Polymorphisms of *DRD2* and *DRD3* genes and Parkinson's disease: A meta-analysis

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Abstract. Parkinson's disease (PD) is the second most common neurodegenerative disorder that affects ~2% of the population aged ≥65 years. The degeneration of dopamine neurons in the substantia nigra contributes to the pathogenesis of PD. *Dopamine receptor D2* (*DRD2*) and *dopamine receptor D3* (*DRD3*) are two key subtypes of dopamine receptors. The aim of our study was to evaluate the association between the polymorphisms of *DRD2* and *DRD3* genes and PD. Meta-analyses were conducted from 16 studies (46 stages) among 4,279 cases and 5,661 controls between PD and 9 polymorphisms (*DRD2*: rs1800497, rs1079597, rs6278, rs6279, rs273482, rs1799732 and rs1076563; *DRD3*: rs6280 and rs2134655). A significant association was observed between *DRD3* rs2134655 polymorphism and PD [P=0.01, odds ratio (OR)=1.17, 95% confidence interval (CI): 1.03-1.32] and a borderline association was observed between *DRD2* rs1800497 polymorphism and PD in Europeans (P=0.05, OR=1.13, 95% CI: 1.00-1.27). Findings of the current meta-analysis suggested that *DRD3* rs2134655 polymorphism was associated with a 17% increased risk of PD and that *DRD2* rs1800497 polymorphism had a potential to increase the risk of PD by 13% in Europeans. Future large-scale studies are required to confirm the ethnic difference of *DRD2* rs1800497 polymorphism and to determine whether there were significant associations of PD with other polymorphisms in *DRD2* and *DRD3* genes.

Introduction

Parkinson's disease (PD, OMIM: 168600) is the second most common neurodegenerative disorder that increases the social and economic burden on societies. PD affects ~2% of the population aged ≥65 years (1,2). The clinical features of PD are resting tremor, muscular rigidity, bradykinesia and postural instability (3). PD can cause pain (4), depression (5,6), visual hallucinations (7), dementia (8) and other non-motor symptoms (9-12).

Environmental and genetic factors may be involved in the pathogenesis of PD. The environmental hypothesis was dominant for much of the 20th century (3). Environmental factors such as encephalitis (13), oxidative stress (14), smoking and coffee (15) and environmental toxins (16) were found to be significantly associated with PD. Recent genetic studies have identified a few genetic markers of PD (17-19), however, the etiology of PD remains unclear.

Findings of previous studies suggested that the degeneration of dopamine neurons in the substantia nigra contributes to the pathogenesis of PD (20,21). Dopamine is a major modulatory neurotransmitter in the central nervous system (CNS) and thus affects neuroendocrine secretion (20), which was shown to be associated with smoking, a well-known risk factor of PD (22-24). There are five subtypes of G-protein-coupled dopamine receptors (*DRD1-5*) comprising D-1-like (*DRD1* and *DRD5*) and D-2-like (*DRD2-4*). Among these subtypes, *DRD2* (25-36) located on chromosome 11q23 and *DRD3* (33,35-40) located on chromosome 3q13.3 are the most studied in the association tests of PD.

Previous case-control studies showed inconsistent results between PD and the two dopamine receptor genes (*DRD2* and *DRD3*). These discrepancies may be due to different ethnic background, or sample size difference (41), or the uncorrected physiological status among various association studies (42). Meta-analysis is a robust method for application to enhance

