSM-IV              | 0.9                 | 0.92                  |
| Zhang et al^10^                     | 2011 | China                  | East Asians   | Population-based     | 28.13                     | DSM-IV              | –                   | –                     |
| Tee et al^12^                       | 2011 | Malaysia               | East Asians   | Population-based     | 38.4                      | –                   | 0.91                | 0.83                  |
| Zheng et al^17^                     | 2012 | China                  | East Asians   | Population-based     | 33.1                      | DSM-IV              | 0.69                | 0.72                  |
| Yang et al^12^                      | 2016 | China                  | East Asians   | Population-based     | 42                        | DSM-IV              | –                   | –                     |

**Notes:** Gender index = (female/male). En dashes indicate data not available.

**Abbreviations:** DSM, Diagnostic and Statistical Manual of Mental Disorders; RDC, Research Diagnostic Criteria; ICD, International Classification of Diseases; ND, not determined; CCMD, Chinese Classification of Mental Disorders.
Table 2 Distribution of genotype and allele frequencies of the DRD3 Ser9Gly polymorphism

| References          | Genotype distribution | P \text{HWE} | Allele frequency |
|---------------------|-----------------------|--------------|------------------|
|                     | Cases, n | Ser/Ser | Ser/Gly | Gly/Gly | Controls, n | Ser/Ser | Ser/Gly | Gly/Gly | Controls, % | Ser | Gly | Ser | Gly |
| Crocq et al\(^a\)  | 37   26  10 | 134 128 24 | 0.3930 | 68 32 69 31 |
| Crocq et al\(^a\)  | 37   18  13 | 170 153 41 | 0.4616 | 67 33 68 32 |
| Yang et al\(^a\)   | 54   45  8  | 56 95 24 | 0.1630 | 65 35 59 41 |
| Nanko et al\(^a\)  | 48   35  8  | 50 40 10 | 0.6300 | 72 28 70 30 |
| Jönsson et al\(^a\) | 34   36  6 | 63 83 37 | 0.3154 | 60 40 55 45 |
| Nöthen et al\(^a\) | 31   22  7  | 26 41 4  | 0.0193 | 68 32 65 35 |
| Nöthen et al\(^a\) | 20   26  14 | 25 34 9 | 0.6289 | 68 32 62 38 |
| Laurent et al\(^a\) | 35   33  8  | 43 47 10 | 0.5832 | 70 30 67 33 |
| Saha et al\(^a\)   | 62   66  9  | 34 25 4 | 0.8341 | 66 34 74 26 |
| Ment et al\(^a\)   | 33   23  10 | 62 41 6 | 0.8178 | 77 23 76 24 |
| Kennedy et al\(^a\) | 37   62  18 | 12 14 1 | 0.2059 | 61 39 70 30 |
| Kennedy et al\(^a\) | 42   43  12 | 73 84 15 | 0.1807 | 63 37 67 33 |
| Inada et al\(^a\)  | 66   40  7  | 34 33 10 | 0.6569 | 67 33 66 34 |
| Durany et al\(^a\) | 53   43  11 | 92 119 24 | 0.1064 | 64 36 64 36 |
| Gaitonde et al\(^a\) | 34   45  5  | 56 51 15 | 0.5255 | 75 25 67 33 |
| Ohara et al\(^a\)  | 54   38  8  | 37 40 9 | 0.707 | 69 31 66 34 |
