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Association of four GSTs gene polymorphisms with Parkinson disease: A meta-analysis

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ABSTRACT

Parkinson disease (PD) is a neurological disorder with huge destruction to human body, which affects approximately 2% of the population aged 65 years or older. As antioxidants in the stress defence systems, glutathione S-transferases (GSTs) are dimeric cytosolic enzymes with an important role in the pathogenesis of PD. The aim of this study was to evaluate the association between the polymorphisms of GST genes and PD. Meta-analyses were conducted from 17 studies (38 stages) among 3419 cases and 5686 controls between four polymorphisms (*GSTT*1 deletion polymorphism; *GSTM*1 deletion polymorphism; *GSTP*1-104: rs1695; *GSTP*1-114: rs1799811) and PD. There is no significant association between the four GST gene variants and PD. A further subgroup study by ethnicity observed a risky role of *GSTM*1 deletion polymorphism with PD in Europeans (p = 0.013, OR = 1.126, 95% CI = 1.025 - 1.236), and a protective role of *GSTM*1 deletion polymorphism with PD in Latin Americans (p = 0.032, OR = 0.750, 95% CI = 0.577 - 0.975). Our meta-analysis suggested that *GSTM*1 deletion polymorphism increased the risk of PD in Europeans, but reduced the risk of PD in Latin Americans. Future large-scale studies might be needed to confirm the ethnic difference of *GSTM*1 deletion polymorphism, and to check whether there was significant association of PD for other GST genetic polymorphisms.

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KEYWORDS

Parkinson; *GSTM*1 Deletion Polymorphism; Meta-Analysis; Europeans; *GSTT*1; *GSTP*1

1. INTRODUCTION

Parkinson disease (PD, OMIM 168600) is a neurological disorder that affects approximately 2% of the population aged 65 years or older [1]. The clinical features of PD are resting tremor, muscular rigidity, bradykinesia, and postural instability [2]. PD can cause a huge destruction to human body, including pain [3], depression [4,5], visual hallucinations [6], dementia [7] and other non-motor symptoms [8-11].

PD is a complex disease that may be contributed by environmental and genetic factors. Environmental hypothesis was dominant for much of the 20th century [2]. PD was shown to be associated with environmental factors such as encephalitis [12], oxidative stress [13], smoking and coffee [14], and environmental toxins [15]. Although recent genetic studies have discovered a handful of genetic markers of PD [16-18], the aetiology of PD remains unknown.

Glutathione S-transferases (GST) conjugate glutathione to electrophilic species that can adduct protein or DNA [19]. GST enzymes can detoxify many oxidative products and thus lower the PD risk in the smokers [20] and the people with pesticides exposure [21]. GST genes that have been studied most in the PD association include *GSTT*1 [22-33] on chromosome 22q11.23, *GSTM*1 [22-28,30,32-38] on chromosome 1p13.3, and *GSTP*1 [23,26,

28-31,33,37,38] on chromosome 11q13. The phenotypic absence of *GSTM*1 and *GSTT*1 activity is the consequences of homozygous deletion of these genes [39, 40]. The *GSTP*1-104 and *GSTP*1-114 were A to G and C to T transitions that may have an impact on gene function [23].

Previous case-control studies showed inconsistent results between GST genes and PD (**Table 1**). Discrepancy among previous studies might be due to different ethnic background, or inefficient sample size [41], or the uncorrected physiological status among different studies [42]. Meta-analysis is a wildly used method to augment statistical power and to draw a more convincing conclusion through the pooling of data from individual association study [43]. The goal of our meta-analyses was to find out the causes of the inconsistent results among various case-control association studies, and to evaluate the contribution of GST variants to PD.

