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ORIGINAL RESEARCH

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

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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

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(ie, Ser9Gly [rs6280]). Ser9Gly is a functional SNP that yields a protein with altered dopamine-binding affinity.[13] The substitution of serine with glycine is thought to yield D3 autoreceptors with a higher affinity for dopamine and more robust intracellular signaling.[14] Other authors have associated Ser9Gly with acute pain in sickle cell disease, bipolar disorder, Parkinson's disease, and suicidal behaviors.[15–18]

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,[19,20] whereas others found no association.[21–23] These inconclusive and discordant findings have been attributed to small sample size, inclusion of various genetic backgrounds, and potential confounding bias.[24]

Meta-analysis has been applied widely as a statistical method in medical studies, particularly for topics that are studied extensively yet yield controversial results.[25] Utsunomiya et al conducted a meta-analysis in 2008 to evaluate the association between Ser9Gly and schizophrenia.[26] Their pooled results of 9 case–control studies indicated that Ser9Gly was unlikely to confer susceptibility to schizophrenia in the Japanese population.[26] In a second meta-analysis conducted in 2008, results involving 51 case–control studies indicated no association of Ser9Gly with schizophrenia.[21] 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.[27] 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.[28]

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.[25] The most suitable genetic model was ascertained from these pairwise differences. Specifically, for $OR_1 = OR_3 \neq 1$ and $OR_2 = 1$, the recessive model was selected (OR =1 means $P>0.05$;

OR ≠1 means $P<0.05$). For $OR_1 = OR_2 \neq 1$ and $OR_3 = 1$, the dominant model was considered. For $OR_2 = 1/OR_3 \neq 1$ and $OR_1 = 1$, the complete-overdominant model was presumed. Lastly, for $OR_1 > OR_2 > 1$ and $OR_1 > OR_3 > 1$ (or $OR_1 < OR_2 < 1$ and $OR_1 < OR_3 < 1$), 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. I^2 was defined as the proportion of observed variance in effect sizes attributable to true differences among studies. Conventional interpretations of I^2 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.[12,19–23,26,34–85] 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[61]	1993	China	East Asians	Population-based	25.05	RDC	0.49	0.56
Nanko et al[64]	1993	Japan	East Asians	Population-based	27.8	DSM-III-R	0.82	0.91
Jönsson et al[67]	1993	Sweden	Caucasian	Population-based	39	DSM-III-R	0.46	0.61
Nöthen et al[72]	1993	Germany	Caucasian	Population-based	–	–	–	–
Nöthen et al[73]	1993	Germany	Caucasian	Population-based	28.2	DSM-III-R	0.5	0.88
Laurent et al[45]	1994	France	Caucasian	Population-based	48	DSM-III-R	0.38	0.72
Saha et al[53]	1994	Singapore	East Asians	Population-based	38	ICD-9	–	–
Mant et al[65]	1994	UK	Caucasian	Population-based	46.6	DSM-III-R	0.74	0.8
Kennedy et al[66]	1995	North America	Caucasian	Hospital-based	–	DSM-III-R	–	–
Kennedy et al[66]	1995	Italy	Caucasian	Hospital-based	–	DSM-III-R	–	–
Inada et al[81]	1995	Japan	East Asians	Population-based	54	–	1.09	1
Durany et al[38]	1996	Spain	Caucasian	Population-based	53	ICD-10	1.38	1.44
Gaitonde et al[41]	1996	UK	Caucasian	Hospital-based	41.7	ND	0.83	0.93
Ohara et al[50]	1996	Japan	East Asians	Population-based	34.4	DSM-IV	–	1.37
Rietschel et al[51]	1996	Germany	Caucasian	Population-based	30.2	DSM-III-R	0.66	0.96
Shaikh et al[54]	1996	UK	Caucasian	Hospital-based	–	DSM-III-R	–	–
Tanaka et al[59]	1996	Japan	East Asians	Population-based	42.7	DSM-III-R	0.92	0.41
Nimgaonkar et al[20]	1996	USA	African-American	Hospital-based	–	DSM-III-R	1.24	1.33
Nimgaonkar et al[20]	1996	USA	Caucasian	Hospital-based	–	DSM-III-R	0.67	1.1
Chen et al[22]	1997	China	East Asians	Hospital-based	45	DSM-III-R	0.86	1.13
Ebstein et al[39]	1997	Italy	Caucasian	Population-based	36.5	DSM-III-R	0.31	1.03
Ebstein et al[39]	1997	Israel	Ashkenazi	Population-based	32.9	DSM-III-R	–	0.94