| Nimgoankar et al\(^a\) | 30   22  13 | 51 66 15 | 0.3559 | 67 33 64 36 |
| Chen et al\(^a\)   | 33   26  6  | 5 13 4 | 0.3874 | 54 46 52 48 |
| Ebstein et al\(^a\) | 89   77  12 | 38 35 6 | 0.5939 | 78 22 70 30 |
| Ebstein et al\(^a\) | 37   31  12 | 49 58 13 | 0.4951 | 66 34 65 35 |
| Mazia et al\(^a\)  | 41   27  2  | 54 34 6 | 0.8354 | 69 31 76 24 |
| Haawi et al\(^a\)  | 83   87  28 | 59 57 9 | 0.3379 | 70 30 69 31 |
| Krebs et al\(^a\)  | 36   42  11 | 57 69 7 | 0.0163 | 66 34 56 44 |
| Spurlock et al\(^a\) | 15   16  5  | 25 23 8 | 0.4763 | 36 64 83 17 |
| Spurlock et al\(^a\) | 25   29  13 | 28 49 8 | 0.042 | 64 36 62 38 |
| Spurlock et al\(^a\) | 28   40  8  | 27 34 10 | 0.8928 | 59 41 62 38 |
| Spurlock et al\(^a\) | 14   15  2  | 6 22 5 | 0.0546 | 63 37 51 49 |
| Spurlock et al\(^a\) | 38   21  12 | 13 16 2 | 0.3137 | 69 31 68 32 |
| Ishigure et al\(^a\) | 84   61  8  | 10 17 4 | 0.4375 | 75 25 60 40 |
| Ishigure et al\(^a\) | 61   31  7  | 67 77 12 | 0.1118 | 72 28 69 31 |
| Joober et al\(^a\)  | 44   50  12 | 119 127 26 | 0.3435 | 75 25 67 33 |
| Meszaros et al\(^a\) | 45   35  15 | 52 43 5 | 0.2991 | 73 27 74 26 |
| Sivagnanasundaram et al\(^a\) | 29   40  4 | 59 67 12 | 0.2476 | 60 40 67 33 |
| Hauser et al\(^a\)  | 62   58  9  | 50 40 8 | 1 71 29 71 29 |
| Cordeiro et al\(^a\) | 56   57  28 | 19 25 4 | 0.2847 | 70 30 66 34 |
| Lovi et al\(^a\)   | 16   29  11 | 291 242 51 | 0.9456 | 70 30 71 29 |
| Rybakowski et al\(^a\) | 54   55  10 | 48 35 7 | 0.8604 | 72 28 73 27 |
| Anney et al\(^a\)  | 152  178 30 | 38 46 13 | 0.8753 | 67 33 63 37 |
| Ventriglia et al\(^a\) | 43   51  20 | 88 81 19 | 0.9546 | 59 41 69 31 |
| Morimoto et al\(^a\) | 23   21  4  | 34 26 4 | 0.7411 | 65 35 73 27 |
| Zhao et al\(^a\)   | 109  109 18 | 27 22 4 | 0.8681 | 68 32 72 28 |
| Tang et al\(^a\)   | 273  210 45 | 138 119 28 | 0.7518 | 67 33 69 31 |
| Jönsson et al\(^a\) | 72   70  14 | 30 30 3 | 0.1859 | 63 37 71 29 |
| Iwata et al\(^a\)  | 73   64  9  | 27 30 8 | 0.9401 | 71 29 65 35 |
| Baritaki et al\(^a\) | 51   46  17 | 70 66 27 | 0.098 | 66 34 63 37 |
| Jönsson et al\(^a\) | 326  255 68 | 50 37 7 | 0.9657 | 70 30 73 23 |
| A et al\(^a\)      | 43   29  8  | 27 21 7 | 0.3735 | 71 29 68 32 |
| Staddon et al\(^a\) | 59   40  10 | 278 267 51 | 0.2413 | 72 28 69 31 |

(Continued)
Frequency of Ser9Gly in the control population

Pooled frequencies of Ser9Gly stratified by ethnicity were determined for controls. The pooled frequency of Ser9Gly was highest among Latinos (56.8%; 95% CI, 55.9–57.6), followed by African-Americans (56.1%; 95% CI, 55.3–57.0), East Asians (38.2%; 95% CI, 35.0–41.4), Caucasians (29.0%; 95% CI, 27.7–30.4), and Indians (22.0%; 95% CI, 21.7–22.3).

