GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Association between Ser311Cys polymorphism in the dopamine D2 receptor gene and schizophrenia risk: a meta-analysis in Asian populations

Z.W. Liu[1]*, J.L. Liu[2]*, Y. An[3], L. Zhang[4] and Y.M. Wang[1]

[1]Department of Hospice,
Shengjing Affiliated Hospital of China Medical University,
Shenyang, Liaoning, China
[2]Department of Oncology,
Fourth Affiliated Hospital of China Medical University,
Shenyang, Liaoning, China
[3]Department of Neurology,
First Affiliated Hospital of China Medical University,
Shenyang, Liaoning, China
[4]Department of Orthopedic Surgery,
Shengjing Affiliated Hospital of China Medical University,
Shenyang, Liaoning, China

*These authors contributed equally to this study.
Corresponding author: Y.M. Wang
E-mail: cmu_jiali@126.com

Genet. Mol. Res. 11 (1): 261-270 (2012)
Received April 20, 2011
Accepted November 10, 2011
Published February 8, 2012
DOI http://dx.doi.org/10.4238/2012.February.8.1

ABSTRACT. Numerous studies have evaluated the association between Ser311Cys (rs1801028, C>G) polymorphism of the dopamine D2 receptor (DRD2) gene and schizophrenia risk. However, the specific association is still controversial. We examined whether DRD2 Ser311Cys polymorphism confers schizophrenia risk in Asian popu-

lations. Sixteen studies were retrieved reporting on a total of 2268 schizophrenia patients and 2423 healthy controls. Meta-analysis of the results showed significant associations between Ser311Cys polymorphism and schizophrenia risk in the comparisons of G versus C (odds ratio (OR) = 1.47, 95% confidence interval (CI) = 1.18-1.83, P = 0.0006) and CG+GG versus CC (OR = 1.45, 95%CI = 1.16-1.82, P = 0.001). In a subgroup analysis by nationality, we found a significant association between Ser311Cys polymorphism and schizophrenia risk in the comparisons of G versus C and CG+GG versus CC genotype in the Japanese population (OR = 1.75, 95%CI = 1.30-2.35, P = 0.0002; OR = 1.72, 95%CI = 1.27-2.33, P = 0.0004; respectively) but not in Chinese and Indian populations. In conclusion, the G allele of DRD2 Ser311Cys polymorphism involves a potential risk factor for schizophrenia in Asian populations, especially in the Japanese population.

Key words: Dopamine D2 receptor; Gene polymorphism; Schizophrenia; Meta-analysis

INTRODUCTION

Schizophrenia (SZ) is a disabling psychiatric disorder characterized by a myriad of symptoms, with a median incidence of 15.2/100,000 persons worldwide (McGrath et al., 2008). The symptoms of SZ represent multiple psychological domains, including perception, inferential thinking, language, attention, social interaction, expression of emotions, and volition (Andreasen et al., 1995). This heterogeneous and complex psychiatric disorder is caused by both genetic and environmental factors and their interactions.

Dopamine system dysfunction has been widely implicated in the pathogenesis of SZ (Glatt et al., 2003). There are five dopamine receptors (DR), grouped into two classes of D1-like (D1a and D1b) and D2-like (D2, D3 and D4) receptors (Himei et al., 2002). The dopamine receptors 2 (DRD2) is the most strongly linked to the pathogenesis of SZ and a target for antipsychotics (Seeman, 2010). Aberrant subcortical DRD2 signaling is implicated in brain disorders such as SZ, drug addiction and Parkinson's disease (Zhang et al., 2007). At present, the DRD2 gene has been highlighted as a candidate gene for susceptibility to SZ (Hori et al., 2001). Animal models of psychosis show that a variety of risk factors, genetic and nongenetic, are associated with behavioral supersensitivity to dopamine, reflected in elevated levels of DRD2 (Seeman, 2010). A large number of studies have also confirmed a significant association between DRD2 polymorphisms with SZ (Glatt et al., 2003; Jönsson et al., 2003).