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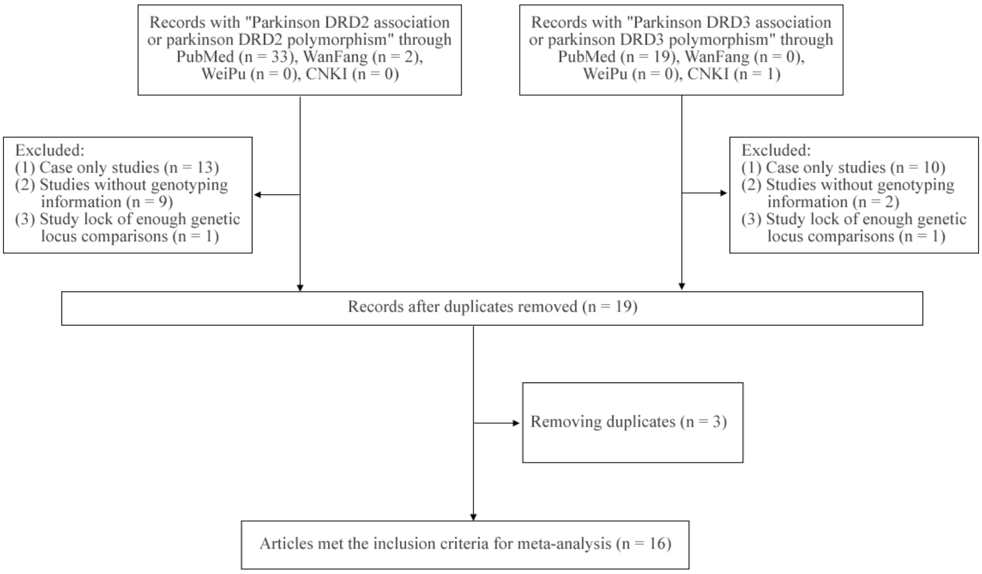
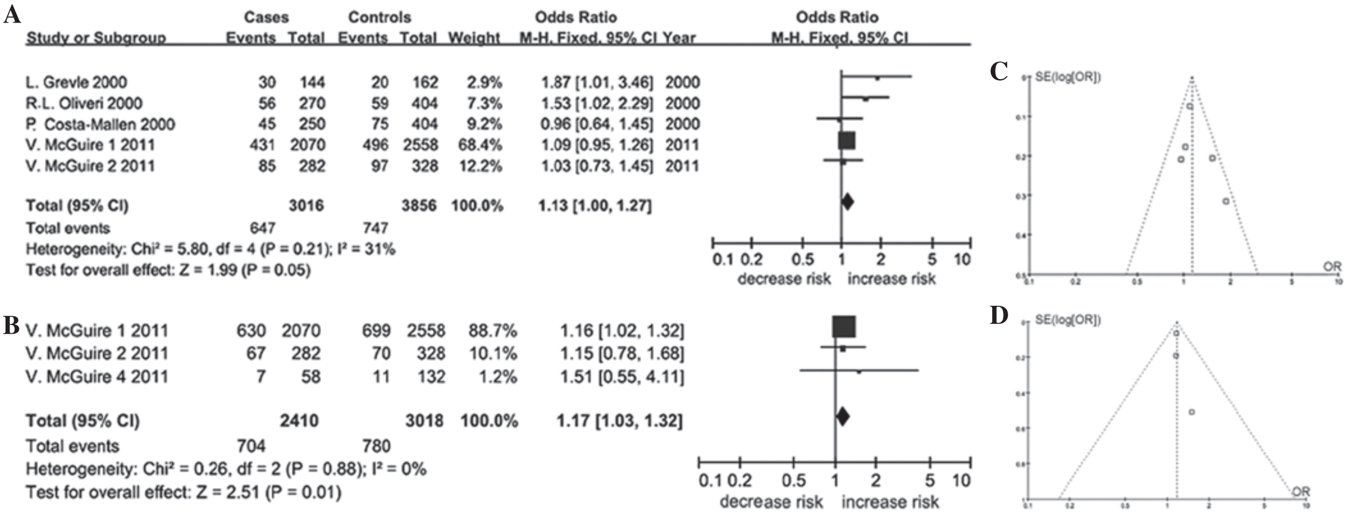


Figure 1. Flowchart of the selection process in the meta-analyses.



Study or Subgroup	Cases Events	Cases Total	Controls Events	Controls Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
L. Grevle 2000	30	144	20	162	2.9%	1.87 [1.01, 3.46]	2000
R.L. Oliveri 2000	56	270	59	404	7.3%	1.53 [1.02, 2.29]	2000
P. Costa-Mallen 2000	45	250	75	404	9.2%	0.96 [0.64, 1.45]	2000
V. McGuire 1 2011	431	2070	496	2558	68.4%	1.09 [0.95, 1.26]	2011
V. McGuire 2 2011	85	282	97	328	12.2%	1.03 [0.73, 1.45]	2011
Total (95% CI)		**3016**		**3856**	**100.0%**	**1.13 [1.00, 1.27]**	
Total events	647		747				

Heterogeneity: Chi² = 5.80, df = 4 (P = 0.21); I² = 31%
Test for overall effect: Z = 1.99 (P = 0.05)