Quantitative synthesis and heterogeneity analysis

Pooled ORs and corresponding 95% CIs were determined for Ser9Gly in the following genetic models: homozygous codominant, heterozygous codominant, dominant, recessive, and allele contrast (Table 3 and Figure 1). The dominant model was found to be most appropriate, according to the principles of genetic model selection.90,96 Summary results indicated no association between Ser9Gly and schizophrenia risk. In the dominant model, the pooled OR using a random effects model was 0.950 (95% CI, 0.847–1.064; P=0.374). Results of subgroup analysis by ethnicity indicated that the Ser9Gly SNP was not associated with schizophrenia among East Asians, Caucasians, or populations evaluated less frequently in the meta-analysis—such as Latino, Indian, and African-American patients (Table 4). Moreover, no association between Ser9Gly and schizophrenia was observed in subgroup analysis according to the source of controls.

Sensitivity analysis

Sensitivity analysis was carried out to ascertain the contribution of each study to the overall result. Corresponding pooled ORs for analyses in which each of the 73 studies was individually removed indicated that no single study produced a significant deviation from the overall pooled OR.

Table 3 Summarized ORs with 95% CIs for the association of DRD3 Ser9Gly polymorphism with schizophrenia

| Polymorphism | Genetic model | n | Statistical model | OR | 95% CI | P (h) | I² (%) | P (r) | P (F) |
|--------------|--------------|---|------------------|----|--------|-------|--------|-------|-------|
| Ser9Gly      | Allele contrast | 73 | Random            | 0.995 | 0.925–1.069 | 0.883 | 28.6 | 0.014 | 0.825 |
|              | Homozygous codominant | 73 | Random            | 0.914 | 0.759–1.102 | 0.346 | 62.3 | <0.0001 | 0.113 |
|              | Heterozygous codominant | 73 | Random            | 0.838 | 0.716–0.981 | 0.028 | 47.1 | <0.0001 | 0.421 |
|              | Dominant      | 73 | Random            | 0.950 | 0.847–1.064 | 0.374 | 68.5 | <0.0001 | 0.040 |
|              | recessive     | 73 | Random            | 1.139 | 0.965–1.345 | 0.125 | 57.0 | <0.0001 | 0.183 |

Notes: n, number of studies; P (h), P-value for association test; P (r), P-value for heterogeneity test; P (F), P-value for publication bias test.

Abbreviations: OR, odds ratio; CI, confidence interval.
Figure 1 Forest plot of the association between the Ser9Gly polymorphism of DRD3 and schizophrenia in the dominant genetic model (Ser/ Gly + Gly/Gly vs Ser/Ser).

Notes: Weights are from random effects analysis. *After the first case-control study, there was a marginally significant association between the Ser9Gly polymorphisms and schizophrenia (P = 0.02). Thus, these positive findings were replicated in an additional 99 Japanese schizophrenia patients and 132 controls.

Abbreviations: OR, odds ratio; CI, confidence interval.
significant change in the overall results of the meta-analysis. Hence, these results are stable and reliable.

Publication bias
A funnel plot was generated to assess potential publication bias (Figure 2), and a small but significant effect of publication bias was detected ($P_e=0.040$) (Table 3).

Discussion
We conducted a meta-analysis of 73 studies (10,634 cases and 11,258 controls) to investigate the potential association of the Ser9Gly SNP in DRD3 with the occurrence of schizophrenia. Our overall findings suggest that no association exists, and results of subgroup analysis stratified by ethnicity and source of controls further validated the distribution disequilibrium of cases and controls.

Several previous meta-analyses have addressed the putative association between DRD3 polymorphisms and schizophrenia.21,26,71,80,87 In general, the results of the current meta-analysis were consistent with those published previously, with the exception of 1 meta-analysis in which DRD3 polymorphisms were found to exert a small but significant effect on schizophrenia susceptibility in Caucasian patients.87 Rather than being superfluous, our meta-analysis has several advantages over previous studies. Most importantly, our analysis involved relevant studies that have been published in the interim since the previous meta-analyses were carried out. We included 73 studies that we believe collectively represent DRD3 polymorphisms more accurately than did previous meta-analyses. In addition, we performed subgroup analyses stratified by ethnicity and source of controls to assess potential sources of heterogeneity and to test study stability. Therefore, the results of our study provide a more precise, comprehensive assertion that no association exists between Ser9Gly and schizophrenia.