The most common variant, Ser311Cys (rs1801028, C>G), has been widely investigated in SZ. Ser311Cys polymorphism is a change from Ser311 (C allele, TCC) to Cys311 (G allele, TGC) at codon 311. The C allele of Ser311Cys polymorphism is the normal allele, encoding the amino acid serine (Ser) at codon 311, whereas the G allele is the risk allele that encodes a cysteine (Cys). Most patients with Cys311 showed significantly severe thought disorder and positive symptoms of schizophrenia than those with Ser311 (Arinami et al.,

1994; Hori et al., 2001). Numerous studies have confirmed the association between DRD2 Ser311Cys polymorphism and SZ risk in Caucasian populations (Jönsson et al., 2003). However, this specific association in Asian populations remains controversial. The aim of this meta-analysis was to investigate the association between DRD2 Ser311Cys polymorphism and SZ risk in Asian populations by conducting a meta-analysis from all eligible case-control studies published to date.

MATERIAL AND METHODS

Literature search

Pubmed and Embase database searches were performed to retrieve papers linking DRD2 Ser311Cys polymorphism and susceptibility to SZ in Asian populations available by October 2010 without language restrictions, using the following query: ["Receptors, Dopamine D2" or "Dopamine D2 receptor" or "DRD2"] and ["Polymorphism, Genetic" or "Polymorphism, Single-Stranded Conformational" or "Polymorphism, Single Nucleotide" or "Polymorphism, Restriction Fragment Length" or "Amplified Fragment Length Polymorphism Analysis" or "DNA Copy Number Variations"] and ["Schizophrenia" or "Schizophrenia, Childhood" or "Schizophrenia, Disorganized" or "Schizophrenia, Paranoid" or "Schizophrenia, Catatonic" or "Schizophrenia and Disorders with Psychotic Features" or "Schizotypal Personality Disorder"]. The reference lists of major textbooks, review articles, and included articles were identified through manual searches to find other potentially eligible studies.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they met the following criteria: i) case-control studies that addressed SZ patients and healthy controls; ii) studies that evaluated the association between DRD2 Ser311Cys polymorphism and SZ risk in Asian populations; iii) all patients with clinically diagnosed SZ according to DSM-III/IV criteria; iv) studies that included sufficient genotype data for extraction; v) genotype frequency of healthy controls were in Hardy-Weinberg equilibrium (HWE). Studies were excluded when: i) not case-control studies that evaluated the association between DRD2 Ser311Cys polymorphism and SZ risk in Asian populations; ii) case reports, letters, reviews, and editorial articles; iii) studies that were based on incomplete raw data and no usable data reported; iv) duplicate data were contained in the studies; v) family-based design; vi) healthy controls were not in HWE.

Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers (Z.W. Liu and J.L. Liu) to populate the necessary information. From each of the included articles the following information was extracted: first author, year of publication, country, nationality, study design, diagnostic criteria, source of controls, number of cases and controls, detection methods, genotype frequency and evidence of HWE in controls. For conflicting evaluations, an agreement was reached following a discussion.

