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Association between Glutathione S-transferase M1/Glutathione S-transferase T1 polymorphisms and Parkinson's disease: A meta-analysis

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ABSTRACT

The Glutathione S-transferase M1 (*GSTM1*) and Glutathione S-transferase T1 (*GSTT1*) genes have been studied extensively as potential candidate genes for the risk of Parkinson's disease (PD). However, direct evidence from genetic association studies remains inconclusive. In order to address this issue, we performed an updated and refined meta-analysis to determine the effect of *GSTM1* and *GSTT1* polymorphisms on Parkinson's disease. A fixed-effect model was utilized to calculate the combined odds ratio (OR), OR of different ethnicities, and 95% confidence intervals (CIs). Potential publication bias was estimated. Homogeneity of the included studies was also evaluated. The pooled OR was 1.13 [95% CI (1.03, 1.24)] and 0.96 [95% CI (0.82, 1.12)] for *GSTM1* and *GSTT1* polymorphisms, respectively. Analysis according to different races found no association between *GSTM1*/*GSTT1* polymorphisms and PD risks except for *GSTM1* variant in Caucasians, which showed a weak correlation (OR 1.16 [95% CI (1.04, 1.29), I squared = 6.2%, p = 0.384]). Neither publication bias nor heterogeneity was found among the included studies. The results of this meta-analysis suggest that *GSTM1* polymorphism is weakly associated with the risk of PD in Caucasians whereas *GSTT1* polymorphism is not a PD risk factor.

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases clinically characterized by resting tremor, bradykinesia, stiffness of movement and postural instability [1]. PD is a complex disorder that results from most likely a combination of genetic and environmental factors. Approximately 85% of PD cases are sporadic, familial clustering as 10–15% and monogenic inheritance is less than 5% [2]. To date, the underlying genetic and molecular mechanisms for PD are remaining largely unknown.

Glutathione S-transferases (GSTs) serve to protect cells by detoxification of endogenous or exogenous toxins [3]. GSTs may modify cellular response against endogenous and/or exogenous reactive intermediates, influencing the individual susceptibility for PD [4,5]. The mammalian *GST* gene family contains at least 16 genes which are assigned to 8 protein enzyme classes: Alpha (GSTA), Kappa (GSTK), Mu (GSTM), Omega (GSTO), Pi (GSTP), Sigma (GSTS), Theta (GSTT), and Zeta (GSTZ) [6]. *GSTM1*, *GSTT1* null alleles and *GSTP1* valine allele (Val/Val) are the most extensively studied *GST* gene variants [7]. Some studies found that Parkinson's disease was associated with *GSTM1* [8,9] and *GSTT1* variants [8,10]. However, negative or conflicting results in sporadic Parkinson's disease were also reported [11,12]. Therefore, we aimed to perform a meta-analysis to assess whether *GSTM1*/*GSTT1* variants are associated with the risk of PD.

2. Methods

2.1. Literature search

Studies were selected through a computerized search of PubMed and EMBASE electronic Database, using the 'Parkinson's disease,' 'Parkinsons disease,' 'Parkinson disease,' 'PD,' and 'GSTM1,' 'Glutathione S-transferases mu', 'GSTT1,' 'Glutathione S-transferases theta'. All researches were limited to English articles published up to Feb, 2013. Studies were selected if the genotypes for the *GSTM1* and/or *GSTT1* were reported for patients with clinically diagnosed PD and for a control population. References in the retrieved papers were examined to identify additional studies.

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The inclusion criteria: (1) case–control study design; (2) presentation of data necessary for calculating odds ratios (ORs); (3) clinical diagnosis of PD. Animal studies, reviews, case reports and unpublished data were excluded. Repeated studies were excluded.

2.2. Data extraction

Studies were included according to our inclusion criteria. The following data were extracted from each study: general information (the first author's name, year of publication, and location of origin or country), number of cases and controls for *GSTM1* null (−/−) vs *GSTM1* present (+/− and +/+) and *GSTT1* null (−/−) vs *GSTT1* present (+/− and +/+) genotype, genotyping method.

2.3. Analysis

Meta-analysis was utilized to evaluate the relation between the *GSTM1/GSTT1* polymorphisms and PD in Mantel–Haenszel model. Pooled OR and corresponding 95% confidence intervals (CIs) for cause and PD risk were calculated. Both the presence of significant heterogeneity at the 10% level of significance and values of I squared >56% were considered as significant heterogeneity [13]. Ethnic differences concerning the association between genotype polymorphisms and clinical outcomes were reported [13,14]. In order to investigate the potential ethnic difference in the relationship between PD and *GSTM1/GSTT1* polymorphisms, the included studies were stratified into subgroups representing different races. Publication bias was assessed by Egger's and Begg's tests. The funnel plots of the associations of *GSTM1* and *GSTT1* polymorphisms with PD were also performed. All data analysis was processed by STATA/SE 11.0 (Stata Corporation, College Station, TX).

