Association between monoamine oxidase B A644G polymorphism and Parkinson's disease risk: a meta-analysis in the Chinese population

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ABSTRACT. Although various individual studies have evaluated the correlation between monoamine oxidase B (MAOB), polymorphism, and Parkinson's disease (PD), the results remain inconclusive. Therefore, we performed a meta-analysis in the Chinese population to provide comprehensive data on the association between the MAOB polymorphism and PD. Eligible studies were identified via databases such as PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure, and Chinese Biology Medicine, throughout November 2015. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strengths of these associations. Eight studies documenting a total of 1385 cases of PD and 1426 controls were

included in this meta-analysis. Overall, no significant association was found between the MAOB A644G polymorphism and PD risk in the Chinese population. However, in subgroup analyses, where results were stratified by geographical areas and source of controls, increased risk for PD in Northern China was observed (allele A *vs* G: OR = 1.33, 95%CI = 1.11-1.58; AA *vs* GG: OR = 1.46, 95%CI = 1.09-1.97; AA + AG *vs* GG: OR = 1.42, 95%CI = 1.06-1.90). Similarly, population-based studies also showed significant association between the MAOB A644G polymorphism and PD risk among different populations (allele A *vs* G: OR = 1.29, 95%CI = 1.11-1.51; AA *vs* GG: OR = 1.41, 95%CI = 1.09-1.82; AA + AG *vs* GG: OR = 1.34, 95%CI = 1.04-1.71). In conclusion, this meta-analysis provided evidence that the MAOB A644G polymorphism may contribute to PD development in Northern China. Further studies conducted in other ethnic groups are required for definite conclusions.

Key words: Meta-analysis; Monoamine oxidase B; Polymorphism; Parkinson's disease

INTRODUCTION

Parkinson's disease (PD), a common neurodegenerative disorder characterized by bradykinesia, muscle rigidity, postural instability, and resting tremor, is the second most prevalent neurodegenerative disease after Alzheimer's disease, and affects more than 1% of the elderly population (Löhle and Reichmann, 2011; Lieu et al., 2013; Chen et al., 2015). A previous study estimated that China has 2 million people with PD, which is approximately 48% of all individuals with PD in the world's 15 most populous countries (Dorsey et al., 2007); this number is expected to increase to 5 million by the year 2030 (Chen et al., 2015). Despite recent therapeutic advances, there is currently no preventive or curative therapy for PD. The exact etiology of PD remains poorly understood; however, it is recognized that genetic factors play an important role in its pathogenesis.

Many common low-penetrant genes have been identified as potential PD susceptibility genes. Of these genes, an important one is monoamine oxidase B (MAOB), which is potentially relevant to PD due to its role in catabolism of dopamine and generation of reactive oxidative free radicals (Riederer et al., 1989; Fahn and Cohen, 1992). The MAOB gene is located on the X chromosome. Its single-stranded conformational polymorphism occurs in intron 13, and leads to a transitional conversion from adenine (A) to guanine (G) 36 bp upstream from the 5'-end of exon 14 (A644G, rs1799836). An association between the MAOB polymorphism and PD in the Caucasian population was first reported by Kurth et al. (1993). Many studies have thereafter attempted to clarify this relationship; however, no definite consensus has been reached. Differences in study results may be due to ethnic and clinical heterogeneity of the patients studied, as well as the limited number of patients included in each study. Meta-analysis combines the available evidence from a number of studies, which may provide a robust result. Therefore, to address the associations between the MAOB polymorphism and PD risk, we performed a meta-analysis of all eligible studies performed in the Chinese population.

MATERIAL AND METHODS

Search strategy and selection criteria

We searched for publications that investigated the association between the MAOB polymorphism and PD using databases such as PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure, and Chinese Biology Medicine. The search terms used were as follows: 1) monoamine oxidase B, MAOB; 2) Parkinson disease; and 3) Chinese, China, Taiwan. Search terms were also combined, to generate more results. Additional studies were identified via manual screening of the reference lists from the original studies or review articles. No publication date or language restrictions were applied during article selection.