Statistical analysis

Meta-analysis was performed using the Review Manager version 5.0.24 (provided by The Cochrane Collaboration) and STATA package version 9.2 (Stata Corporation, College Station, TX, USA). The following contrasts for DRD2 Ser311Cys polymorphism were evaluated: the comparison of variant allele with ancestral allele (G allele *vs* C allele); the comparison of each homozygote with the other combined with heterozygote (CC *vs* CG+GG; GG *vs* CC+CG), the comparison of ancestral homozygote with heterozygote and variant homozygote (GG *vs* CC; GG *vs* CG). The strength of the associations between DRD2 Ser311Cys polymorphism and SZ risk was estimated by odds ratio (OR) and 95% confidence interval (95%CI). Between-study heterogeneities were estimated using the Cochran Q-test (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005). We also quantified the effect of heterogeneity by using the I^2 test. I^2 ranges between 0 and 100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. When a significant Q-test ($P < 0.10$) or $I^2 > 50\%$ indicated heterogeneity across studies, the random effects model was used for meta-analysis, or else the fixed effects model was used (Viechtbauer, 2007). We tested whether genotype frequencies of controls were in HWE using the χ^2 test. Subgroup analysis based on nationality was used to explore and to explain the diversity among the results of different studies. Sensitivity analysis was mainly performed by sequential omission of individual studies. Publication bias was investigated by Begg's funnel plot, and funnel plot asymmetry was assessed by the Egger linear regression test (Peters et al., 2006); statistical significance was considered when the P value of the Egger test was <0.05. All the P values were two-sided. To ensure the reliability and the accuracy of the results, two reviewers (Z.W. Liu and J.L. Liu) populated the data in the statistic software programs independently and got the same results.

RESULTS

Studies included in the meta-analysis

The search strategy retrieved 240 potentially relevant studies. According to the inclusion criteria, 16 studies with full texts were included in this meta-analysis (Itokawa et al., 1993; Hattori et al., 1994; Nanko et al., 1994; Arinami et al., 1994, 1996; Chen et al., 1996; Ohara et al., 1996; Tanaka et al., 1996; Fujiwara et al., 1997; Harano, 1997; Kaneshima et al., 1997; Hori et al., 2001; Himei et al., 2002; Morimoto et al., 2002; Gupta et al., 2009; Fan et al., 2010) and 224 studies were excluded. The flow chart of study selection is summarized in Figure 1. These 16 case-control studies selected included a total of 2268 SZ cases and 2423 healthy controls. All studies were case-control studies, which evaluated the association of DRD2 Ser311Cys polymorphism and susceptibility to SZ. The publishing year of the included studies ranged from 1993 to 2010. All patients fulfilled DSM-III/IV criteria for the diagnosis of SZ. The source of controls was based on a healthy population. The HWE test was performed on the genotype distribution of the controls in all studies included, all of them showed to be in HWE ($P > 0.05$). The baseline characteristics and methodological quality of all studies included are summarized in Table 1. The genotype distribution and risk allele frequency are summarized in Table 2.

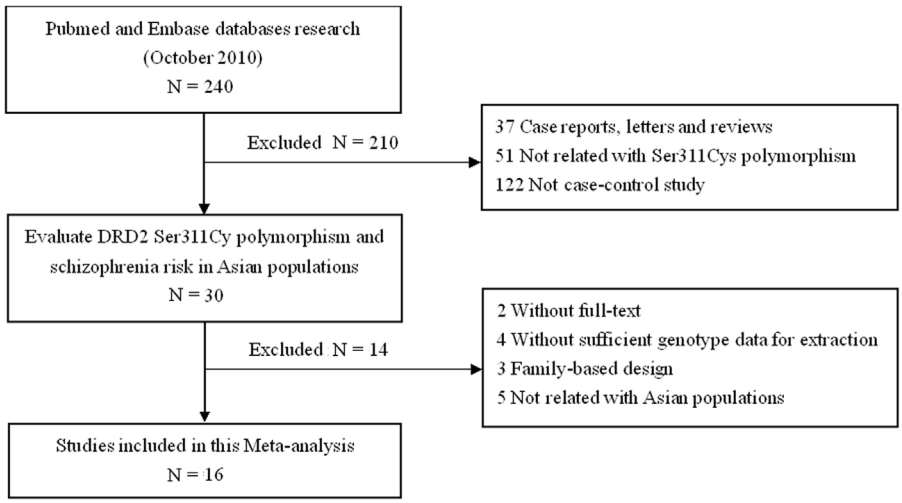

Figure 1. Flow diagram of study selection procedure.

Table 1. Baseline characteristics of the studies included in meta-analysis.

