Research Article

Open Access

Chen Weikang, Li Jie*, Lan Likang, Qiu Weiwen, Lu Liping

A meta-analysis of association between glutathione S-transferase M1 gene polymorphism and Parkinson's disease susceptibility

Abstract: The aim of this meta-analysis was to evaluate whether there was an association between glutathione S-transferase M1(GSTM1)gene polymorphism and Parkinson's disease (PD) susceptibility by pooling published data.

We performed comprehensive electronic database search for articles published between February12,2015 and April30 2016. The published case-control or cohort studies related to GSTM1 gene polymorphism and Parkinson's disease susceptibility were screened, reviewed, and included in this meta-analysis. The correlation between GSTM1 gene polymorphism and PD susceptibility was expressed by odds ratio (OR) and its corresponding 95% confidence interval (95%CI). Publication bias was evaluated by Begg's funnel plot and Egger's line regression test. All analysis was done by stata11.0 software.

After searching the PubMed, EMBASE, and CNKI databases, seventeen case-control studies with 3,538 PD and 5,180 controls were included in the final meta-analysis. The data was pooled by a fixed-effect model for lack of statistical heterogeneity across the studies; the results showed GSTM1 null expression can significant increase the susceptibility of PD (OR=1.11, 95% CI:1.01-1.21, P<0.05). Subgroup analysis indicated GSTM1 gene polymorphism was associated with PD susceptibility in the Caucasian ethnic group (OR=1.15, 95% CI:1.05-1.27,P<0.05) but not in the Asian ethnic group (OR=0.89, 95% CI:0.70-1.12,P>0.05). Begg's funnel plot and Egger's line regression test showed no significant publication bias.

Based on the present evidence, GSTM1 null expression can significant increase the susceptibility of PD in persons of Caucasian ethnicity.

1 Introduction

Parkinson's disease (PD) is a degenerative disorder of the central nervous system, mainly affecting the motor system. In most patients, it is considered idiopathic. But recent studies have demonstrated that some cases can be attributed to known genetic factors such as single nucleotide polymorphisms. Glutathione S-transferases (GSTs) are a family of cytosolic enzymes involved in the detoxification of various exogenous, as well as endogenous, reactive species [1,2]. The GST family alleviates oxidative stress and can expel such toxicants from the body by increasing watersolubility. The coding region of GSTM1 polymorphisms was considered to confer different catalytic activities [3]. The GSTM1 gene with the homozygous deletion polymorphism is the null genotype. For the null genotype, the protein lacks enzyme activities. Theoretically, theGSTM1 null genotype could cause neuronal demise that may increase PD risk. Several case-control studies have discussed the relationship between GSTM1 polymorphisms and PD susceptibility. However, for the small number of cases and controls included in each of the studies, the statistical power was limited and could not reach a consistent conclusion. Thus, in this study, we searched and included the open published papers related to the association between GSTM1gene polymorphism and PD susceptibility by pooling the published to further discuss their correlation.

*Corresponding author: Li Jie, Department of Neurology, Lishui People's Hospital (the 6th affiliated hospital of Wenzhou medical university) Zhejiang Lishui 323000 PR China, E-mail:lijie_ls@163.com
Chen Weikang, Lan Likang, Qiu Weiwen, Lu Liping, Department of Neurology, Lishui People's Hospital (the 6th affiliated hospital of Wenzhou medical university) Zhejiang Lishui 323000 PR China

1.1 Search strategy

Open published case-control or cohort studies about glutathione S-transferase M1(GSTM1)gene polymorphism and PD risk were searched and screened from the databases of PubMed, EMBASE and CNKI by two reviewers (Chen Weikang and Li Jie) independently from February12 2015 to April 30 2016. The following search terms: "Parkinson's disease", "Parkinsons disease", "Parkinson disease", "PD", "gstml", "Glutathione S-transferase M1" and "polymorphism" were used as free text words in the publication-searching procedure. The studies were restriction to humans, with the language restriction English and Chinese. All potential relevant case-control or cohort studies were evaluated, and additional citations of the included articles were further investigatedto identify additional suitable studies.

1.2 Inclusion criteria and data extraction

The inclusion criteria were: (1) Open published case-control or cohort studies related to GSTM1 gene polymorphism and PD susceptibility (2) PD was confirmed by clinical diagnosis; (3) Single-nucleotide polymorphism of GSTM1 gene was clearly reported or can be calculated from the original included studies; (4) The genotype distributions of controls should be accord with Hardy-Weinberg equilibrium (HWE). (5) The language was limited to English or Chinese. The exclusion criteria were: (1) Case report or review publications; (2) The original paper did not provide enough data to pool the odds ratio of GSTM1 gene polymorphism and PD susceptibility; (3) The paper was published in other languages.