2. MATERIALS AND METHODS

2.1. Data Collection

We performed a systematic literature searching in online databases (PubMed Wan Fang, Wei Pu and CNKI) without time and language restriction, using the following keywords "Parkinson GSTT1 association or Parkinson *GSTT*1 polymorphism", "Parkinson *GSTM*1 association or Parkinson *GSTM*1 polymorphism", "Parkinson *GSTP*1 association or Parkinson GSTP1 polymorphism" to identify available articles. The inclusion criteria of the literatures for the meta-analyses comprise the following items: (1) It was an original case-control study with an assessment of the association between *GSTT*1, *GSTM*1, *GSTP*1 and PD in humans; (2) It contains sufficient information to infer the odd ratios (ORs) and 95% confidential intervals (95% CIs); (3) Genotype distribution of each polymorphism in controls met Hardy-Weinberg equilibrium (HWE). All of the case-control studies about GSTs and PD were fully considered and carefully selected in August 2013. The following information was extracted or calculated from each study: Genetic locus, first author's name, year of publication, country, ethnicity, numbers of cases and controls, control source, HWE for controls, if the study had significant association with PD and power analysis for each study involved in the meta-analyses.

2.2. Statistical Analysis

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] to decide the type of analysis. For the studies with minimal to moderate heterogeneity ($I^2 < 50\%$), the fixed-effect model would be used for the meta-analysis. For the studies with significant heterogeneity ($I^2 >= 50\%$), the random-effect model would be used. Funnel plots were also drawn to observe the potential publication bias. Statistical analysis of meta-analysis was carried out in Review Manager 5 and STATA statistical software [46,47]. Power and Sample Size Calculation program was applied to calculate the power of each study [48].

3. RESULT

As is shown in **Figure 1**, 21 potentially relevant articles were selected after removing duplicates. Among them, 17 studies [22-38] that met the inclusion criteria were involved in our meta-analyses. Among the involved studies, 3 studies for *GSTP*1-104 variant [26,29,31] were excluded for the deviation from HWE in controls ($p <$

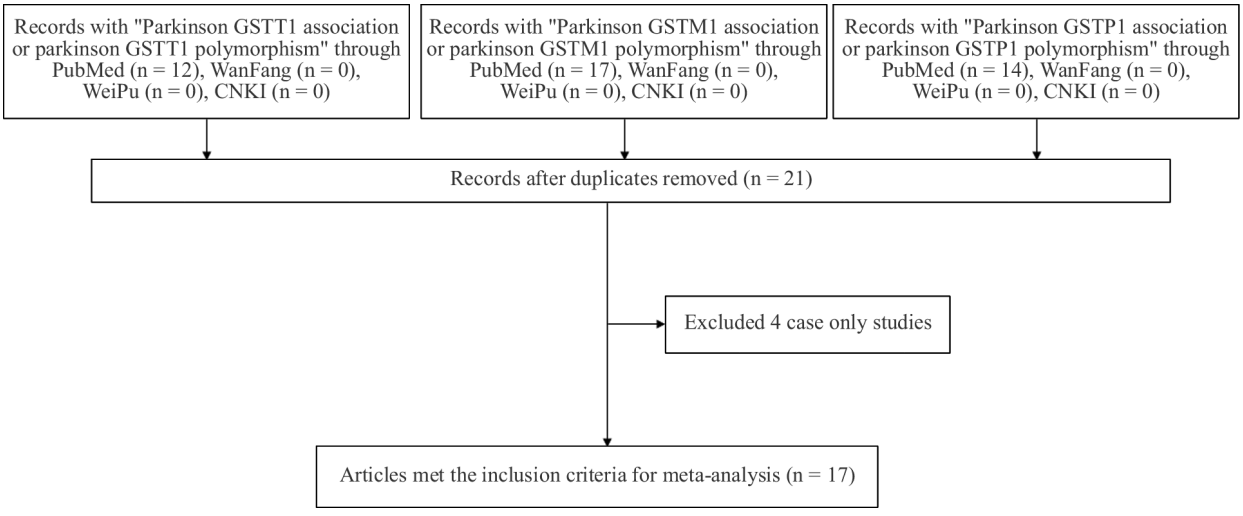

Figure 1. Flowchart of selection process in the meta-analyses.