First author (year)	Country	Ethnicity	Study design	Source of controls	Detection method	Number of patients		Quality score
						Cases	Controls	
Itokawa (1993)	Japan	Japanese	Case-control	Population-based	PCR-SSP	50	110	18
Arinami (1994)	Japan	Japanese	Case-control	Population-based	PCR-SSP	156	300	19
Hattori (1994)	Japan	Japanese	Case-control	Population-based	PCR-RFLP	100	100	17
Nanko (1994)	Japan	Japanese	Case-control	Population-based	PCR-SSP	100	100	18
Arinami (1996)	Japan	Japanese	Case-control	Population-based	PCR-SSP	136	279	19
Chen (1996)	China	Chinese	Case-control	Population-based	PCR-SSP	114	88	20
Ohara (1996)	Japan	Japanese	Case-control	Population-based	PCR-SSP	153	121	22
Tanaka (1996)	Japan	Japanese	Case-control	Population-based	PCR-SSP	106	106	21
Fujiwara (1997)	Japan	Japanese	Case-control	Population-based	PCR-SSP	52	26	19
Harano (1997)	Japan	Japanese	Case-control	Population-based	PCR-SSP	70	101	23
Kaneshima (1997)	Japan	Japanese	Case-control	Population-based	PCR-SSP	78	112	21
Hori (2001)	Japan	Japanese	Case-control	Population-based	PCR-SSP	241	201	24
Himei (2002)	Japan	Japanese	Case-control	Population-based	PCR-RFLP	190	103	25
Morimoto (2002)	Japan	Japanese	Case-control	Population-based	PCR-SSP	48	48	24
Gupta (2009)	India	Indian	Case-control	Population-based	PCR-SSP	254	225	23
Fan (2010)	China	Chinese	Case-control	Population-based	PCR-SSP	420	403	26

PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; SSP = single-strand polymorphism.

Main results, subgroup and sensitivity analysis

A summary of the meta-analysis findings of the association between the DRD2 Ser311Cys polymorphism and SZ risk are provided in Table 3. Meta-analysis results identified a significant association between DRD2 Ser311Cys polymorphism and SZ risk in the comparisons of G versus C and CG+GG versus CC (Figure 2). However, no association was found in the comparisons of GG versus CC+CG, G versus CC and GG versus CG. In the subgroup analysis based on nationality, the studies included were divided into Japanese, Chinese and Indian populations; results showed a significant association between

DRD2 Ser311Cys polymorphism and SZ risk in the comparisons of G versus C and CG+GG versus CC in the Japanese population. Nevertheless, no significant association was detected in the comparisons of GG versus CC+CG, G versus CC and GG versus CG in the Japanese population. Unfortunately, no association was found between DRD2 Ser311Cys polymorphism and SZ risk in all comparisons in both Chinese and Indian populations. Sensitivity analysis was performed by sequential omission of individual studies. The significance of pooled OR in all individual analyses and subgroup analyses was not influenced excessively by omitting any single study.

Table 2. Genotype distribution and risk allele frequency of all studies included.