(*Continued*)

Table 1 (*Continued*)

References	Year	Location	Ethnicity	Controls source	Mean age of control group	Diagnostic criteria	Gender index (case)	Gender index (control)
Ebstein et al[39]	1997	Israel	Non-Ashkenazi	Population-based	32.9	DSM-III-R	–	0.94
Maziade et al[48]	1997	Canada	Caucasian	Population-based	–	DSM-III-R	0.46	–
Hawi et al[42]	1998	Ireland	Caucasian	Population-based	–	DSM-III-R	0.47	0.79
Krebs et al[92]	1998	France	Caucasian	Population-based	35.47	DSM-III-R	0.62	1
Spurlock et al[56]	1998	Ireland	Caucasian	Population-based	–	DSM-III-R	–	–
Spurlock et al[56]	1998	Northern Sweden	Caucasian	Population-based	–	DSM-III-R	–	–
Spurlock et al[56]	1998	Portugal	Caucasian	Population-based	–	DSM-III-R	–	–
Spurlock et al[56]	1998	Wales	Caucasian	Population-based	–	DSM-III-R	–	–
Spurlock et al[56]	1998	Austria	Caucasian	Population-based	–	DSM-III-R	–	–
Spurlock et al[56]	1998	France	Caucasian	Population-based	–	DSM-III-R	–	–
Ishiguro et al[43]	2000	Japan	East Asians	Population-based	47.2	DSM-III-R or ICD-10	0.74	1.07
Ishiguro et al[43]	2000	Japan	East Asians	Population-based	48.5	DSM-III-R or ICD-11	0.9	0.81
Joober et al[44]	2000	Canada	Caucasian	Hospital-based	–	DSM-IV	–	–
Meszaros et al[49]	2000	Austria	Caucasian	Population-based	–	DSM-III-R	–	–
Sivagnanasundaram et al[55]	2000	UK	Caucasian	Population-based	–	DSM-III-R	–	–
Hauser et al[77]	2000	Poland	Caucasian	Population-based	28.76	DSM-IV	–	–
Cordeiro et al[37]	2001	Brazil	Latinos	Population-based	–	ICD-10	–	–
Løvlie et al[47]	2001	India	Indians	Population-based	43	DSM-IV	–	0.83
Rybakowski et al[52]	2001	Poland	Caucasian	Population-based	27	DSM-IV, ICD-10	0.61	1.13
Anney et al[35]	2002	UK and Ireland	Caucasian	Population-based	43	DSM-IV	0.28	0.28
Ventriglia et al[60]	2002	Italy	Caucasian	Population-based	–	DSM-IV	–	–
Morimoto et al[62]	2002	Japan	East Asians	Population-based	–	ICD-10	1.14	–
Zhao et al[83]	2002	China	East Asians	Population-based	55.9	DSM-III-R	0.83	1.4
Tang et al[84]	2002	China	East Asians	Population-based	33	CCMD-II-R	0.76	1.06
Jönsson et al[71]	2003	Sweden	Caucasian	Population-based	–	DSM-III-R	–	–
Iwata et al[76]	2003	Japan	East Asians	Population-based	–	DSM-IV	–	–
Baritaki et al[36]	2004	Greece	Caucasian	Population-based	45.1	DSM-IV	0.7	0.63