V. McGuire 1 2011	630	2070	699	2558	88.7%	1.16 [1.02, 1.32]
V. McGuire 2 2011	67	282	70	328	10.1%	1.15 [0.78, 1.68]
V. McGuire 4 2011	7	58	11	132	1.2%	1.51 [0.55, 4.11]
Total (95% CI)		**2410**		**3018**	**100.0%**	**1.17 [1.03, 1.32]**
Total events	704		780			

Heterogeneity: Chi² = 0.26, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.51 (P = 0.01)

Figure 2. Forest plots and funnel plots of *DRD2* rs1800497 and *DRD3* rs2134655 polymorphisms with Parkinson's disease (PD). (A) Forest plot of *DRD2* rs1800497 polymorphism with PD. (B) Forest plot of *DRD3* rs2134655 polymorphism with PD. (C) Funnel plot of *DRD2* rs1800497 polymorphism with PD. (D) Funnel plot of *DRD3* rs2134655 polymorphism with PD.

statistical power and to draw a more convincing conclusion through the pooling of data from each of the involved studies (43). The aim of this meta-analysis was to evaluate the contribution of *DRD2* and *DRD3* gene polymorphisms to PD and to determine the causes of the inconsistent results among various case-control association studies.

Materials and methods

Data collection. Studies were selected through a search of PubMed by using the combinations, including 'Parkinson *DRD2* association or Parkinson *DRD2* polymorphism' and 'Parkinson *DRD3* association or Parkinson *DRD3* polymorphism'. Studies were included if they met the following criteria: i) It was an original case-control study with an assessment of the association of *DRD2* and *DRD3* genes with PD in humans; ii) it contained sufficient information to infer the odd ratios (ORs) and 95% confidence intervals (CIs); and iii) the genotype distribution of each polymorphism in controls met the Hardy-Weinberg equilibrium (HWE). We extracted and calculated the following information from each study: Genetic locus, first author's name, year of publication, country, ethnicity, number of cases and controls, HWE for controls, reported association results and power of each case-control study.

Statistical analysis. The Arlequin program was used to test HWE (44). Statistical heterogeneity across studies included in the meta-analysis was assessed by Cochran's Q statistic and I^2 test (45). In our meta-analysis, the fixed-effect model was used for the studies with minimal to moderate heterogeneity (I^2<50%) and the random-effect model was used for the studies with significant heterogeneity (I^2≥50%). Funnel plots were also drawn to observe the potential publication bias. Statistical analyses of meta-analyses were carried out by

Table I. Characteristics of the case-control studies in the current meta-analyses.