First author (year)	Genotype distribution										HWE test in controls	
	Case					Control					χ^2	P value
	No.	CC	CG	GG	G (frequency)	No.	CC	CG	GG	G (frequency)		
Itokawa (1993)	50	46	3	1	0.040	110	105	5	0	0.023	0.059	0.808
Arinami (1994)	156	140	15	1	0.054	300	289	11	0	0.018	0.112	0.738
Hattori (1994)	100	92	8	0	0.040	100	96	4	0	0.020	0.042	0.838
Nanko (1994)	100	92	8	0	0.040	100	96	4	0	0.020	0.042	0.838
Arinami (1996)	136	125	11	0	0.040	279	268	11	0	0.020	0.112	0.738
Chen (1996)	114	109	5	0	0.020	88	86	2	0	0.010	0.048	0.827
Ohara (1996)	153	152	1	0	0.003	121	118	3	0	0.012	0.024	0.878
Tanaka (1996)	106	97	9	0	0.042	106	98	8	0	0.038	0.161	0.688
Fujiwara (1997)	52	50	2	0	0.019	26	25	1	0	0.019	0.010	0.919
Harano (1997)	70	62	8	0	0.057	101	93	8	0	0.040	0.169	0.681
Kaneshima (1997)	78	74	4	0	0.026	112	105	7	0	0.031	0.119	0.730
Hori (2001)	241	218	22	1	0.050	201	193	8	0	0.020	0.082	0.774
Himei (2002)	190	175	15	0	0.049	103	97	6	0	0.029	0.094	0.760
Morimoto (2002)	48	45	3	0	0.031	48	45	3	0	0.031	0.051	0.821
Gupta (2009)	254	208	42	4	0.098	225	186	37	2	0.091	0.011	0.915
Fan (2010)	420	387	32	1	0.040	403	377	26	0	0.032	0.456	0.499

HWE = Hardy-Weinberg equilibrium. All $P < 0.05$ was considered to be statistically significant.

Table 3. Meta-analysis of the association between Ser311Cys polymorphism and SZ risk.

Comparison	OR	95%CI	P value	Heterogeneity		Effects model
				I^2	P value	
G versus C	1.47	1.18-1.83	0.0006	0%	0.60	Fixed
Japanese	1.75	1.30-2.35	0.0002	0%	0.67	
Chinese	1.32	0.81-2.17	0.27	0%	0.62	
Indian	1.09	0.71-1.68	0.70	-	-	
CG+GG versus CC	1.45	1.16-1.82	0.001	0%	0.65	Fixed
Japanese	1.72	1.27-2.33	0.0004	0%	0.72	
Chinese	1.30	0.78-2.15	0.32	0%	0.60	
Indian	1.05	0.66-1.69	0.82	-	-	
GG versus CC+CG	0.89	0.40-2.02	0.79	43%	0.12	Fixed
Japanese	0.60	0.21-1.67	0.32	64%	0.04	
Chinese	2.89	0.12-71.04	0.52	-	-	
Indian	1.78	0.32-9.83	0.51	-	-	
GG versus CC	0.35	0.11-1.12	0.08	0%	0.94	Fixed
Japanese	0.21	0.03-1.36	0.10	0%	0.90	
Chinese	0.34	0.01-8.43	0.51	-	-	
Indian	0.56	0.10-3.09	0.50	-	-	
GG versus CG	0.49	0.15-1.63	0.24	0%	0.98	Fixed
Japanese	0.44	0.06-3.05	0.41	0%	0.84	
Chinese	0.41	0.02-10.45	0.59	-	-	
Indian	0.57	0.10-3.28	0.53	-	-	

OR = odds ratio; 95%CI = 95% confidence interval.

