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Letter to the Editor

Case-control study and meta-analysis of Ser311Cys polymorphism in the *DRD2* gene demonstrate lack of association with risk for schizophrenia in the Japanese population

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Dear Dr. Duarte,

Liu et al. (2012) recently reported a meta-analysis showing an association between the Ser311Cys polymorphism (rs1801028) in the dopamine D2 receptor (*DRD2*) gene and schizophrenia in Asian populations (odds ratio [OR] = 1.47, 95% confidence interval [CI] = 1.18-1.83), which was particularly strong in the Japanese population (OR = 1.75, 95%CI =

1.30-2.35). However, their meta-analysis included studies in the Japanese population with overlapping subjects and a Japanese study that did not include genotype frequencies to test deviations from Hardy-Weinberg equilibrium (HWE; Table 1). In addition, earlier studies in the Japanese population were performed with relatively small sample sizes (N = 78-870). To systematically assess whether *DRD2* Ser311Cys polymorphism confers increased susceptibility to schizophrenia in the Japanese population, we carried out a case-control study of the largest sample examined to date (N = 1312) and we conducted an updated meta-analysis (N = 3484).

Table 1. Case-control association studies between *DRD2* Ser311Cys polymorphism and schizophrenia in the Japanese population.

Case-control study	Meta-analysis		Notes
	Liu et al. (2012)	Current meta-analysis	
Itokawa et al. (1993)	Included	Excluded	Overlap with Arinami et al. (1996)
Arinami et al. (1994)	Included	Excluded	Overlap with Arinami et al. (1996)
Nanko et al. (1994)	Included	Excluded	Overlap with Hattori et al. (1994)
Hattori et al. (1994)	Included	Included	
Arinami et al. (1996)	Included	Included	
Ohara et al. (1996)	Included	Included	
Tanaka et al. (1996)	Included	Excluded	Overlap with current study
Fujiwara et al. (1997)	Included	Included	
Harano (1997)	Included	Included	
Kaneshima et al. (1997)	Included	Included	
Hori et al. (2001)	Included	Excluded	Lack of genotype frequencies
Himei et al. (2002)	Included	Included	Overlap with Tsutsumi et al. (2011)
Morimoto et al. (2002)	Included	Included	
Tsutsumi et al. (2011)	Not included	Excluded	HWE deviation in controls as well as patients
Current study	Not included	Included	

DRD2 = dopamine receptor D2; HWE = Hardy-Weinberg equilibrium.

Our study was approved by the Ethics Committee of Genetics at the Niigata University School of Medicine, and written informed consent was obtained from all participants. All participants were unrelated and of Japanese descent. The study population comprised 648 patients with schizophrenia (348 men and 300 women; mean age 39.8 ± 13.8 years), diagnosed according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition criteria, and 664 mentally healthy individuals (337 men and 327 women; mean age 38.4 ± 10.8 years), with no personal or family history (within first-degree relatives) of psychiatric disorders. These individuals partially overlapped with those in a report by Tanaka et al. (1996). Patient and control groups were matched for gender. However, differences in mean age between the groups were relatively small (1.4 years). A psychiatric assessment of each participant was conducted, as previously described (Watanabe et al., 2006).

We genotyped Ser311Cys using the TaqMan 5'-exonuclease assay (Applied Biosystems, Foster City, CA, USA), as previously described (Fukui et al., 2011). HWE deviations were tested using the χ^2 test for goodness of fit. Genotypic and allelic associations were tested using the Cochran-Armitage test for trends and the χ^2 test, respectively. A fixed effects model meta-analysis was performed using CATMAP (http://cran.r-project.org/src/contrib/Archive/catmap/), as previously described (Watanabe et al., 2007). A probability level of $P < 0.05$ indicated statistical significance. A power calculation was performed using the Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/).

The genotype distributions of Ser311Cys did not deviate significantly from HWE in either group (Table 2). There was no significant association between Ser311Cys and schizophrenia. In the meta-analysis, we included nine independent case-control studies of the Japanese population (Table 1). Six studies were excluded because of overlap with other reports (Itokawa et al., 1993; Arinami et al., 1994; Nanko et al., 1994; Tanaka et al., 1996), lack of genotype frequencies (Hori et al., 2001), or HWE deviation in controls as well as patients (Tsutsumi et al., 2011). The analysis did not reveal a significant association between Ser311Cys and schizophrenia, without heterogeneity across studies (Table 3).

Table 2. Genotype and allele frequencies of the *DRD2* Ser311Cys polymorphism in the current study.

Patients						Controls						P	
N	P for HWE	Genotype			MAF	N	P for HWE	Genotype			MAF	Genotype	Allele
		Ser/Ser	Ser/Cys	Cys/Cys				Ser/Ser	Ser/Cys	Cys/Cys			
648	0.689	607	40	1	0.032	664	0.883	617	46	1	0.036	0.601	0.599

DRD2 = dopamine receptor D2; HWE = Hardy-Weinberg equilibrium; MAF = minor allele frequency.

Table 3. Meta-analysis of case-control association studies between the *DRD2* Ser311Cys polymorphism and schizophrenia in the Japanese population.

Study	Patients			Controls			OR	95%CI
	N	Ser	Cys	N	Ser	Cys		
Hattori et al. (1994)	100	193	7	100	192	8	0.87	0.31-2.45
Arinami et al. (1996)	291	553	29	579	1133	25	2.38	1.38-4.10
Ohara et al. (1996)	153	305	1	121	239	3	0.26	0.03-2.53
Fujiwara et al. (1997)	52	102	2	26	51	1	1.00	0.09-11.3
Harano (1997)	70	132	8	101	194	8	1.47	0.54-4.01
Kaneshima et al. (1997)	78	152	4	112	217	7	0.82	0.23-2.84
Himei et al. (2002)	190	365	15	103	200	6	1.37	0.52-3.59
Morimoto et al. (2002)	48	93	3	48	93	3	1.00	0.20-5.08
Current study	648	1254	42	664	1280	48	0.89	0.59-1.36
Pooled[a]	1630			1854			1.20	0.92-1.58

DRD2 = dopamine receptor D2; OR = odds ratio; CI = confidence interval. [a]$\chi^2 = 1.77$, d.f. = 1, P = 0.184 for the association; $Q = 10.7$, d.f. = 8, P = 0.219 for the heterogeneity.

Our case-control study and updated meta-analysis did not provide evidence supporting the contribution of the *DRD2* Ser311Cys polymorphism to schizophrenia susceptibility in the Japanese population. However, considering the relatively small total sample size (1630 patients and 1854 controls) and low frequencies of the Cys allele (0.012-0.040 in controls), the findings of our meta-analysis should be interpreted with caution. Approximately 2000 patients and 2000 controls are needed to adequately detect an association with a power of 0.80 and an α of 0.05, assuming a disease prevalence of 0.01, a risk allele frequency of 0.036, and the genotypic relative risk of 1.38 under the dominant model of inheritance (Glatt and Jönsson, 2006). Thus, further studies should be performed using larger sample sizes.

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