1.3 Data extraction

Lu Liping and Lan Likang independently extracted the data from all the included studies. If there was disagreement for paper inclusion/exclusion or data extraction, the third reviewer (Chen Weikang) was consulted. The general characteristics of publication year, patients' ethnicity, age, gender, country the research was done, and genotyping method were extracted from the original studies. The number of patient controls, the distribution of GSTM1 null and positive expression subjects were further carefully extracted, which was important for calculation of the odds ratio.

1.4 Statistical analysis

The data was analyzed by stata11.0 software (StataCorp LP, http://www.stata.com). The odds of null and present genotype in PD patients and healthy controls was showed by odds ratio (OR) and its corresponding 95% confidence intervals (95% CI). Statistical heterogeneity among studies was evaluated by I^2 [4]. If significant heterogeneity was found ($I^2 > 50\%$), the random-effect method (Der Simonian-Laird method) was used to pool the data. Inversely, fixed-effect method was applied. The publication bias was evaluated by Begg's funnel plot and Egger's line regression test [5].

2 Results

2.1 General characteristics of the included studies

After searching PubMed, EMBASE, and CNKI databases, 987 studies were initially found. Twelve studies were excluded for duplicated publication or duplicated used data. After reading the title and abstract, 914 publications were excluded. And after reading the entire paper, 44 publications were excluded and 17 case-control studies with 3,538 PD and 5,180 controls were finally included in this meta-analysis (Figure 1). For the included 17 case-control studies, 14 papers were conducted on persons of Caucasian ethnicity and other 3 studies were on persons of Asian ethnicity. The general characteristics of the included 17 papers are shown in Table 1.

2.2 Statistical Heterogeneity evaluation

The statistical heterogeneity among studies was evaluated by I^2 test. For all the included studies, the $I^2 = 26.8\%$, which indicated no statistical heterogeneity across the 17 manuscripts. Subgroup analysis also showed no statistical heterogeneity in Caucasian ethnic group ($I^2 = 19.4\%$) and Asian ethnic group ($I^2 = 0.00\%$). Because of no statistical heterogeneity across the studies, all data was pooled by fixed effects model.

2.3 Meta-analysis

The data was pooled by fixed effect model for the lack of statistical heterogeneity across the studies; the result

Table 1: The general characteristics of the included 17studies

Author	Year	Area	Genotyping	PD		Control	
				Null	Positive	Null	Positive
Tison [6]	1994	French	NA	20	20	60	40
Stroombergen [7]	1996	Caucasian	PCR	82	40	43	41
Bandmann [8]	1997	Europe	NA	115	85	58	42
Menegon [9]	1998	Caucasian	PCR	49	46	48	47
Nicholl [10]	1999	Caucasian	PCR	101	104	100	106
Stroombergen [11]	1999	Caucasian	PCR	105	62	114	111
Ahmadi [12]	2000	Swedish	PCR-RFLP	17	18	154	129
Rahbar [13]	2000	German	PCR	76	73	51	48
Harada [14]	2001	Japanese	PCR	32	49	51	49
Kelada [15]	2003	Caucasian	NA	108	106	149	178
Vilar [16]	2007	Caucasian	PCR-RFLP	58	36	51	44
Carolina [17]	2007	Amerindian	NA	164	185	244	367
Wahner [18]	2007	Caucasian	NA	114	121	106	114
Giuseppe [19]	2010	Caucasian	NA	405	337	973	950
Kiyohara [20]	2010	Japanese	Taqman assays	122	115	197	172
Biswas [21]	2012	Indian	PCR	101	230	55	122
Pinhel [22]	2013	Brazil	PCR-RFLP	112	130	86	80
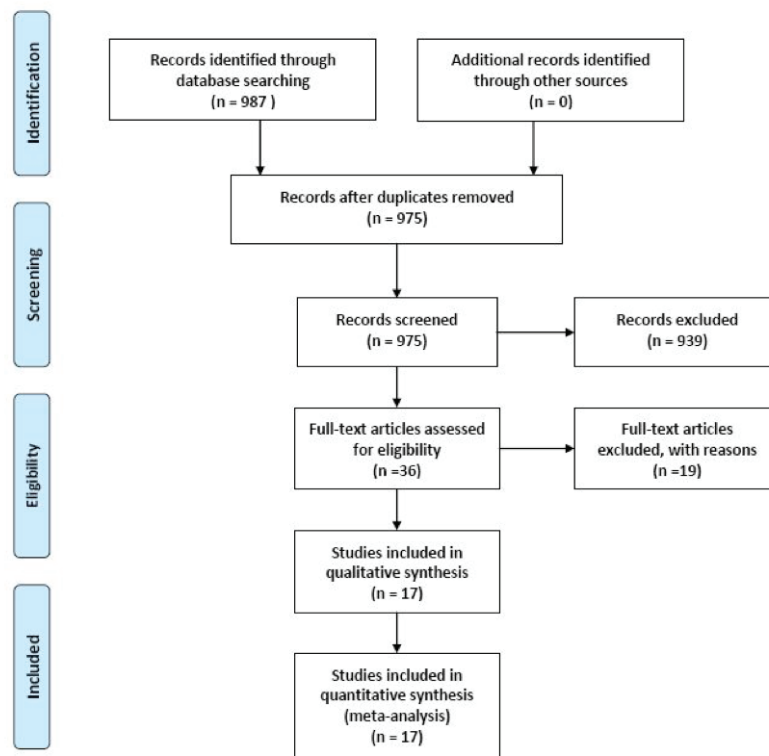
Figure 1: The searching strategy flow chart