3. Results

3.1. Study characteristics

1088 potential papers for *GSTM1* variant were identified. Among these papers, twenty papers were selected for further review after 1068 articles were excluded. Among those excluded papers, 14 papers were not performed in humans, 15 of these literatures did not report the desired gene data as numbers of cases and controls, and the others were neither study of *GSTM1* gene polymorphism nor original research.

It was noteworthy that one study [15] was excluded because this study investigated the interaction of *GSTM1*-null and *CYP2D6*-deficient alleles in PD (without *GSTM1* gene polymorphism data). Two other studies were also excluded due to case-only design [16,17]. As a result, a total of 16 case–control studies (3296 cases and 5014 controls) for *GSTM1* variant were included in this study (as shown in Fig. 1A).

According to the inclusion criteria, ten studies involving 3728 individuals (1733 cases and 1995 controls) for *GSTT1* variant were included in this meta-analysis (as shown in Fig. 1B). Descriptions and characteristics of all the included studies are shown in Tables 1 and 2.

3.2. GSTM1 variant and PD

Meta-analysis was used to calculate the combined OR for the *GSTM1* and *GSTT1* variants. No significant association between *GSTM1* null genotype and PD risk was observed (Fig. 2). The combined OR for the *GSTM1* variant among these studies was 1.13 [95% CI (1.03, 1.24)]. Heterogeneity was not significant across these *GSTM1* studies (I squared = 21.6%, p = 0.207). This result demonstrated poor association between *GSTM1* variant and PD risk.

If the studies were stratified into subgroups representing different races, the OR value was 1.16 [95% CI (1.04, 1.29), I squared = 6.2%, p = 0.384], 0.89 [95% CI (0.7, 1.12), I squared = 0.0%, p = 0.451], and 1.33 for Caucasians, Asians, and Amerindian population, respectively. I squared value and p value were not calculated for the Amerindinic ethnics (Chilean) because only one study was included. The result of subgroup analysis showed a weak association between *GSTM1* and PD in Caucasians. In contrast, there is no association between *GSTM1* polymorphism and PD in Asians.

3.3. GSTT1 variant and PD

The combined OR for *GSTT1* variant was 0.96 [95% CI (0.82, 1.12)]. And heterogeneity was not significant among *GSTT1* studies (I squared = 37%, p = 0.113). In subgroup studies, the OR value was 1.05 [95% CI (0.86, 1.28), I squared = 42.5%, p = 0.108] and 0.82 (95% CI (0.63, 1.07), I squared = 0.0%, p = 0.413) for Caucasians and Asians, respectively (Fig. 3). No difference was found between different races, indicating that *GSTT1* variant was not associated with the risk of PD.

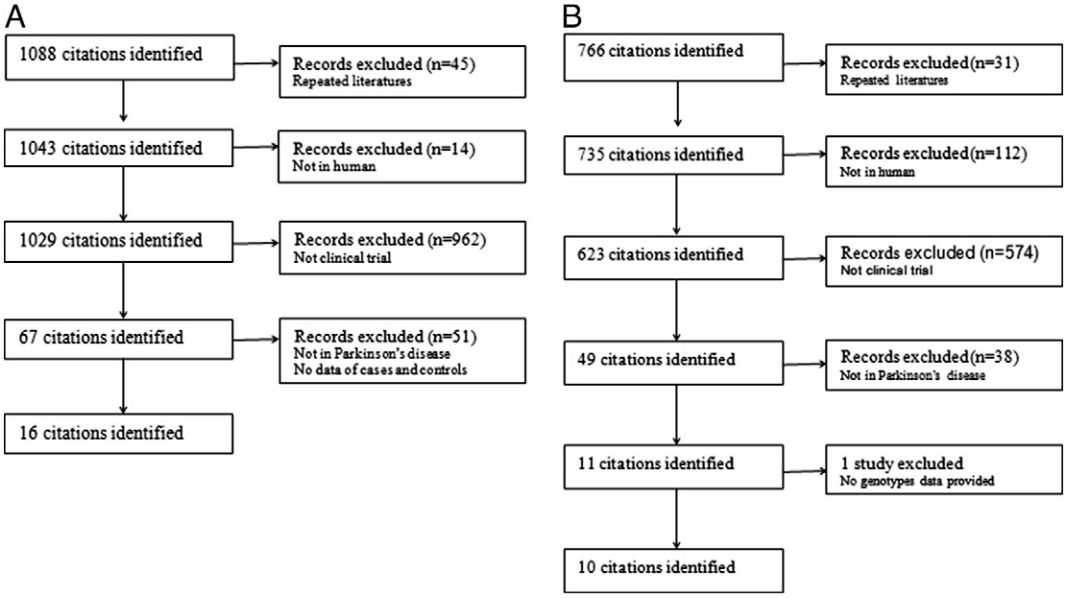

Fig. 1. Flow chart of literature search and selection for *GSTM1/GSTT1* polymorphism in Parkinson's disease. A: flow chart for *GSTM1* polymorphism. B: Flow chart for *GSTT1* polymorphism.