Our inclusion criteria were as follows: 1) the case-control or cohort study describes the association between the MAOB A644G polymorphism and PD; 2) the study provides the distribution of the MAOB A644G polymorphism in patients and controls; 3) the study consists of Chinese participants only. Studies were excluded if they 1) were duplicate publications; 2) were meta-analyses, letters, meeting abstracts, reviews, or editorial articles, 3) had incomplete data, 4) or lacked controls.

Data extraction

Data from all included publications were extracted by 2 independent investigators, and a consensus was reached following discussions. Titles and abstracts of all potentially relevant articles were screened to determine their relevance. Full articles were examined if the title and abstract were ambiguous. Data were recorded as follows: first author's surname, year of publication, geographic areas, source of controls, sample size, and number of subjects with MAOB A644G genotypes.

Statistical analysis

Statistical analysis was conducted using the Stata 10.0 software (StataCorp., College Station, TX, USA), and $\alpha = 0.05$ was applied as the significance level. The strength of association was estimated by means of odds ratio (OR) and its 95% confidence interval (CI). The statistical significance of pooled ORs was examined by the Z-test. Genetic heterogeneity was evaluated by Q-tests with $P < 0.10$. The Hardy-Weinberg equilibrium of control subjects was calculated using the goodness-of-fit test, and a deviation was defined when $P < 0.05$. We used the fixed-effect model and the random-effect model based on the Mantel-Haenszel and the DerSimonian and Laird method, respectively, to evaluate the sensitivity of our analysis. To explore potential sources of heterogeneity, stratified analyses according to geographic areas and source of controls were also performed.

RESULTS

Description of included studies

Figure 1 illustrates the literature search process in the form of a flow chart. We

identified 128 articles that investigated the association between the MAOB polymorphism and risk of PD in various databases. After screening the titles and abstracts, 117 articles were excluded according to the exclusion criteria described. Of the 11 potentially relevant articles identified for full-study retrieval (Hwang et al., 1997; Shao et al., 2001; Wu et al., 2001; Jiang et al., 2004; Gu et al., 2010; Wang and Zhang, 2010; Li, 2011; Zeng et al., 2012; Zhang et al., 2013; Hao et al., 2015; Song et al., 2015), 3 were excluded owing to being duplicate studies or lacking controls (Zeng et al., 2012; Hao et al., 2015; Song et al., 2015). Finally, 8 studies (Hwang et al., 1997; Shao et al., 2001; Wu et al., 2001; Jiang et al., 2004; Gu et al., 2010; Wang and Zhang, 2010; Li, 2011; Zhang et al., 2013) met the inclusion criteria. The publication years of the studies ranged from 1997 to 2013. In total, 1385 cases of PD and 1426 controls were included in this meta-analysis. The characteristics of these studies are summarized in Table 1.

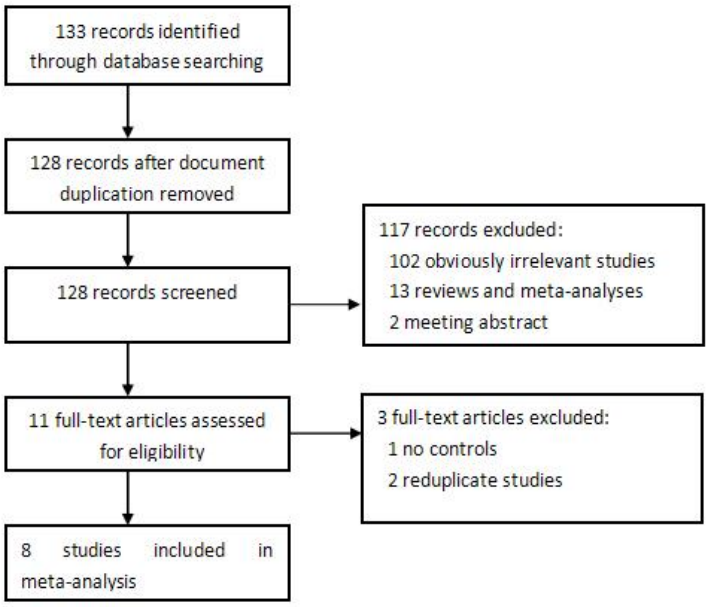

Figure 1. Flow diagram of the literature search.