showed GSTM1 null expression can significantly increase the susceptibility of PD (OR=1.11, 95% CI:1.01-1.21, *P*<0.05), Figure 2.

2.4 Subgroup analysis

The association between GSTM1 gene polymorphism and PD susceptibility was further analyzed as related to the patient's ethnicity. GSTM1 gene polymorphism was associated with PD susceptibility in the Caucasian ethnic group (OR=1.15, 95% CI:1.05-1.27,*P*<0.05) but not in the Asian ethnic group (OR=0.89, 95% CI:0.70-1.12,*P*>0.05).

2.5 Publication bias

The Begg's funnel plot and Egger's line regression test were used to evaluate publication bias [5]. The Begg's funnel plot was somewhat asymmetrical at the bottom (Figure 3). However, Egger's line regression test, which can gi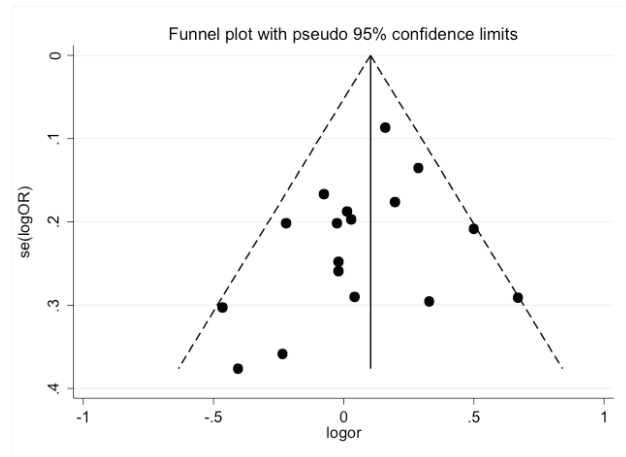ve exact extent of asymmetry of the funnel plot, did not indicate any statistical evidence for publication bias (t=-1.28, *P*=0.22).

Figure 3: Begg's funnel plot for GSTM1 polymorphism and PD susceptibility
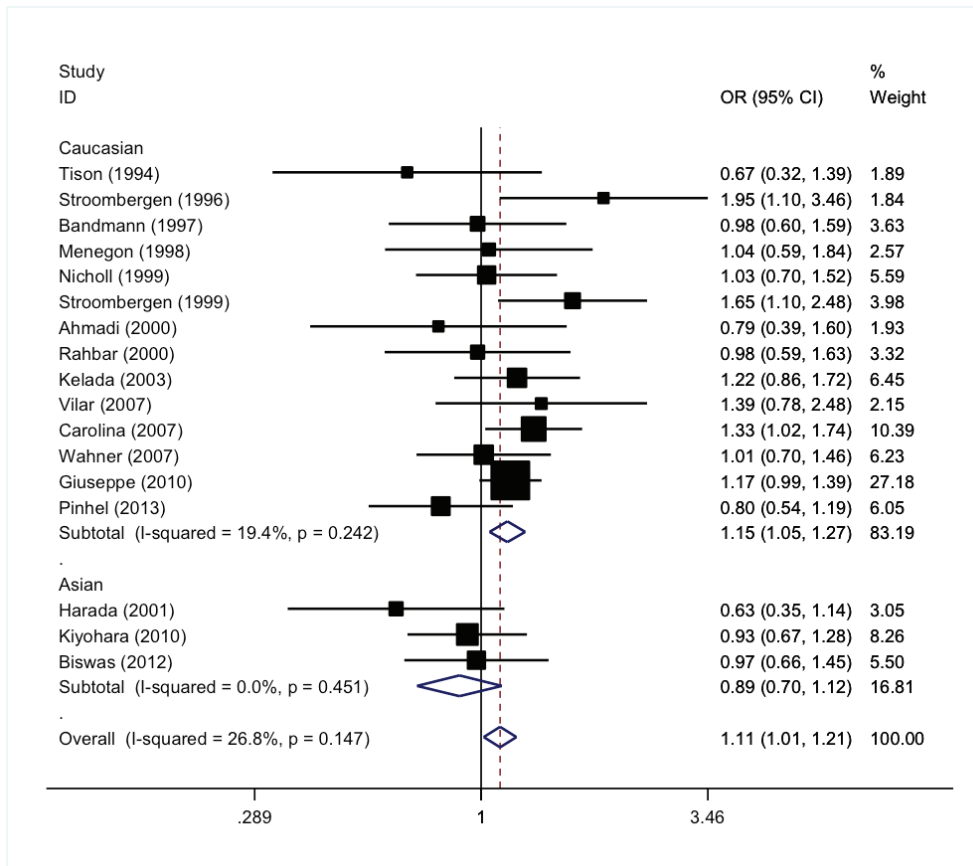