Jönsson et al[63]	2004	Germany	Caucasian	Population-based	30.2	DSM-IV	0.85	0.25
A et al[82]	2004	China	East Asians	Population-based	–	–	0.63	–
Staddon et al[57]	2005	Northern Spain	Basque	Population-based	–	DSM-IV	0.54	1
Yang[93]	2005	China	East Asians	Population-based	35.04	DSM-IV	1.12	1.09
Liang[94]	2005	China	East Asians	Population-based	25	DSM-IV, CCMD-3	0.98	0.98
Talkowski et al[58]	2006	USA	Caucasian	Population-based	–	DSM-IV	–	–
Yi et al[85]	2006	China	East Asians	Population-based	35	DSM-IV	1.12	1.13
Ma et al[21]	2008	China	East Asians	Hospital-based	35.02	DSM-IV	0.62	0.81
Lorenzo et al[46]	2007	Spain	Caucasian	Population-based	–	DSM-IV	–	–
Chang et al[68]	2007	China	East Asians	Population-based	–	DSM-IV	–	–
Güzey et al[34]	2007	Italy	Caucasian	Population-based	–	DSM-IV	0.2	0.17
Fathalli et al[40]	2008	Canada, Tunisia, and Hungary	Caucasian	Hospital-based	–	DSM-III-R or DSM-IV	0.37	0.85
Utsunomiya et al[26]	2008	Japan	East Asians	Population-based	55	DSM-IV	0.92	0.92
Krelling et al[78]	2008	Brazil	Latinos	Population-based	40.27	–	–	–
Barlas et al[23]	2009	Turkey	Caucasian	Population-based	31.7	DSM-IV	0.21	0.23
Zai et al[69]	2010	Europe	Caucasian	Population-based	–	DSM-IV	0.57	0.42
Sáiz et al[75]	2010	Asturia, Northern Spain	Caucasian	Population-based	40.6	DSM-IV	0.66	0.95
Nunokawa et al[80]	2010	Japan	East Asians	Population-based	38.1	DSM-IV	0.9	0.92
Zhang et al[70]	2011	China	East Asians	Population-based	28.13	DSM-IV	–	–
Tee et al[74]	2011	Malaysia	East Asians	Population-based	38.4	–	0.91	0.83
Zheng et al[79]	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_{HWE}	Allele frequency			
	Cases, n			Controls, n				Cases, %		Controls, %	
	Ser/Ser	Ser/Gly	Gly/Gly	Ser/Ser	Ser/Gly	Gly/Gly		Ser	Gly	Ser	Gly
Crocq et al[19]	37	26	10	134	128	24	0.3930	68	32	69	31
Crocq et al[19]	37	18	13	170	153	41	0.4616	67	33	68	32
Yang et al[61]	54	45	8	56	95	24	0.1630	65	35	59	41
Nanko et al[64]	48	35	8	50	40	10	0.6300	72	28	70	30
Jönsson et al[67]	34	36	6	63	83	37	0.3154	60	40	55	45
Nöthen et al[72]	31	22	7	26	41	4	0.0193	68	32	65	35
Nöthen et al[73]	20	26	14	25	34	9	0.6289	68	32	62	38
Laurent et al[45]	35	33	8	43	47	10	0.5832	70	30	67	33
Saha et al[53]	62	66	9	34	25	4	0.8341	66	34	74	26
Mant et al[65]	33	23	10	62	41	6	0.8178	77	23	76	24
Kennedy et al[66]	37	62	18	12	14	1	0.2059	61	39	70	30