Table 1. Characteristics of the case-control studies in the current meta-analyses.

First author	Year	Country	Ethnicity	Cases/controls	Control source	HWE	Result*	Power
*GSTT*1 deletion								
Alessandra Menegon	1998	Australia	Europeans	95/95	Hospital	NA	NS	0.123
Maudy CMJ Stroombergen	1999	UK	Europeans	167/225	Hospital	NA	S	0.216
A. Rahbar	2000	Germany	Europeans	149/99	Population	NA	NS	0.137
A. Ahmadi	2000	Sweden	Europeans	35/283	Hospital	NA	NS	0.095
Samir N. Kelada	2003	USA	Europeans	214/327	Hospital	NA	NS	0.231
Angelika D. Wahner	2007	America	Europeans	235/220	Population	NA	NS	0.234
F D Dick	2007	UK	Europeans	200/400	Population	NA	NS	NA
Madhu Singh	2008	India	Asians	70/100	Population	NA	NS	0.094
C. Kiyohara	2010	Japan	Asians	237/369	Hospital	NA	NS	0.340
Arindam Biswas	2012	India	Asians	331/177	Hospital	NA	NS	0.184
Samuel M. Goldman	2012	USA	Europeans	87/343	Population	NA	NS	NA
Tommaso Cornetta	2013	Italy	Europeans	125/112	Hospital	NA	NS	0.124
*GSTM*1 deletion								
Alessandra Menegon	1998	Australia	Europeans	95/95	Population	NA	NS	0.143
Nicholl	1999	UK	Europeans	205/206	Hospital	NA	NS	0.257
Maudy CMJ Stroombergen	1999	UK	Europeans	166/225	Hospital	NA	S	0.241
A. Rahbar	2000	Germany	Europeans	149/99	Hospital	NA	NS	0.168
A. Ahmadi	2000	Sweden	Europeans	35/283	Hospital	NA	NS	0.107
Shoji Harada	2001	Japan	Asians	81/100	Hospital	NA	NS	0.137
Samir N. Kelada	2003	USA	Europeans	214/327	Hospital	NA	NS	0.310
Angelika D. Wahner	2007	America	Europeans	235/220	Population	NA	NS	0.279
F D Dick	2007	UK	Europeans	200/400	Population	NA	NS	NA
Carolina Perez-Pastene	2007	Chile	L.A	349/611	Population	NA	S	0.458
R. Vilara	2007	Portugal	Europeans	94/95	Population	NA	NS	0.142
C. Kiyohara	2010	Japan	Asians	237/369	Hospital	NA	NS	0.335
Giuseppe De Palma	2010	Italy	Europeans	742/1923	Population	NA	NS	0.845
Arindam Biswas	2012	India	Asians	331/177	Hospital	NA	NS	0.251
Samuel M. Goldman	2012	UK	Europeans	87/343	Population	NA	S	NA
Tommaso Cornetta	2013	Italy	Europeans	125/112	Hospital	NA	NS	0.160
*GSTP*1-104								
Alessandra Menegon	1998	Mix*a	Europeans	96/95	Hospital	NA	S	0.071
Samir N. Kelada	2003	America	Europeans	213/329	GHC	NO	S	NA
Angelika D. Wahner	2007	America	Europeans	235/220	Population	YES	NS	0.254
R. Vilar	2007	Portuguese	Europeans	96/96	Population	NA	S	0.109
Madhu Singh	2008	India	Asians	70/100	Population	NO	NS	NA