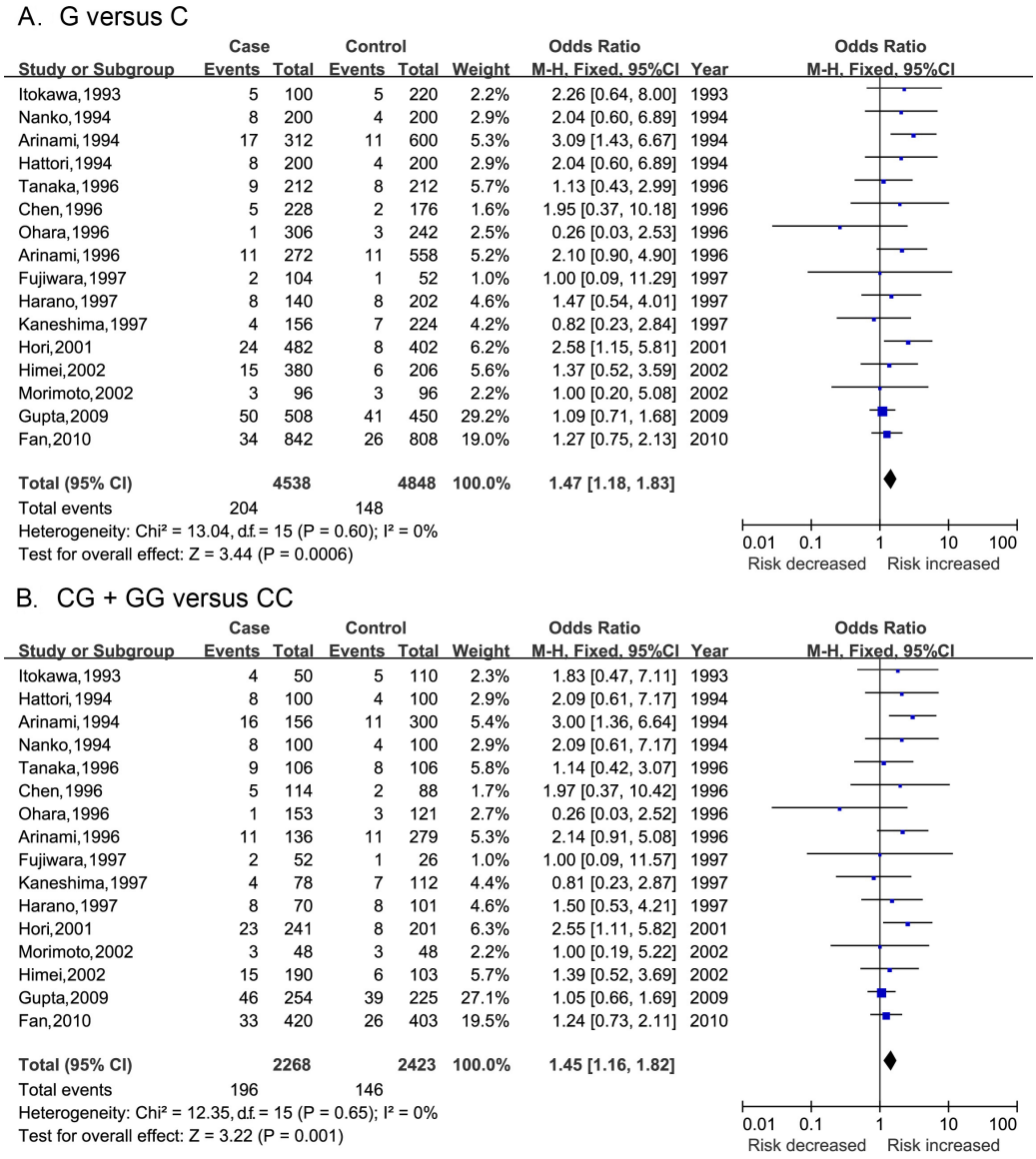

Figure 2. Forest plots for statistically significant meta-analysis.

Publication bias

Publication bias of the literature was accessed by Begg's funnel plot and the Egger linear regression test. The Egger linear regression test was used to measure the asymmetry of the funnel plot. The results of the Egger linear regression test are shown in Table 4. Results showed that there was no publication bias (all $P > 0.05$).

Table 4. Evaluation of publication bias by the Egger linear regression test.

Comparison	Coefficient	Standard error	*t*	P > |t|	95%CI
G versus C	0.12	0.56	0.22	0.83	-1.07-1.32
CG+GG versus CC	0.08	0.56	0.15	0.89	-1.12-1.28
GG versus CC+CG	0.28	2.15	0.13	0.90	-5.70-6.25
GG versus CC	-1.13	0.47	-2.43	0.09	-2.61-0.35
GG versus CG	-0.37	0.51	-0.72	0.52	-1.99-1.25