Kennedy et al[66]	42	43	12	73	84	15	0.1807	63	37	67	33
Inada et al[81]	66	40	7	34	33	10	0.6569	67	33	66	34
Durany et al[38]	53	43	11	92	119	24	0.1064	64	36	64	36
Gaitonde et al[41]	34	45	5	56	51	15	0.5255	75	25	67	33
Ohara et al[50]	1	152	0	59	58	15	0.8961	77	23	67	33
Rietschel et al[51]	61	71	14	42	43	4	0.0865	65	35	71	29
Shaikh et al[54]	33	56	20	20	27	5	0.3386	65	35	64	36
Tanaka et al[59]	54	38	8	37	40	9	0.707	69	31	66	34
Nimgaonkar et al[20]	30	22	13	51	66	15	0.3559	67	33	64	36
Nimgaonkar et al[20]	33	26	6	5	13	4	0.3874	54	46	52	48
Chen et al[22]	89	77	12	38	35	6	0.5939	78	22	70	30
Ebstein et al[39]	37	31	12	49	58	13	0.4951	66	34	65	35
Ebstein et al[39]	24	15	2	3	118	0	–	75	25	76	24
Ebstein et al[39]	20	16	10	49	42	9	1	66	34	70	30
Maziade et al[48]	41	27	2	54	34	6	0.8354	69	31	76	24
Hawi et al[42]	83	87	28	59	57	9	0.3379	70	30	69	31
Krebs et al[92]	36	42	11	57	69	7	0.0163	66	34	56	44
Spurlock et al[56]	15	16	5	25	23	8	0.4763	36	64	83	17
Spurlock et al[56]	25	29	13	28	49	8	0.042	64	36	62	38
Spurlock et al[56]	28	40	8	27	34	10	0.8928	59	41	62	38
Spurlock et al[56]	14	15	2	6	22	5	0.0546	63	37	51	49
Spurlock et al[56]	38	21	12	13	16	2	0.3137	69	31	68	32
Spurlock et al[56]	17	11	2	23	28	6	0.554	68	32	65	35
Ishiguro et al[43]	84	61	8	10	17	4	0.4375	75	25	60	40
Ishiguro et al[43]	61	31	7	67	77	12	0.1118	72	28	69	31
Joober et al[44]	44	50	12	119	127	26	0.3435	75	25	67	33
Meszaros et al[49]	45	35	15	52	43	5	0.2991	73	27	74	26
Sivagnanasundaram et al[55]	29	40	4	59	67	12	0.2476	60	40	67	33
Hauser et al[77]	62	58	9	50	40	8	1	71	29	71	29
Cordeiro et al[37]	56	57	28	19	25	4	0.2847	70	30	66	34
Løvlie et al[47]	16	29	11	291	242	51	0.9456	70	30	71	29
Rybakowski et al[52]	54	55	10	48	35	7	0.8604	72	28	73	27
Anney et al[35]	152	178	30	38	46	13	0.8753	67	33	63	37
Ventriglia et al[60]	43	51	20	88	81	19	0.9546	59	41	69	31
Morimoto et al[62]	23	21	4	34	26	4	0.7411	65	35	73	27
Zhao et al[83]	109	109	18	27	22	4	0.8681	68	32	72	28
Tang et al[84]	273	210	45	138	119	28	0.7518	67	33	69	31
Jönsson et al[71]	72	70	14	30	30	3	0.1859	63	37	71	29
Iwata et al[76]	73	64	9	27	30	8	0.9401	71	29	65	35
Baritaki et al[36]	51	46	17	70	66	27	0.098	66	34	63	37
Jönsson et al[63]	326	255	68	50	37	7	0.9657	70	30	73	23
A et al[82]	43	29	8	27	21	7	0.3735	71	29	68	32
Staddon et al[57]	59	40	10	278	267	51	0.2413	72	28	69	31