Continued

C. Kiyohara	2010	Japan	Asians	238/370	Hospital	YES	NS	0.223
Giuseppe De Palma	2010	Mix*b	Europeans	409/1016	Population	NA	NS	0.210
Arindam Biswas	2012	India	Africans	331/177	Hospital	NO	NS	NA
Tommaso Cornetta	2013	Italy	Europeans	125/112	Hospital	NA	S	NA
*GSTP*1-114								
Alessandra Menegon	1998	Mix*a	Europeans	96/95	Hospital	NA	S	0.137
Samir N. Kelada	2003	America	Europeans	214/330	GHC	YES	S	NA
Angelika D. Wahner	2007	America	Europeans	235/220	Population	YES	NS	0.164
Giuseppe De Palma	2010	Mix*b	Europeans	409/1016	Population	NA	NS	0.123

Mix*a, Queensland, Australia, America; Mix*b, Italy, Malta, Romania, Scotland, Sweden; GHC, Group Health Cooperative; HWE, Hardy-Weinberg equilibrium; L.A, Latin Americans; NA, Not applicable; Result*, The association between GST genes and PD; NS, No significant; S, Significant.

0.05). We were unable to test HWE for *GSTT*1 and *GSTM*1 deletions because there was no genotype information in the original reports. At last, we included 17 studies (38 stages) among 3419 cases and 5686 controls in the current meta-analyses of four GST gene variants (**Table 1**).

We observed no significant association between the four GST genes variants and PD (**Table 2**, **Figure 2**). A further subgroup study by ethnicity observed a risky role of *GSTM*1 deletion polymorphism with PD in Europeans (p = 0.013, OR = 1.126, 95% CI = 1.025 - 1.236, **Figure 2** and **Table 2**), and a protective role of *GSTM*1 deletion polymorphism with PD in Latin Americans (p = 0.032, OR = 0.750, 95% CI = 0.577 - 0.975, **Figure 2** and **Table 2**). Statistically significant heterogeneity was found for the meta-analysis of *GSTP*1-104 (I^2 = 79%, **Table 2**). No publication bias was observed for the meta-analyses of the four GST variants (**Figure 3**).

4. DISCUSSION

Our meta-analyses showed that *GSTM*1 deletion polymorphism was a risky and protective factor in PD for Europeans and Latin Americans, respectively (**Table 2** and **Figure 2**). *GSTM*1 encodes a key GST that plays an important role against oxidative stress [49], and thus defenses PD. *GSTM*1 deletion polymorphism showed a wide association with diseases such as coronary heart disease [50], thyroid carcinoma [51], myelodysplastic syndrome [52], oral cancer [53] and PD [22,32,34]. Homozygous deletion genotypes of *GSTM*1 and *GSTT*1 were relatively common in Caucasian populations [54], and disease prevalence by WHO showed that Europe was the most severe region of PD in the world. We performed a further subgroup study by ethnicity that showed a significant association between *GSTM*1 deletion polymorphism and PD in Europeans (p = 0.013, OR = 1.126, 95% CI = 1.025 - 1.236, I^2 = 0%, **Table 2**). On the contrary, there was a significant protective role of *GSTM*1 deletion polymorphism for PD in Latin American population (p = 0.032, OR = 0.750, 95% CI = 0.577 - 0.975, **Table 2**). Since the latter result was produced by only one study [34] with relative low power (power = 0.458), future study was needed to confirm this ethnic difference of *GSTM*1 deletion polymorphism in the risk of PD.

Although we didn't observe a significant association between *GSTP*1-104 and PD in the combined samples, subgroup meta-analyses by ethnicity indicated a trend of significance in Europeans (p = 0.104, **Table 2**) and Asians (p = 0.096, **Table 2**). *GSTP*1-104-A allele frequency showed a significant ethnic difference between Asians (Hapmap-JPT: 0.907) and Europeans (Hapmap-CEU: 0.593, Fst = 0.16). As is shown in **Table 2**, the power is 0.476 in Europeans and 0.223 in Asians, indicating that larger sample size is needed to validate the association of *GSTP*1-104 and PD in the future.