Figure 2: The forest plot of GSTM1 polymorphism and PD susceptibility

3 Discussion

Glutathione S-transferases (GSTs) are a family of related isoenzymes protect against xenobiotic chemicals that continuously enter the body, largely through mucous membranes [23]. The GST family alleviates oxidative stress by expelling toxicants from the body by increasing water-solubility. To date, eight types of different GSTs, namely GSTα, GSTκ, GSTδ, GSTω, GSTμ, GSTπ, GSTξ, and GSTθ have been found in humans and other mammals [24]. Several previously published studies have discussed the relationship between GST family polymorphisms and PD susceptibility [18-20]. Pinhel and his colleagues performed a population-based case-control study to evaluate the influence of genetic variants of GSTT1/GSTM1 and their association with PD [22]. In this study, the authors included 254 cases with PD and 169 healthy controls. The genotype of GSTT1/GSTM1 was tested by PCR assay. They found that the present and deletion of GSTT1/GSTM1 were not statistical different in PD and healthy controls which indicating that there was no significant association between GSTT1/GSTM1 present/absence polymorphism and PD susceptibility. However, another case-control study performed by Stroombergen *et al* found the opposite results [11]. In their study, the authors included 167 PD and 225 non-neurological disease subjects. The association between GSTM1 present/absence polymorphism and PD was investigated by PCR, using primers specific for both genes. The authors found that males with a deletion of the GSTM1or GSTT1gene were more susceptible to PD. Therefore, the results for the above two independent case-control studies were not in agreement with each other. Because of the small number of cases and controls included in each of the individual study, the statistical power was limited and could not reach a consistent conclusion. Thus, in this study, we searched and included the open published papers related to the correlation between GSTM1gene polymorphism and PD susceptibility by pooling the published data to further discuss their correlation. In the present study, 17 case-control publications with 3,538 PD and 5,180 controls were included in this meta-analysis. All of the included manuscripts were published in English. The pooled results showed persons with the GSTM1 null genotype had an increased risk of developing PD (odds ratio 1.11, 95% CI1.01-1.21). The subgroup analysis indicated GSTM1 gene polymorphism was associated with PD susceptibility in the Caucasian ethnic group but not in the Asian ethnic group. The lack of correlation for GSTM1 gene polymorphism and PD susceptibility in the Asian ethnic group maybe related to the small number of studies (only 3) included in this meta-analysis with limited statistical power. It is believed that the homozygous deletion of GSTM1*0 (null expression) could result in a lack of enzyme activity. For that reason, we considered that the inactivity of a phase II enzyme may contribute to the increased susceptibility to PD. However, the cause of PD is complex and related to a variety of genes. The gene–gene and gene–environment interactions may have more obvious effects on the incidence of PD. We suggest that the entire genome-wide analysis may need to be further evaluated for gene polymorphism and PD susceptibility.

Conflict of interest statement: Authors state no conflict of interest.