(*Continued*)

Table 2 (*Continued*)

References	Genotype distribution						P_{HWE}	Allele frequency			
	Cases, n			Controls, n				Cases, %		Controls, %	
	Ser/Ser	Ser/Gly	Gly/Gly	Ser/Ser	Ser/Gly	Gly/Gly		Ser	Gly	Ser	Gly
Yang[93]	35	28	7	377	341	50	0.019	70	30	71	29
Liang[94]	65	30	6	213	193	36	0.3993	69	31	70	30
Talkowski et al[58]	173	136	12	28	27	5	0.6699	70	30	69	31
Yi et al[85]	35	28	7	14	30	16	0.9931	55	45	48	52
Ma et al[21]	145	157	7	47	34	9	0.4449	72	28	71	29
Lorenzo et al[46]	78	82	18	66	78	13	0.1281	67	34	67	33
Chang et al[68]	120	105	31	115	75	8	0.3241	69	32	77	23
Güzey et al[34]	30	29	4	164	188	43	0.3158	62	38	65	35
Fathalli et al[40]	158	199	51	39	45	16	0.619	71	29	62	39
Utsunomiya et al[26]	120	97	29	26	15	7	0.0729	72	28	70	30
Krelling et al[78]	22	56	25	65	39	7	0.7251	71	30	76	24
Barlas et al[23]	47	37	8	15	26	20	0.2682	49	52	46	54
Zai et al[69]	66	82	15	177	162	24	0.1038	69	31	71	29
Sáiz et al[75]	103	123	39	306	243	46	0.815	71	29	72	28
Nunokawa et al[80]	301	239	54	28	19	1	0.2734	76	24	78	22
Zhang et al[70]	345	274	66	52	42	11	0.5655	79	21	70	31
Tee et al[74]	120	107	34	153	145	17	0.0195	69	31	72	28
Zheng et al[79]	133	121	26	141	89	11	0.5175	72	28	77	23
Yang et al[12]	459	343	78	50	37	7	0.9657	70	30	73	27

Note: P_{HWE} represents the *P*-value of Hardy–Weinberg equilibrium test in the genotype distribution of controls.

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.[29,86] 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

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_z	I^2 (%)	P_h	P_e
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_z, *P*-value for association test; P_h, *P*-value for heterogeneity test; P_e, *P*-value for publication bias test.
Abbreviations: OR, odds ratio; CI, confidence interval.