To be noted, a former meta-analysis with 4 studies in *GSTT*1 and *GSTM*1, and 1 study in *GSTP*1 in 2000 [55] showed a significant association between *GSTT*1 and PD, and no significant results were found in *GSTM*1 and *GSTP*1. Compared with the former meta-analysis, our study included 8, 12 and 8 more studies in *GSTT*1, *GSTM*1 and *GSTP*1, respectively. We also performed an ethnic subgroup study that previous study did not perform. We performed HWE test for the controls in *GSTP*1 and excluded 3 case-control studies that failed to meet HWE in the control samples [26,29,31]. With an enhanced power, more comprehensive analysis and stricter selection criteria, our meta-analyses produced a more reliable conclusion than the previous meta-analysis studies.

Several limitations in our study needed to be carefully considered. Firstly, the number of associations in non-Caucasian populations was limited. This suggested that

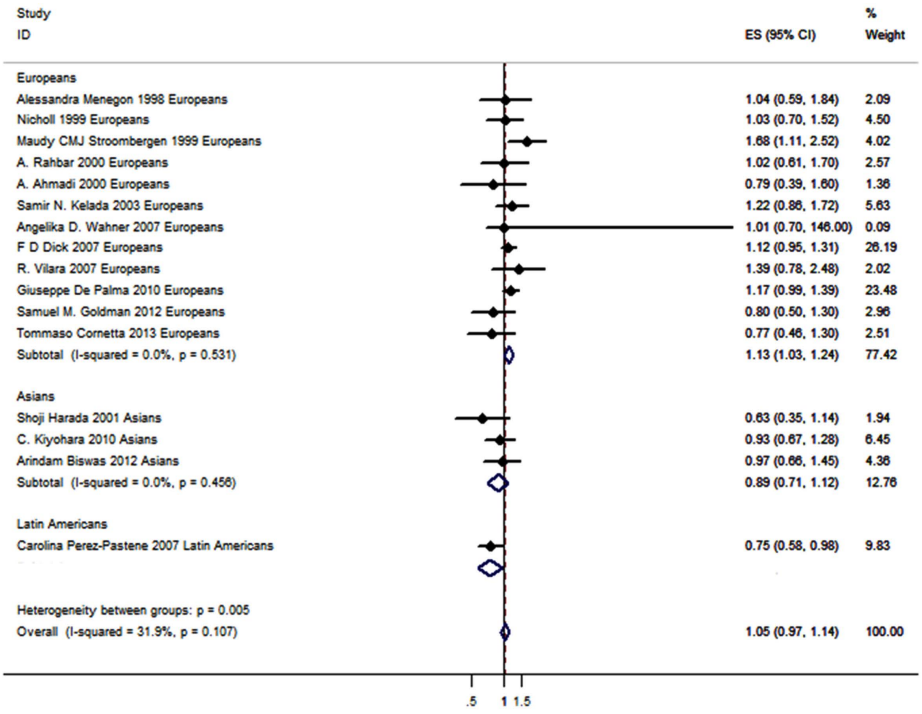

Figure 2. Forest plot of *GSTM*1 deletion polymorphism with PD.

Table 2. Meta-analyses of the *GSTT*1 deletion polymorphism, *GSTM*1 deletion polymorphism, *GSTP*1-104 and *GSTP*1-114 with PD.