DISCUSSION

It has been well documented that heredity plays an important role in the pathophysiology of SZ (Fan et al., 2010). A number of family, twin, and animal studies have suggested that genetic factors may contribute to the development of SZ (Sawa and Snyder, 2002). However, the specific genes involved in the genetic mechanism and etiology of SZ have yet to be identified. A large number of studies have confirmed a significant association between DRD2 polymorphisms and SZ (Glatt et al., 2003; Jönsson et al., 2003). Biochemistry and pharmacology studies have also strongly suggested that SZ may be a result of dysfunction of the dopaminergic system (Fatemi and Folsom, 2009). During the last ten years, associations between polymorphisms involved in the promoter region of DRD2 gene and SZ risk have been also reported in many molecular genetic studies. However, the specific associations in Asian populations are still controversial.

In the current study, we quantitatively assessed the association between DRD2 Ser311Cys polymorphism and SZ risk in Asian populations. Finally, 16 case-control studies were included with a total of 2268 SZ patients and 2423 healthy controls. The main meta-analysis results showed a significant association between DRD2 Ser311Cys polymorphism and susceptibility to SZ in Asian populations. There were significant differences in the comparisons of G versus C and CG+GG versus CC, which indicated that the G allele of DRD2 Ser311Cys polymorphism might be a potential risk factor for SZ. In the subgroup analysis by nationality, a significant association was found between DRD2 Ser311Cys polymorphism and SZ risk in the comparisons of G versus C and CG+GG versus CC in the Japanese population but not in Chinese and Indian populations, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in.

There were some limitations in our meta-analysis. First, some relevant studies could not be included in our analysis due to incomplete raw data. Secondly, we were not able to address the sources of heterogeneity among all studies. Thirdly, differences in racial descent of the population investigated might cause different results. Our subgroup analysis by nationality confirmed that only the Japanese population showed a significant result, but there are not enough studies available to confirm a significant association in other Asian populations. In addition, although all cases and controls of each study were well defined with similar inclusion criteria, there may be potential factors that were not taken into account that may have influenced our results. Most important of all, meta-analysis is a type of retrospective study and is limited by the qualities of primary studies.

In conclusion, our meta-analysis demonstrates that the G allele of DRD2 Ser311Cys polymorphism might be a potential risk factor for SZ in Asian populations, especially in the Japanese population. As the number of eligible studies was limited in this meta-analysis, these results still need further investigation.

ACKNOWLEDGMENTS

We would like to thank Wu Yan (Department of Dermatology, First Affiliated Hospital of China Medical University) for her valuable contribution and kindly revising the manuscript.

REFERENCES

Andreasen NC, Arndt S, Alliger R, Miller D, et al. (1995). Symptoms of schizophrenia. Methods, meanings, and mechanisms. *Arch. Gen. Psychiatry* 52: 341-351.

Arinami T, Itokawa M, Enguchi H, Tagaya H, et al. (1994). Association of dopamine D2 receptor molecular variant with schizophrenia. *Lancet* 343: 703-704.

Arinami T, Itokawa M, Aoki J, Shibuya H, et al. (1996). Further association study on dopamine D2 receptor variant S311C in schizophrenia and affective disorders. *Am. J. Med. Genet.* 67: 133-138.

Chen CH, Chien SH and Hwu HG (1996). No association of dopamine D2 receptor molecular variant Cys311 and schizophrenia in Chinese patients. *Am. J. Med. Genet.* 67: 418-420.

Fan H, Zhang F, Xu Y, Huang X, et al. (2010). An association study of DRD2 gene polymorphisms with schizophrenia in a Chinese Han population. *Neurosci. Lett.* 477: 53-56.

Fatemi SH and Folsom TD (2009). The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophr. Bull* 35: 528-548.

Fujiwara Y, Yamaguchi K, Tanaka Y, Tomita H, et al. (1997). Polymorphism of dopamine receptors and transporter genes in neuropsychiatric diseases. *Eur. Neurol.* 38 (Suppl 1): 6-10.