Table 1. Characteristics of studies included in the meta-analysis.

References (first author)	Source of controls	Geographic areas	Cases (N)	Controls (N)	Cases			Controls			HWE	
					AA	AG	GG	AA	AG	GG	χ^2	P value
Hwang, 1997	PB	Taiwan	65	108	49	11	5	76	19	13	23.52	0.00
Shao, 2001	PB	Guangdong	126	136	65	25	36	62	34	40	32.20	0.00
Wu, 2001	PB + HB	Taiwan	220	191	169	14	37	158	16	17	76.24	0.00
Jiang, 2004	PB	Beijing	266	154	207	31	28	114	13	27	87.09	0.00
Gu, 2010	PB	Beijing	176	354	153	23		323	31			
Wang, 2010	PB	Tianjin	125	66	88	23	14	34	19	13	8.52	0.00
Li, 2011	PB	Hebei	166	170	111	24	31	103	30	37	58.06	0.00
Zhang, 2013	PB	Xinjiang	241	247	177	34	30	179	32	36	91.99	0.00

PB = population-based; HB = hospital-based.

Meta-analysis

Table 2 lists the primary results of our meta-analysis. We did not find elevated PD risk in any of the evaluated models. However, when we stratified our analysis based on geographical areas, increased PD risk was found in individuals from Northern China (A *vs* G: OR = 1.33, 95%CI = 1.11-1.58; AA *vs* GG: OR = 1.46, 95%CI = 1.09-1.97; AA + AG *vs* GG: OR = 1.42, 95%CI = 1.06-1.90); however, this increase was not observed in those from Southern China. In the subgroup analysis based on source of controls, significant association was found in population-based studies (A *vs* G: OR = 1.29, 95%CI = 1.11-1.51; AA *vs* GG: OR = 1.41, 95%CI = 1.09-1.82; AA + AG *vs* GG: OR = 1.34, 95%CI = 1.04-1.71).

Table 2. Association between the monoamine oxidase B A644G gene polymorphism and Parkinson's disease susceptibility.

Analysis model		OR_r (95%CI)	OR_f (95%CI)	P_h	
A *vs* G	Total analysis	7	1.19 (0.92-1.53)	1.16 (1.00-1.33)	0.005
	Population-based	6	1.30 (1.11-1.52)	1.29 (1.11-1.51)	0.396
	Southern China	3	0.96 (0.59-1.58)	0.92 (0.73-1.16)	0.016
	Northern China	4	1.35 (1.08-1.69)	1.33 (1.11-1.58)	0.201
AA *vs* GG	Total analysis	7	1.24 (0.87-1.76)	1.19 (0.94-1.50)	0.047
	Population-based	6	1.41 (1.09-1.82)	1.41 (1.09-1.82)	0.685
	Southern China	3	0.92 (0.45-1.85)	0.86 (0.59-1.25)	0.057
	Northern China	4	1.47 (1.09-1.98)	1.46 (1.09-1.97)	0.476
AA *vs* AG	Total analysis	7	1.19 (0.93-1.53)	1.19 (0.93-1.52)	0.483
	Population-based	6	1.19 (0.90-1.57)	1.18 (0.91-1.54)	0.359
	Southern China	3	1.28 (0.84-1.93)	1.28 (0.84-1.93)	0.887
	Northern China	4	1.17 (0.76-1.76)	1.14 (0.84-1.55)	0.166
AA *vs* (AG + GG)	Total analysis	8	1.12 (0.87-1.44)	1.11 (0.93-1.33)	0.062
	Population-based	7	1.20 (0.95-1.53)	1.20 (0.99-1.44)	0.159
	Southern China	3	1.02 (0.66-1.55)	1.00 (0.73-1.36)	0.163
	Northern China	5	1.18 (0.85-1.64)	1.17 (0.95-1.45)	0.058
(AA + AG) *vs* GG	Total analysis	7	1.18 (0.84-1.66)	1.14 (0.91-1.44)	0.055
	Population-based	6	1.34 (1.04-1.72)	1.34 (1.04-1.71)	0.678
	Southern China	3	0.86 (0.45-1.66)	0.82 (0.57-1.18)	0.073
	Northern China	4	1.42 (1.06-1.91)	1.42 (1.06-1.90)	0.575