Some authors have described specific ethnic groups for which associations exist between polymorphisms at certain DRD3 loci and schizophrenia. However, findings of an association of a DRD3 SNP with schizophrenia in 1 population may not be supported in another population. This phenomenon may result from 2 factors. First, different genetic backgrounds may contribute to divergence. The distribution of DRD3 allele frequencies varies among Latinos, African-Americans, East Asians, Caucasians, and Indians. Evidently, genetic liability is a high risk factor for schizophrenia.88 Gly9 allele frequencies vary almost as much in the Japanese control populations (22%–34%) as they do in northern and western Caucasian control populations (30%–44%).71 Second, patients from different populations may have disparate lifestyles and may be affected by different environmental factors.89 Epigenetic modifications that contribute to schizophrenia may be a product of transregulatory or environmental risk factors.90

The relatively small sample sizes of Latino, African-American, Indian, Ashkenazi, and non-Ashkenazi patients limited our ability to isolate stable effects for these subgroups. More studies need to be performed to explore the association between Ser9Gly polymorphism and the risk of schizophrenia in these above populations. Moreover, the lack of an association between Ser9Gly and schizophrenia was upheld when the analysis was stratified by the source of controls. However, control patients in hospital-based studies do not necessarily represent the general population, particularly when the polymorphism being evaluated is related

| Subgroup analysis | Ser9Gly |
|-------------------|---------|
|                   | n  | OR  | 95% CI    | $P_\text{a}$ | $P_\text{a}$ (%) | $P_e$ |
| Overall           | 73 | 0.950 | 0.847–1.064 | 0.374 | 68.5 | <0.0001 |
| Ethnicity         |     |       |       |       |       |       |
| East Asians       | 25 | 0.915 | 0.751–1.114 | 0.377 | 72.8 | <0.0001 |
| Caucasians        | 41 | 0.981 | 0.880–1.094 | 0.733 | 36.2 | 0.012 |
| Others            | 7  | 0.862 | 0.368–2.017 | 0.732 | 92.2 | <0.0001 |
| Source of controls|     |       |       |       |       |       |
| Hospital-based    | 11 | 1.022 | 0.861–1.214 | 0.803 | 4.6  | 0.399  |
| Population-based  | 62 | 0.938 | 0.847–1.064 | 0.334 | 72.0 | <0.0001 |

Notes: n, number of studies; $P_\text{a}$, $P$-value for association test; $P_e$, $P$-value for heterogeneity test. Others included the ethnicities with the rare studies, such as Latino, Indian, and African-American.

Abbreviations: OR, odds ratio; CI, confidence interval.

Figure 2 Funnel plot analysis depicting publication bias in the association between the Ser9Gly polymorphism of DRD3 and schizophrenia. Abbreviation: OR, odds ratio.
to a disorder that affects hospital-based control patients. Thus, the negative results by the source of controls should be interpreted carefully. Because this Gly allele is known to alter dopamine-binding affinity, it can, to some degree, influence the function of dopamine neurotransmitter. Thus, more effort is needed to explore whether it is involved in the risk of schizophrenia.

The present study had several limitations. We observed significant heterogeneity in overall and subgroup analyses. Although we performed subgroup analysis to investigate potential sources of heterogeneity, no single factor completely accounted for this heterogeneity. Therefore, other unidentified aspects might partially contribute to heterogeneity. Second, we detected a slight but significant publication bias in the included studies. This bias can be explained, in part, by our inclusion of only English- and Chinese-language studies. Another main reason is that the negative results are not easier to publish than the positive results. Third, gene–gene interactions and epigenetics were not examined in this meta-analysis, owing to insufficient information in the included studies. By evaluating only 1 SNP in DRD3, we may have limited our analysis to a polymorphism that plays a minute role in the overall genetic influences of schizophrenia. This disorder is thought to arise from the mutual influence of multiple genes.

In summary, we found no evidence of an association between the Ser9Gly SNP in DRD3 and risk of schizophrenia. Studies involving larger sample sizes will be necessary to confirm the results of this meta-analysis—especially for certain ethnic subpopulations—and to address the epigenetic mechanisms and environmental influences that contribute to schizophrenia risk.

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Author contributions
All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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

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