Genetic locus	First author	Year	Ethnicity	Cases/controls	HWE	Results[a]	Power	(Refs.)
DRD2 rs1800497	Costa-Mallen *et al*	2000	Europeans	125/202	Yes	NS	0.154	(27)
DRD2 rs1800497	Grevle *et al*	2000	Europeans	72/81	Yes	S	0.085	(26)
DRD2 rs1800497	Oliveri *et al*	2000	Europeans	135/202	Yes	NS	0.139	(25)
DRD2 rs1800497	Tan *et al*	2003	Asians	209/216	Yes	NS	0.258	(29)
DRD2 rs1800497	Chen	2006	Asians	180/387	Yes	NS	0.293	(30)
DRD2 rs1800497	Singh *et al*	2008	Asians	70/100	Yes	NS	0.125	(31)
DRD2 rs1800497	Lee *et al*	2009	Asians	402/558	Yes	NS	0.496	(33)
DRD2 rs1800497	Li	2009	Asians	166/170	Yes	NS	0.218	(32)
DRD2 rs1800497	Kiyohara *et al*	2011	Asians	238/369	Yes	NS	0.335	(34)
DRD2 rs1800497	Lee *et al*	2011	Asians	500/559	Yes	NS	0.545	(35)
DRD2 rs1800497	McGuire *et al* 1	2011	Europeans	1,035/1,279	Yes	NS	0.708	(36)
DRD2 rs1800497	McGuire *et al* 2	2011	Europeans	141/164	Yes	NS	0.181	(36)
DRD2 rs1800497	McGuire *et al* 3	2011	Asians	120/226	No	NS	0.201	(36)
DRD2 rs1800497	McGuire *et al* 4	2011	Africans	29/66	Yes	S	0.089	(36)
DRD2 rs1079597	Oliveri *et al*	2000	Europeans	135/202	Yes	S	0.119	(25)
DRD2 rs1079597	Costa-Mallen *et al*	2000	Europeans	152/231	Yes	NS	0.146	(27)
DRD2 rs1079597	Kelada *et al*	2002	Europeans	179/290	Yes	NS	0.174	(28)
DRD2 rs1079597	Tan *et al*	2003	Asians	204/216	Yes	NS	0.26	(29)
DRD2 rs1079597	Chen	2006	Asians	180/387	Yes	NS	0.297	(30)
DRD2 rs1079597	Singh *et al*	2008	Asians	70/100	Yes	NS	0.121	(31)
DRD2 rs1079597	Li	2009	Asians	166/170	Yes	NS	0.217	(32)
DRD2 rs1076563	McGuire *et al* 1	2011	Europeans	1,035/1,279	Yes	NS	0.844	(36)
DRD2 rs1076563	McGuire *et al* 2	2011	Europeans	141/164	Yes	NS	0.2	(36)
DRD2 rs1076563	McGuire *et al* 3	2011	Asians	120/226	Yes	NS	0.119	(36)
DRD2 rs1076563	McGuire *et al* 4	2011	Africans	29/66	Yes	NS	0.089	(36)
DRD2 rs6279	McGuire *et al* 1	2011	Europeans	1,035/1,279	Yes	NS	0.797	(36)
DRD2 rs6279	McGuire *et al* 2	2011	Europeans	141/164	Yes	NS	0.191	(36)
DRD2 rs6279	McGuire *et al* 3	2011	Asians	120/226	No	NS	0.207	(36)
DRD2 rs6279	McGuire *et al* 4	2011	Africans	29/66	No	NS	0.089	(36)
DRD2 rs6278	McGuire *et al* 1	2011	Europeans	1,035/1,279	Yes	NS	0.628	(36)
DRD2 rs6278	McGuire *et al* 2	2011	Europeans	141/164	No	NS	0.153	(36)
DRD2 rs6278	McGuire *et al* 3	2011	Asians	120/226	No	NS	0.201	(36)
DRD2 rs6278	McGuire *et al* 4	2011	Africans	29/66	Yes	NS	0.071	(36)
DRD2 rs273482	McGuire *et al* 1	2011	Europeans	1,035/1,279	Yes	NS	0.798	(36)
DRD2 rs273482	McGuire *et al* 2	2011	Europeans	141/164	Yes	NS	0.196	(36)
DRD2 rs273482	McGuire *et al* 3	2011	Asians	120/226	No	NS	0.207	(36)
DRD2 rs273482	McGuire *et al* 4	2011	Africans	29/66	No	NS	0.089	(36)
DRD2 rs1799732	McGuire *et al* 1	2011	Europeans	1,035/1,279	No	NS	0.463	(36)
DRD2 rs1799732	McGuire *et al* 2	2011	Europeans	141/164	Yes	NS	0.147	(36)
DRD2 rs1799732	McGuire *et al* 3	2011	Asians	120/226	Yes	NS	0.134	(36)
DRD2 rs1799732	McGuire *et al* 4	2011	Africans	29/66	Yes	NS	0.084	(36)
DRD3 rs6280	Nanko *et al*	1993	Europeans	60/90	Yes	NS	0.111	(37)
DRD3 rs6280	Nanko *et al*	1994	Asians	70/81	Yes	NS	0.104	(38)
DRD3 rs6280	Higuchi *et al*	1995	Asians	70/70	Yes	NS	0.439	(39)
DRD3 rs6280	Lee *et al*	2009	Asians	398/558	Yes	NS	0.485	(33)
DRD3 rs6280	Wang *et al*	2000	Asians	122/104	Yes	NS	0.141	(40)
DRD3 rs6280	Lee *et al*	2011	Asians	497/558	Yes	NS	0.835	(35)
DRD3 rs6280	McGuire *et al* 1	2011	Europeans	1,035/1,279	Yes	NS	0.201	(36)
DRD3 rs6280	McGuire *et al* 2	2011	Europeans	141/164	Yes	S	0.178	(36)
DRD3 rs6280	McGuire *et al* 3	2011	Asians	120/226	Yes	NS	0.074	(36)
DRD3 rs6280	McGuire *et al* 4	2011	Africans	29/66	Yes	NS	0.11	(36)

Table I. Continued.