Glatt SJ, Faraone SV and Tsuang MT (2003). Meta-analysis identifies an association between the dopamine D2 receptor gene and schizophrenia. *Mol. Psychiatry* 8: 911-915.

Gupta M, Chauhan C, Bhatnagar P, Gupta S, et al. (2009). Genetic susceptibility to schizophrenia: role of dopaminergic pathway gene polymorphisms. *Pharmacogenomics* 10: 277-291.

Harano M (1997). Ser-311-Cys polymorphism of the dopamine D2 receptor gene and schizophrenia - an analysis of schizophrenic patients in Fukuoka. *Kurume Med. J.* 44: 201-208.

Hattori M, Nanko S, Dai XY, Fukuda R, et al. (1994). Mismatch PCR RFLP detection of DRD2 Ser311Cys polymorphism and schizophrenia. *Biochem. Biophys. Res. Commun.* 202: 757-763.

Higgins JP and Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat. Med.* 21: 1539-1558.

Himei A, Koh J, Sakai J, Inada Y, et al. (2002). The influence on the schizophrenic symptoms by the DRD2Ser/Cys311 and -141C Ins/Del polymorphisms. *Psychiatry Clin. Neurosci.* 56: 97-102.

Hori H, Ohmori O, Shinkai T, Kojima H, et al. (2001). Association analysis between two functional dopamine D2 receptor gene polymorphisms and schizophrenia. *Am. J. Med. Genet.* 105: 176-178.

Itokawa M, Arinami T, Futamura N, Hamaguchi H, et al. (1993). A structural polymorphism of human dopamine D2 receptor, D2(Ser311→Cys). *Biochem. Biophys. Res. Commun.* 196: 1369-1375.

Jönsson EG, Sillen A, Vares M, Ekholm B, et al. (2003). Dopamine D2 receptor gene Ser311Cys variant and schizophrenia: association study and meta-analysis. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 119B: 28-34.

Kaneshima M, Higa T, Nakamoto H and Nagamine M (1997). An association study between the Cys311 variant of dopamine D2 receptor gene and schizophrenia in the Okinawan population. *Psychiatry Clin. Neurosci.* 51: 379-381.

McGrath J, Saha S, Chant D and Welham J (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol. Rev.* 30: 67-76.

Morimoto K, Miyatake R, Nakamura M, Watanabe T, et al. (2002). Delusional disorder: molecular genetic evidence for dopamine psychosis. *Neuropsychopharmacology* 26: 794-801.

Nanko S, Hattori M, Dai XY, Fukuda R, et al. (1994). DRD2 Ser311/Cys311 polymorphism in schizophrenia. *Lancet* 343: 1044.

Ohara K, Nakamura Y, Xie DW, Ishigaki T, et al. (1996). Polymorphisms of dopamine D2-like (D2, D3, and D4) receptors in schizophrenia. *Biol. Psychiatry* 40: 1209-1217.

Peters JL, Sutton AJ, Jones DR, Abrams KR, et al. (2006). Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 295: 676-680.

Sawa A and Snyder SH (2002). Schizophrenia: diverse approaches to a complex disease. *Science* 296: 692-695.

Seeman P (2010). Dopamine D2 receptors as treatment targets in schizophrenia. *Clin. Schizophr. Relat. Psychoses* 4: 56-73.

Tanaka T, Igarashi S, Onodera O, Tanaka H, et al. (1996). Lack of association between dopamine D2 receptor gene

Cys311 variant and schizophrenia. *Am. J. Med. Genet.* 67: 208-211.
Viechtbauer W (2007). Confidence intervals for the amount of heterogeneity in meta-analysis. *Stat. Med.* 26: 37-52.
Zhang Y, Bertolino A, Fazio L, Blasi G, et al. (2007). Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. *Proc. Natl. Acad. Sci. U. S. A.* 104: 20552-20557.
Zintzaras E and Ioannidis JP (2005). Heterogeneity testing in meta-analysis of genome searches. *Genet. Epidemiol.* 28: 123-137.