References

[1] Ketterer B. Protective role of glutathione and glutathione transferases in mutagenesis and carcinogenesis[J]. Mutat Res, 1988,202(2):343-361

[2] Hengstler JG, Arand M, Herrero ME, et al. Polymorphisms of N-acetyltransferases, glutathione S-transferases, microsomal epoxide hydrolase and sulfotransferases: influence on cancer susceptibility[J]. Recent results in cancer research. Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer, 1998,154:47-85

[3] Yang LM, Li XH, Bao CF. Glutathione S-transferase P1 and DNA polymorphisms influence response to chemotherapy and prognosis of bone tumors[J]. Asian Pac J Cancer Prev, 2012,13(11):5883-5886

[4] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses[J]. BMJ, 2003,327(7414):557-60

[5] Egger M, Davey SG, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test[J]. BMJ, 1997,315(7109):629-634

[6] Tison F, Coutelle C, Henry P, et al. Glutathion S-transferase (class mu) phenotype in Parkinson's disease[J]. Mov Disord, 1994,9(1):117-118

[7] Stroombergen MC, Waring RH, Bennett P, et al. Determination of the GSTM1 gene deletion frequency in Parkinson's disease by allele specific PCR[J]. Parkinsonism Relat Disord, 1996,2(3):151-154

[8] Bandmann O, Vaughan J, Holmans P, et al. Association of slow acetylator genotype for N-acetyltransferase 2 with familial Parkinson's disease[J]. Lancet (London, England), 1997,350(9085):1136-1139

[9] Menegon A, Board PG, Blackburn AC, et al. Parkinson's disease, pesticides, and glutathione transferase polymorphisms[J]. Lancet (London, England), 1998,352(9137):1344-1346

[10] Nicholl DJ, Bennett P, Hiller L, et al. A study of five candidate genes in Parkinson's disease and related neurodegenerative disorders. European Study Group on Atypical Parkinsonism[J]. Neurology, 1999,53(7):1415-1421

[11] Stroombergen MC, Waring RH. Determination of glutathione S-transferase mu and theta polymorphisms in neurological disease[J]. Hum Exp Toxicol, 1999,18(3):141-145

[12] Ahmadi A, Fredrikson M, Jerregard H, et al. GSTM1 and mEPHX polymorphisms in Parkinson's disease and age of onset[J]. Biochem Biophys Res Commun, 2000,269(3):676-680

[13] Rahbar A, Kempkes M, Muller T, et al. Glutathione S-transferase polymorphism in Parkinson's disease[J]. Journal of neural transmission (Vienna, Austria : 1996), 2000,107(3):331-334

[14] Harada S, Fujii C, Hayashi A, et al. An association between idiopathic Parkinson's disease and polymorphisms of phase II detoxification enzymes: glutathione S-transferase M1 and quinone oxidoreductase 1 and 2[J]. Biochem Biophys Res Commun, 2001,288(4):887-892

[15] Kelada SN, Stapleton PL, Farin FM, et al. Glutathione S-transferase M1, T1, and P1 polymorphisms and Parkinson's disease[J]. Neurosci Lett, 2003,337(1):5-8

[16] Vilar R, Coelho H, Rodrigues E, et al. Association of A313 G polymorphism (GSTP1*B) in the glutathione-S-transferase P1 gene with sporadic Parkinson's disease[J]. European journal of neurology, 2007,14(2):156-161

[17] Perez-Pastene C, Graumann R, Diaz-Grez F, et al. Association of GST M1 null polymorphism with Parkinson's disease in a Chilean population with a strong Amerindian genetic component[J]. Neurosci Lett, 2007,418(2):181-185

[18] Wahner AD, Glatt CE, Bronstein JM, et al. Glutathione S-transferase mu, omega, pi, and theta class variants and smoking in Parkinson's disease[J]. Neurosci Lett, 2007,413(3):274-278

[19] De Palma G, Dick FD, Calzetti S, et al. A case-control study of Parkinson's disease and tobacco use: gene-tobacco interactions[J]. Mov Disord, 2010,25(7):912-919

[20] Kiyohara C, Miyake Y, Koyanagi M, et al. GST polymorphisms, interaction with smoking and pesticide use, and risk for Parkinson's disease in a Japanese population[J]. Parkinsonism Relat Disord, 2010,16(7):447-452

[21] Biswas A, Sadhukhan T, Bose K, et al. Role of glutathione S-transferase T1, M1 and P1 polymorphisms in Indian Parkinson's disease patients[J]. Parkinsonism Relat Disord, 2012,18(5):664-665

[22] Pinhel MA, Sado CL, Longo GS, et al. Nullity of GSTT1/GSTM1 related to pesticides is associated with Parkinson's disease[J]. Arquivos de neuro-psiquiatria, 2013,71(8):527-532

[23] Coles BF, Kadlubar FF. Human alpha class glutathione S-transferases: genetic polymorphism, expression, and susceptibility to disease[J]. Methods Enzymol, 2005,401:9-42

[24] Salinas AE, Wong MG. Glutathione S-transferases – a review[J]. Curr Med Chem, 1999,6(4):279-309