Genetic locus	First author	Year	Ethnicity	Cases/controls	HWE	Results[a]	Power	(Refs.)
DRD3 rs2134655	McGuire *et al* 1	2011	Europeans	1,035/1,279	Yes	S	0.791	(36)
DRD3 rs2134655	McGuire *et al* 2	2011	Europeans	141/164	Yes	NS	0.157	(36)
DRD3 rs2134655	McGuire *et al* 3	2011	Asians	120/226	No	NS	0.189	(36)
DRD3 rs2134655	McGuire *et al* 4	2011	Africans	29/66	Yes	NS	0.07	(36)

[a]The association between *DRD2* and *DRD3* genes and Parkinson's disease. HWE, Hardy-Weinberg equilibrium; *DRD2*, *dopamine receptor D2*; NS, not significant; S, significant; *DRD3*, *dopamine receptor D3*.

Table II. Meta-analyses of the eight polymorphisms *DRD2*: rs1079597, rs6278, rs6279, rs273482, rs1799732 and rs1076563; *DRD3*: rs6280 and rs2134655 with Parkinson's disease.

Genetic locus	Cases/controls	Amount of stages	OR (95% CI)	P-value	I^2 (%)	Power
DRD2 rs1079597 (G vs. A)	1,086/1,506	7	1.11 (0.97-1.25)	0.12	25.00	0.855
DRD3 rs6280 (G vs. A)	2,542/3,192	10	1.04 (0.96-1.13)	0.33	0.00	0.996
DRD3 rs2134655 (A vs. G)	1,205/1,509	3	1.17 (1.03-1.32)	0.01	0.00	0.847
DRD2 rs6278 (T vs. G)	1,064/1,345	2	0.45 (0.04-4.94)	0.51	68.00	0.637
DRD2 rs6279 (G vs. C)	1,176/1,443	2	1.03 (0.92-1.16)	0.57	0.00	0.851
DRD2 rs273482 (G vs. C)	1,064/1,345	2	0.99 (0.88-1.22)	0.91	46.00	0.825
DRD2 rs1799732 (D vs. C)	290/456	3	0.94 (0.72-1.24)	0.67	0.00	0.313
DRD2 rs1076563 (G vs. T)	1,325/1,735	4	0.96 (0.86-1.07)	0.44	0.00	0.941

DRD2, *dopamine receptor D2*; *DRD3*, *dopamine receptor D3*; OR, odds ratio; CI, confidence interval; NA, not applicable.

Table III. Meta-analyses of *DRD2* rs1800497 polymorphism with Parkinson's disease.

Genetic locus	Cases/controls	Ethnicity	Amount of stages	OR (95% CI)	P-value	I^2 (%)	Power
DRD2 rs1800497 (T vs. C)	3,297/4,353	Overall	13	0.97 (0.84-1.13)	0.73	73.00	0.999
	1,508/1,928	Europeans	5	1.13 (1.00-1.27)	0.05	31.00	0.862
	1,789/2,425	Asians	8	0.87 (0.71-1.06)	0.16	76.00	0.983

DRD2, *dopamine receptor D2*; OR, odd ratio; CI, confidence interval.

Review Manager 5 (46). The power of each study was calculated by the Power and Sample Size Calculation program (47).

Results

As shown in Fig. 1, 33 relevant studies of *DRD2* and 19 studies of *DRD3* were included from PubMed. In addition, we also retrieved two articles on *DRD2* gene from the Chinese Wangfang database and one article on *DRD3* gene from the China National Knowledge Internet. Following removal of three duplicates, 16 articles for the current meta-analysis (Table I) (25-40). Moreover, nine stages (36) (Table I) were excluded with significant deviation from HWE ($P<0.05$). Altogether there were 4,279 PD patients and 5,661 controls in the current meta-analyses of 9 polymorphisms (Tables II and III).

As shown in Tables II and III, no significant associations were observed in the meta-analyses of five *DRD2* polymorphisms. A further subgroup study by ethnicity showed a borderline association between *DRD2* rs1800497 polymorphism and PD in Europeans ($P=0.05$, $OR=1.13$, 95% CI: 1.00-1.27; Table III and Fig. 2). Significant results was found in the meta-analysis of *DRD3* rs2134655 polymorphism ($P=0.01$, $OR=1.17$, 95% CI: 1.03-1.32; Table II and Fig. 2). No significant results were observed in other meta-analyses. There was no publication bias for any of the meta-analyses (Figs. 2 and 3).