OR_r = odds ratio for random-effect model; OR_f = odds ratio for fixed-effect model; P_h P value for the heterogeneity test; Northern China included Beijing, Tianjin, Hebei, Xinjiang; Southern China included Guangdong, Taiwan.

Sensitive analysis

In order to evaluate the sensitivity of the analysis, we used the fixed-effect and random-effect model to determine the stability of our meta-analysis. None of the results were materially altered in either the total or the subgroup analysis (Table 2), suggesting that the data included in this study are relatively stable and reliable.

DISCUSSION

Several studies have offered evidence that individual susceptibility to PD is partially determined by genetic predisposition. The relationship between the MAOB A644G polymorphism and PD risk attracted the attention of both doctors and researchers. To date, 3 meta-analyses regarding the MAOB A644G polymorphism and PD risk have been published (Liu et al., 2014; Sun et al., 2014; Zhang et al., 2015). Of these, 1 meta-analysis reported that

there was a significant association between the MAOB A644G polymorphism and PD risk in both Asians and Caucasians (Liu et al., 2014). However, the other 2 studies suggested that there was no significant association between the MAOB polymorphism and PD risk among Caucasians (Sun et al., 2014; Zhang et al., 2015). It is possible that regional and racial differences have contributed to the conflicting results. Therefore, we conducted this meta-analysis to provide a more precise estimation of the association between the MAOB A644G polymorphism and PD susceptibility in only the Chinese population in order to reduce the effect of regional and racial differences.

In the overall analysis, no significant association was found between the MAOB A644G polymorphism and PD in the Chinese population. To examine whether environmental risk factors can modulate PD risk, subgroup analyses stratified by geographical areas and sources of controls were performed. We found that the MAOB A644G polymorphism significantly increased the risk of PD in Northern China, and similar results were observed in population-based studies; in contrast, this increase was not observed in Southern China. This result suggested that differences in genetic backgrounds as well as in the environment may influence the association between the MAOB A644G polymorphism and PD risk.

As compared to previous meta-analyses (Liu et al., 2014; Sun et al., 2014; Zhang et al., 2015), the current study included more researches conducted in the Chinese population. Furthermore, our study has higher statistical power than that of previous meta-analyses conducted in other ethnic groups. The effects of gene-environment interactions with respect to PD risk were also determined by subgroup analyses. Sensitivity analyses confirmed the reliability and stability of the meta-analysis. Therefore, our results indicated that the MAOB A644G polymorphism is associated with PD in individuals from Northern China.

Several limitations were present in our meta-analysis. First, this ethnic-specific meta-analysis only included data from Chinese patients, and thus, our results are only applicable to this ethnic group. Second, because this meta-analysis was primarily based on unadjusted effect estimates and CIs, we did not control for confounding factors. Third, results from the Hardy-Weinberg equilibrium test for genotype distribution in the control groups suggested that significant differences in genetic background existed among the subjects. Finally, due to the limitations in funnel plotting, which requires a range of studies, we did not evaluate publication bias in this meta-analysis.

In conclusion, our meta-analysis results support the hypothesis that the MAOB A644G polymorphism may contribute to individual susceptibility to PD in Northern China. Further studies are required to determine whether the MAOB A644G polymorphism confers PD risk in other ethnic groups.

Conflicts of interest

The authors declare no conflict of interest.

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