Genetic model	Ethnicity	Stages*	Cases/Controls	OR (95% CI)	*P* value	I^2	Power
*GSTT*1 deletion							
Overall (Null vs Present)	Overall	12	1945/2750	1.042 (0.933 - 1.164)	0.467	39.10%	NA
	Europeans	9	1307/2104	1.099 (0.972 - 1.242)	0.132	35.00%	NA
	Asians	3	638/646	0.820 (0.632 - 1.064)	0.135	0.00%	NA
*GSTM*1 deletion							
Overall (Null vs Present)	Overall	16	3345/5585	1.050 (0.967 - 1.139)	0.249	31.90%	NA
	Europeans	12	2347/4328	1.126 (1.025 - 1.236)	0.013	0.00%	NA
	Asians	3	649/646	0.889 (0.706 - 1.119)	0.318	0.00%	NA
	Latin Americans	1	349/611	0.750 (0.577 - 0.975)	0.032	NA	NA
*GSTP*1-104							
Overall (A vs G)	Overall	5	994/1727	1.140 (0.630 - 2.070)	0.66	92.00%	0.679
	Europeans	4	756/1357	1.435 (0.928 - 2.218)	0.104	76.00%	0.476
	Asians	1	238/320	0.760 (0.550 - 1.050)	0.096	NA	0.223
Dominant (AA/AG vs GG)	Overall	3	598/702	1.110 (0.890 - 1.400)	0.36	33.00%	0.629
Recessive (GG vs AG/GG)	Overall	2	473/590	0.960 (0.740 - 1.240)	0.77	36.00%	0.52
Additive (AA vs GG)	Overall	2	298/390	0.980 (0.550 - 1.720)	0.09	0.00%	0.134
*GSTP*1-114							
Overall (C vs T)	Overall	4	874/1591	1.030 (0.810 - 1.330)	0.79	0.00%	0.314
Dominant (CC/CT vs TT)	Overall	2	448/549	1.150 (0.840 - 1.590)	0.38	0.00%	0.364
Recessive (CC vs CT/TT)	Overall	2	448/549	0.280 (0.070 - 1.160)	0.08	20.00%	0.09
Additive (CC vs TT)	Overall	2	360/459	0.290 (0.070 - 1.210)	0.09	23.00%	0.089

Stages*: Amount of stages; NA, Not applicable.

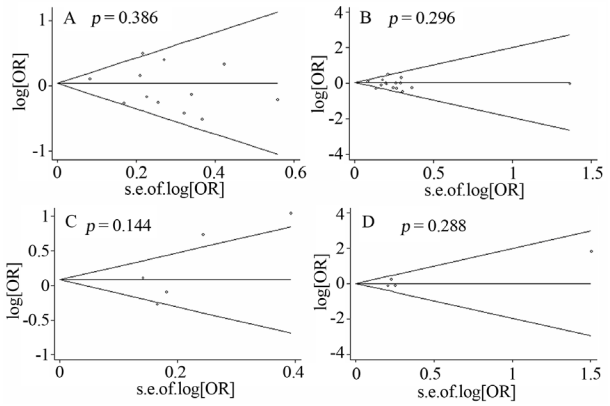

Figure 3. Funnel plots of four SNPs with PD. A) Funnel plot of *GSTT*1 deletion polymorphism with PD; B) Funnel plot of *GSTM*1 deletion polymorphism with PD; C) Funnel plot of *GSTP*1-104 polymorphism with PD; D) Funnel plot of *GSTM*1-114 polymorphism with PD.

non-significant results in Asians needed to be taken with caution. Future studies with larger samples size are required to establish the association of GST gene polymorphisms with PD. Secondly, PD is a complex disease that different physiological status of PD may exist in the cases. All the existing case-control studies didn't perform a stratified analysis by the PD stage. This may partially explain the discrepancies in the current case-control studies. Thirdly, genetic heterogeneity may exist for the polymorphisms of GST genes. Our meta-analyses only focused on four polymorphisms that might not fully represent the overall contribution of GST gene polymorphisms. Other GST gene polymorphisms need to be analyzed for their contribution to PD in the future. Fourthly, all the p values are not corrected by the number of tests. The positive findings in the present study need to be validated in the future study in order to prevent the false positives caused by multiple testing in our analyses.

In conclusion, our meta-analysis observed a significant association of *GSTM*1 deletion polymorphism with PD in Europeans. Further large-scale studies are required to evaluate the polymorphisms of GSTs that might contribute to the risk of PD.

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