As shown in Tables II and III, there was no statistically significant heterogeneity ($I^2<50\%$) in the meta-analyses of five *DRD2* polymorphisms (rs1079597, rs6279, rs273482, rs1799732 and rs1076563) and two *DRD3* polymorphisms (rs6280 and rs2134655). Significant heterogeneity was observed in *DRD2* rs1800497 ($I^2=73\%$) and *DRD2* rs6278

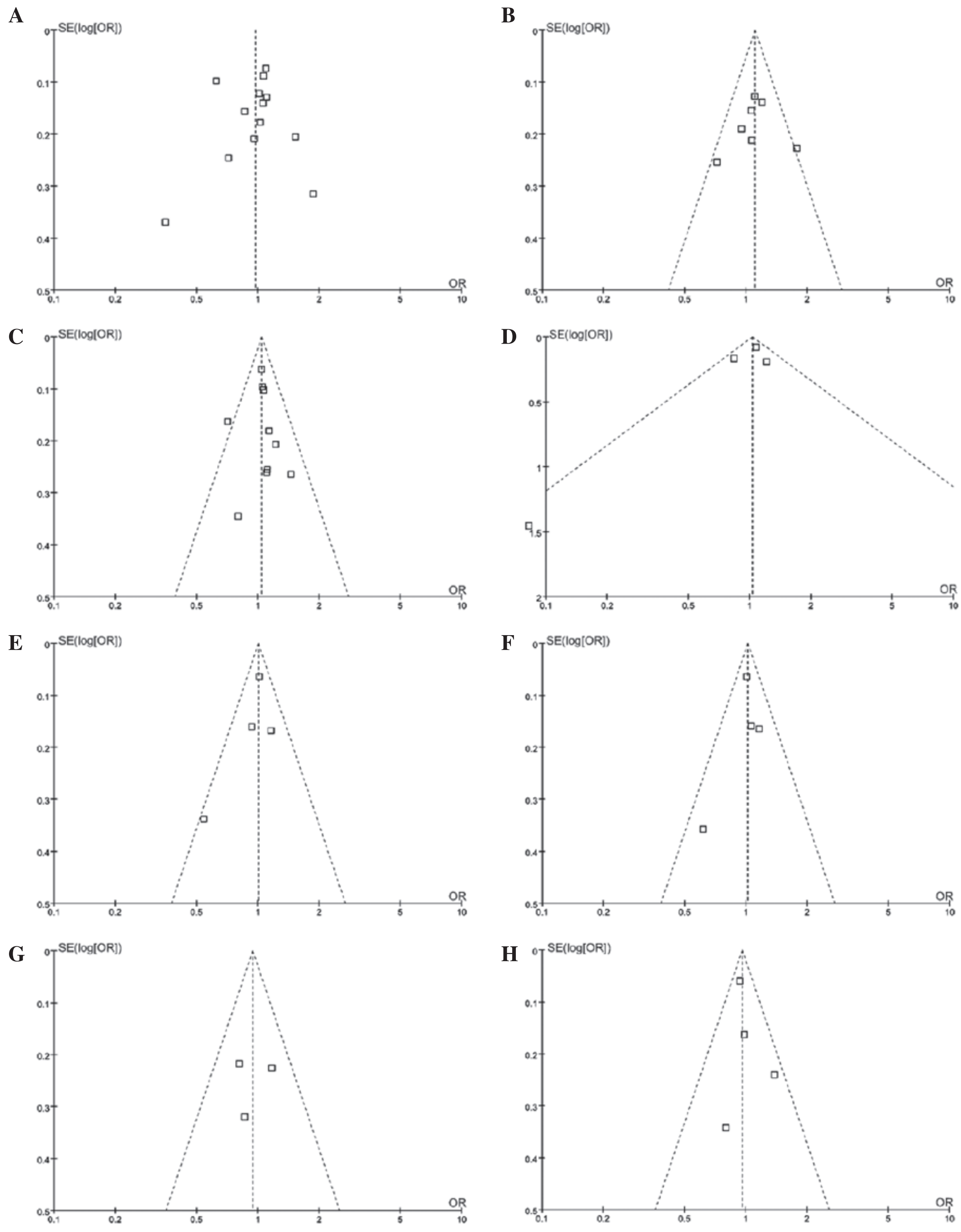


Figure 3. (A) Funnel plot of *DRD2* rs1800497 polymorphism with Parkinson's disease (PD). (B) Funnel plot of *DRD2* rs1079597 polymorphism with PD. (C) Funnel plot of *DRD3* rs6280 polymorphism with PD. (D) Funnel plot of *DRD2* rs6278 polymorphism with PD. (E) Funnel plot of *DRD2* rs6279 polymorphism with PD; (F) Funnel plot of *DRD2* rs273482 polymorphism with PD; (G) Funnel plot of *DRD2* rs1799732 polymorphism with PD; (H) Funnel plot of *DRD2* rs1076563 polymorphism with PD.