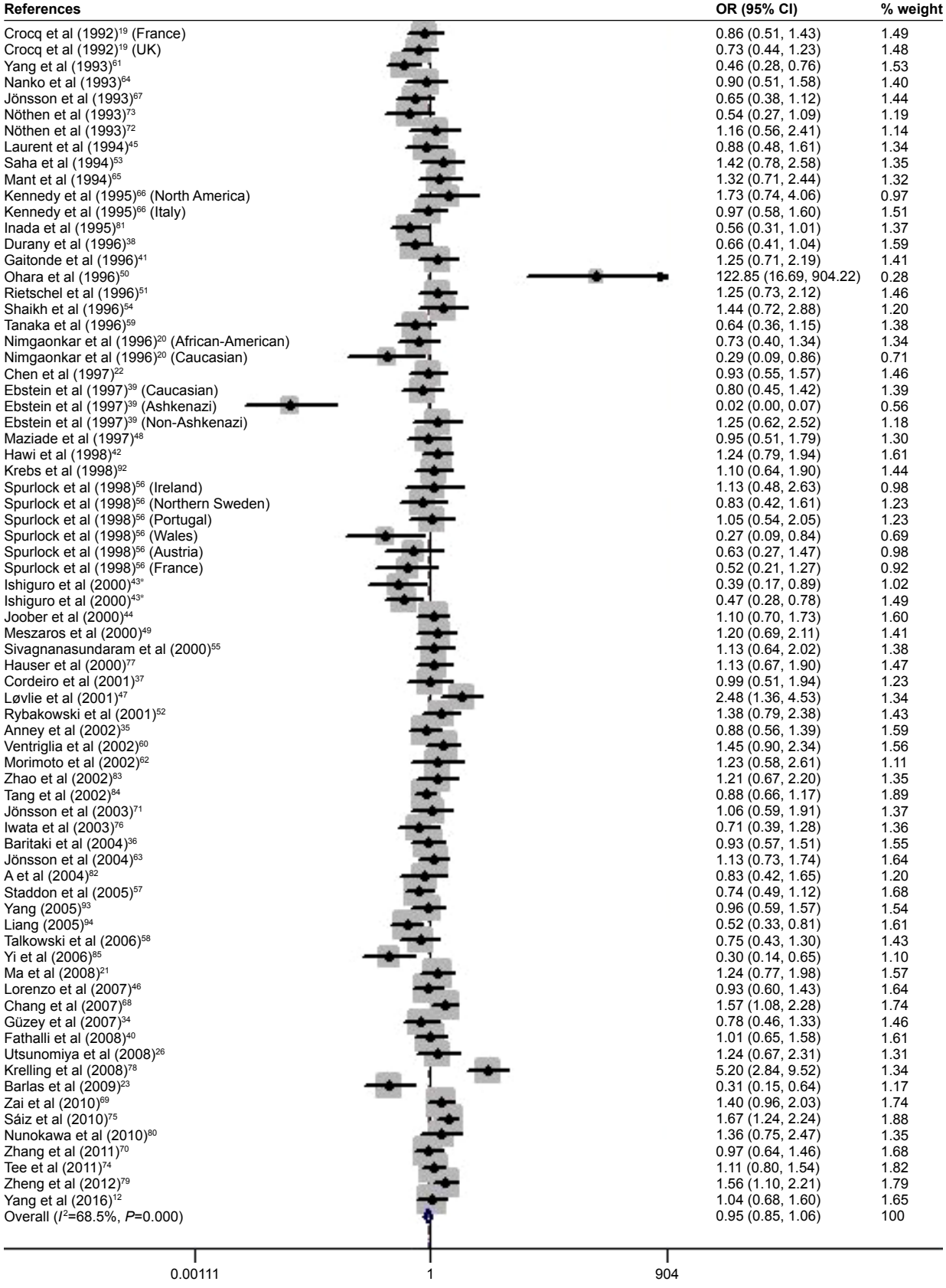

Figure 1 Forest plot of the association between the Ser9Gly polymorphism of *DRD3* and schizophrenia in the dominant genetic model (Ser/Gly + Gly/Gly vs Ser/Ser).
Notes: Weights are from random effects analysis. *After the first case-control study, there was a marginally significant association between the Ser9Gly polymorphisms and schizophrenia (P=0.02). Thus, these positive findings were replicated in an additional 99 Japanese schizophrenia patients and 132 controls.[43]
Abbreviations: OR, odds ratio; CI, confidence interval.

Table 4 Stratified analysis of the association of *DRD3* polymorphisms with schizophrenia under dominant model

Subgroup analysis	Ser9Gly					
	n	OR	95% CI	P_z	I^2 (%)	P_h
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_z, *P*-value for association test; P_h, *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.

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.

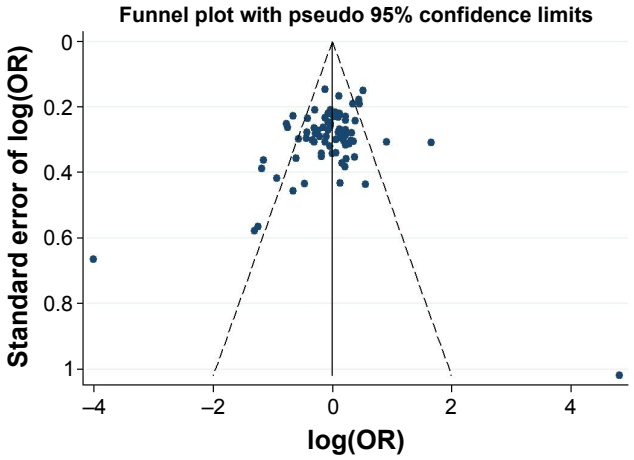

Figure 2 Funnel plot analysis depicting publication bias in the association between the Ser9Gly polymorphism of *DRD3* and schizophrenia.
Abbreviation: OR, odds ratio.

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

to a disorder that affects hospital-based control patients.[91] 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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