(I^2=68%). The allele frequency of rs1800497-G in Asians (HapMap-HCB) is 0.512 which is much lower to the 0.805 in Europeans (HapMap-CEU). A further analysis of the rs1800497 polymorphism showed a moderate ethnic difference between Asians and Europeans (Fst=0.1). Since there existed different genotypic distribution of rs1800497 polymorphism between Asians and Europeans, we performed subgroup ethnic meta-analyses for the two populations. A significant heterogeneity was found in Asians (I^2=76%, Table III), which may be explained by various types of allele frequency in Asians (HapMap-CHB=0.223, HapMap-JPT=0.349 and HapMap-CHD=0.310).

Power analyses showed that sufficient power (power>0.8) for the meta-analyses of five *DRD2* polymorphisms (rs1800497, rs1079597, rs6279, rs273482 and rs1076563) and two *DRD3* polymorphisms (rs6280 and rs2134655). The results also indicated that there was a lack of power for the meta-analyses of *DRD2* rs6278 (power=0.637) and rs1799732 (power=0.313) polymorphisms.

Discussion

In the current meta-analysis, we summarized the associations of *DRD2* (n=7) and *DRD3* (n=2) gene variants with PD from 16 studies (46 stages) among 4,279 cases and 5,661 controls. Our meta-analyses demonstrated a borderline significant association with PD for *DRD2* rs1800497 in Europeans and a significant association with PD for *DRD3* rs2134655. Previous studies have shown that the *DRD2* rs1800497-T allele reduced *DRD2* density in the postmortem brain (48) and decreased dopamine activity in the CNS (49), which may play an important role in the pathogenesis of PD. *DRD3* rs2134655 was a C to T transition that showed significant associations with neurological diseases such as schizophrenia (50).

Our study was the only meta-analysis for *DRD2* and *DRD3* gene polymorphisms in PD with strict selection criteria. Although power analyses showed our meta-analyses have much larger power than that of each of the individual studies, we did not exclude the possibility of false-negative results in the meta-analyses for *DRD2* rs6278 (power=0.637) and rs1799732 (power=0.313). We excluded 9 stages that failed to meet HWE in their control samples (36). We also performed subgroup analyses by ethnicity for *DRD2* rs1800497, rs1079597 and *DRD3* rs6280.

Our study has several limitations that need to be carefully considered. Firstly, although the power in most meta-analyses is sufficient, the number of involved stages in the Europeans was limited for polymorphisms (including rs2134655 of *DRD3* gene; and rs1800497, rs1076563, rs1799732, rs6278, rs6279 and rs273482 of the *DRD2* gene). Studies with a larger sample size are therefore needed. Secondly, factors such as gender, age and other different physiological status of PD patients may have influenced the result of our study and partially explain the discrepancies in the involved case-control studies. Future case-control studies may need to provide detailed information to better estimate the contribution of these factors to PD susceptibility. Thirdly, we have performed multiple association tests for the 9 polymorphisms, however, we did not provide correction of P-values that cause false-positive results in our findings. Additionally, genetic heterogeneity may exist for the polymorphisms of *DRD2* and *DRD3* genes. There are 134 polymorphisms in *DRD2* and 88 polymorphisms in *DRD3*. Our meta-analyses only focused on 9 polymorphisms that might not fully represent the overall contribution of *DRD2* and *DRD3* gene polymorphisms. Analyses of other polymorphisms in *DRD2* and *DRD3* genes are required in future investigations to evaluate their contribution to PD.

In conclusion, our meta-analysis observed a borderline significant association of *DRD2* rs1800497 polymorphism with PD in Europeans and a significant association of *DRD3* rs2134655 with PD. Large-scale well-designed studies are required in future to evaluate the polymorphisms of *DRD2* and *DRD3* genes that might contribute to the risk of PD.

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